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Vitamin C as an Adjunct Therapy in Sepsis Management

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Abstract

In the United States, sepsis afflicts nearly one in three ICU patients, is associated with monumental healthcare costs, and is among the leading causes of death. The burden of sepsis is felt globally, and efforts are underway to discover an effective adjunctive therapy. Vitamin C is a novel treatment showing promising early evidence. Additionally, vitamin C's use in combination therapy with hydrocortisone and thiamine has been postulated. These components are thought to work congruently to attenuate the pathophysiologic process of sepsis.

To answer whether vitamin C improves septic patient outcomes, a variety of methods were used to obtain information. Primarily, the electronic database PubMed was utilized to perform a literature search. Most sources had full-text versions available and those that did not were obtained through Augsburg University's interlibrary loan system. Finally, expert interviews were conducted with practicing physician's and physician assistants that have experience managing sepsis.

Standard care protocols, definitions and recommendations implemented by the Surviving Sepsis Campaign and the Sepsis-3 Task Force have improved septic patient outcomes substantially, however, sepsis continues to burden patients and health systems globally. Offering affordability and accessibility, vitamin C may be the adjunct sepsis treatment the medical community has been searching for. Overall, the available evidence suggests vitamin C is safe, improves mortality and reduces hospital resource consumption, among other various measured outcomes. Many clinical trials are currently in progress or awaiting publishing. Results from these studies will further define the efficacy of vitamin C alone and in combination with hydrocortisone and thiamine.

Introduction

Hospital beds within intensive care units (ICUs) around the world are occupied by the critically ill fighting for their lives. Of these patients, approximately one in three are admitted with sepsis, or will develop nosocomial sepsis during their stay in the ICU.[1] Sepsis, defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection", develops in 750,000 patients in the United States alone.[2] This disease process accounts for six million deaths worldwide each year, it ranks as the third leading cause of death in the United States, and is a contender for most expensive cause of hospitalization.[3,4] The sequela of sepsis go beyond short-term mortality. Among survivors, as many as 50% go on to develop post-sepsis syndrome, characterized by an increased risk of death along with physical, psychological, and neurological manifestations.[5,6] Sepsis also carries rehospitalization rates of 40% at 90 days for various reasons such as reinfection or exacerbation of an underlying condition.[6] The Surviving Sepsis Campaign (SSC) is a multidisciplinary group of professionals with an initiative aimed at providing standardized protocols in the management of septic patients to reduce worldwide sepsis morbidity and mortality. These standardized protocols were last updated in 2016 and include initial resuscitation, sepsis screening and diagnosis, antimicrobial therapy, and supportive care interventions.[2] Although these standards of care have improved patient outcomes, sepsis continues to be a leading cause of mortality in ICUs and a major burden economically.[7] Given the scope of the issue, research centered around methods to identify septic patients and prospective therapies and interventions is ongoing. Research has proven difficult, as there have been more than 100 phase II and III clinical trials utilizing pharmacologic agents acting on specific molecular targets that have failed to improve clinical outcomes in septic patients.[5,8]

One such prospective intervention garnering promise is vitamin C. Also known as ascorbic acid, vitamin C has been implicated in providing immune benefits to critically ill patients, and interestingly, a multitude of studies have shown vitamin C levels to be significantly depleted in said patients.[3,9,10] It is thought that this novel therapy addresses the inflammation and oxidative stress placed on a body under septic conditions.[8] The purpose of this literature review was to determine if adjunctive treatment with vitamin C improves patient outcomes in the management of sepsis. It was hypothesized that exogenous administration of vitamin C decreases mortality and complications in sepsis survivors. Objectives for this research include outlining the pathophysiologic effects of sepsis, current standards of care, the physiologic effects of vitamin C, and analysis of the clinical evidence of vitamin C alone and in combination with other agents as adjunctive therapy in septic patients.

Background

Pathophysiology of Sepsis

Sepsis begins as an isolated infection in the body that gains access to the bloodstream and spreads systemically. Previously, the devastating effects of sepsis were believed to be due to the pathogen itself, however, it is now hypothesized that the host's immune response to the pathogen is responsible for the effects seen.[7] With the infection no longer isolated, the body responds with a dysregulated widespread inflammatory response via pro-inflammatory mediators.[3] It is this systemic reaction to these mediators that induces the classic effects of sepsis on the body: hypotension, hemodynamic instability, poor tissue perfusion, and multi-organ dysfunction.[8] Ultimately, organs no longer receive adequate perfusion and become hypoxic, or lack oxygen delivery.[11] Hypoxic tissues overproduce free radicals called reactive oxygen species (ROS) and reactive nitrogen species (RNS) which cause oxidative stress throughout the cells in affected

tissues.[3] The scavenging of free radicals performed by antioxidants is important to prevent damage to cellular components. When this process occurs systemically, extensive damage ensues. Left untreated, organ dysfunction develops, and eventual organ failure follows. As the disease state progresses, septic shock sets in.[12] Even when providers follow standard treatment protocol, an unprecedented amount of these patients do not survive. Although there is some understanding to the pathophysiology of sepsis, this is a very complicated disease process, and further study of the mechanisms at play is necessary.[3]

Current Standards of Sepsis Care

Guidelines for the current management of sepsis were released by the SSC first in 2004 with the most recent revisions having been released in 2016. As previously mentioned, this group of individuals have made it their mission to improve sepsis management and patient outcomes worldwide. The SSC has implemented standardized protocols called "bundles" that include a checklist of tasks to be completed for initial management of sepsis patients. These bundles were initially expected to be achieved within a 3-hour window from time of presentation. However, after studies strongly supported the use of these bundles, the SSC updated their guidelines in 2018 to initiate bundle components within a 1-hour window.[7] Tasks to be performed in this 1-hour guideline include measuring serum lactate levels, administration of broad-spectrum antibiotics after blood cultures are obtained, and infusion of crystalloid fluids at 30 mL/kg if the patient is hypotensive with subsequent administration of vasopressors.[13] These guidelines are used to initially manage septic patients regardless of whether they are presenting to the ED or are already in the ICU and have now developed sepsis. Based on interviews conducted with practicing physicians and physician assistants (PA-Cs) that have experience managing septic patients, the guidelines set forth by the SSC are standard operating procedure within numerous

health systems and departments within those health systems. One such interviewee is Meredith Wold, a hospitalist PA-C practicing at a large tertiary care hospital in St. Paul, MN, states that her practice follows the 1-hour bundle guidelines, and that patients coming in via the emergency department typically have the bundle initiated by ED staff. Another interviewee, Vanessa Bester, EdD, a PA-C and PA educator with experience caring for ICU patients amongst many other patient populations, expressed the use of the SSC guidelines as well during her time in the ICU. Shari Robbins, MD, the Sepsis Director for Emergency Care Physicians Northeast Division in Minnesota, also includes the bundle components in her initial work-up of septic patients presenting to the emergency department.

Although not included in the 1-hour bundle, the SSC also recommends implementing source control measures as soon as possible after a diagnosis of sepsis or septic shock is made.[2] Source control involves defining the anatomic site of infection and providing subsequent interventions to control the infection at that site.[2] A few examples of source control measures include the removal of an infected device, necrotic tissue debridement, and abscess drainage.[2] Eric Van Hecke, an emergency medicine PA-C, considers source identification an important part of his initial workup with septic patients presenting to the ED. Eric mentions that depending on the suspected source, the imaging and serum studies used in his initial workup of these patients varies. After initial workup and resuscitative efforts in the ED, these patients typically are admitted to the ICU, where subsequent management varies as lab results are obtained and are monitored for possible organ dysfunction and progressive organ failure.

Organ failure is believed to occur in 33.6% of septic patients, and of those that develop organ failure of three or more organs, 70% will not survive.[14] Therefore, prognosis of a septic patient is largely dependent on organ dysfunction. It is for this reason that clinical scoring tools

were created to determine patient prognosis and the severity of organ dysfunction. There are multiple tools available, such as the Multiple Organ Dysfunction Score (MODS), however, the Sequential Organ Failure Assessment (SOFA) score (Table 1), is the most commonly used system in practice today.[12,15] The SOFA score evaluates various body systems, which include the respiratory, hematologic, hepatic, cardiovascular, neurologic, and renal systems. The status of each system is scored individually from zero to four based on clinical and laboratory criteria, with higher scores indicating failure of that organ system, and thus a worse prognosis.[15,16] Aside from the iatrogenic effects of sedatives on the neurological evaluation, the scoring system takes clinical interventions into account.[12] Patients with a score that increases by two or more points from baseline are associated with an in-hospital mortality of 10%.[12] Patients are assumed to have a baseline SOFA score of zero unless underlying organ dysfunction prior to infection is already known, and the scoring can be performed serially to reassess a patient's organ dysfunction. The SOFA score has been validated in numerous studies as an effective clinical tool in assessing morbidity in the critically ill patient.[17]

For out-of-hospital patients, such as those in the emergency department, a quick SOFA (qSOFA) score can be used to rapidly identify a poor prognosis in patients with a suspected infection. The clinical criteria used in qSOFA are respiratory rate greater than or equal to 22 per minute, altered mentation utilizing the Glasgow Coma Scale, and a systolic blood pressure less than or equal to 100 mmHg. The qSOFA requires no laboratory testing, as the tool includes only respiratory rate, mental status examination, and blood pressure.[12] The concept driving the utilization of qSOFA is its ability to allow the clinician to promptly assess whether a patient requires further SOFA criteria workup and possible escalation of care or referral, which is typically indicated with a score of 2 or more.[12]

Physiologic Effects of Vitamin C

Although humans are incapable of synthesizing ascorbic acid, the vitamin plays a crucial role in various physiologic processes.[18] Vitamin C is an antioxidant, meaning it prevents the oxidation of free radicals, such as ROS and RNS, by reducing them and protecting the cells from oxidative stress. Additionally, the vitamin works to improve microvascular perfusion and inactivate enzymes implicated in causing endothelial dysfunction and vascular compromise during septic states.[8]

Vitamin C also plays a role in the synthesis of vasopressors and catecholamines.[5] Antidiuretic Hormone (ADH), a vasopressor, prevents fluid loss in the kidneys and works against the development of hypotension. A role of catecholamines, such as epinephrine, is to increase arterial pressure and cardiac output when the body is under stress. ADH and catecholamine levels initially rise substantially in the septic patient, however, eventually deplete in these critically ill patients and hypotension ensues with subsequent shock.[8]

Finally, vitamin C is an important player in proper function of the immune system. Leukocytes have been found to have high levels of intracellular vitamin C, and studies show this facilitates chemotaxis, supports the proliferation of lymphocytes and causes oxidative destruction of bacteria.[8] Furthermore, vitamin C has been shown to have bacteriostatic properties.[3] Being that vitamin C is described as a vital component to physiologic roles throughout the body, it is no surprise that it is a frontrunner prospective treatment in current sepsis research.

Vitamin C as a Solo Adjunctive Therapy

The physiologic understanding of vitamin C, along with its potential role in sepsis management, has garnered the attention and enthusiasm of the medical community. Additionally,

serum ascorbic acid levels have been documented as being deficient in critically ill patients, with participants in a study by Fowler et al. having baseline levels of 17.9 +/- 2.4 μM (N = 50-70 μM) at admission.[9] For these reasons, numerous studies revolving around the vitamin being an adjunct intervention to standard sepsis management have been conducted. Research focusing on the use of vitamin C in septic patients utilize various measures to determine how exactly vitamin C may benefit this patient population, and often include these measures as primary or secondary outcomes in the study at hand. Measures typically included are patient hemodynamics, serum biomarker levels, SOFA scores, mortality rate, resource allocation, and adverse events.

As mentioned previously, a complication septic patients face is hypotension, and if severe enough, may precipitate septic shock. The blood pressure of these patients typically does not improve with the administration of intravenous fluids alone, and thus often require the use of vasopressor medications. According to the SSC, norepinephrine is the first-line vasopressor of choice in septic shock refractory to fluids.[2] Therefore, norepinephrine is the drug of choice when studying vitamin C's effects on the need for vasopressors in cases of septic shock. A meta-analysis of two different studies demonstrated vitamin C significantly reduces the dose and duration of norepinephrine administered to patients undergoing septic shock.[19] This meta-analysis included a study by Zabet et al., which tested vitamin C's effects on vasopressor requirements in 28 septic shock patients, the results of which can be seen in Table 2.[20] In this study, the mean dose of norepinephrine required was found to be less in the vitamin C treatment group than the control (7.44 +/- 3.65 vs. 13.79 +/- 6.48 mcg/min).[20] Additionally, the time patients spent requiring norepinephrine was also found to be less in the treatment group (49.64 +/- 25.67 vs. 71.57 +/- 1.60 hours).[20]

Several studies have observed the effects of vitamin C on biomarkers in septic patients. Various biomarkers are measured to indicate and follow the severity and course of sepsis. Elevated levels of these biomarkers suggest an increased mortality rate in septic patients.[8] One study found a reduction in both procalcitonin and C-reactive protein biomarkers, and another found a reduction in two relatively new biomarkers, cell-free DNA (Figure 1) and mitochondrial DNA, with the administration of intravenous vitamin C in critically ill septic patients.[9,21] C-reactive protein and procalcitonin both serve as inflammatory biomarkers, meaning elevated levels indicate tissue inflammation in the body, a hallmark of sepsis. The cell-free DNA biomarker is exhibited when cells undergo necrosis or apoptosis and release DNA fragments into the serum, which accounts for the elevated levels seen in septic patients.[21] The mitochondrial DNA biomarker measures mitochondrial nucleotides that serve to signal circulating neutrophils to the site of infection.[21] Understanding the function of these biomarkers makes it apparent that elevated levels in a suspected sepsis patient are worrisome, so trending serum levels may be helpful in predicting patient outcomes and guiding resuscitative efforts.

The importance of clinical scoring tools in determining the prognosis of septic patients was mentioned previously, so it is to no surprise that these scores are measured and trended to understand vitamin C's efficacy in clinical trials. One particular trial utilized high and low doses of ascorbic acid infusion, with the high dose infusion group showing a significant decrease in SOFA scores compared to placebo (Figure 2), which is suggestive of an improvement to these patients' organ dysfunction.[9] Another study, a randomized controlled trial by Nathens et al., showed improvement in organ dysfunction scores in patients receiving antioxidant supplementation (which included vitamin C) compared to placebo.[22] The study included 595 critically ill patients and utilized the MODS score to determine the extent of organ dysfunction.

The antioxidant treatment group had multiple organ failure rates of 2.7% compared to 6.1% in the control group upon follow-up scoring.[22]

One of the major patient outcomes recorded in the literature is the patient mortality rate. A diagnosis of sepsis carries a high yet variable mortality rate, with estimates ranging from 30-50%, so any improvement in mortality would surely be welcomed.[6,14] Vitamin C infusion appears to have beneficial effects on the body beyond the initial hospital stay, touting reduced mortality rates within a month from the treatment start date. The CITRIS-ALI randomized controlled trial by Fowler et al. showed a 28-day mortality rate of 46.3% in the placebo group, compared to 29.8% in the vitamin C treatment group.[23] Another study showed even more impressive differences, with 28-day mortality rates for placebo versus treatment group of 64.28% and 14.28%, respectively.[20]

Other patient outcomes often measured in the literature is that of resource allocation by means of time a patient spends in the ICU, on mechanical ventilation, and in the hospital. The study by Nathens et al. showed the intervention group to have a reduction in the time spent on a mechanical ventilator, the time spent in the ICU, and the overall length of hospital stay (0.9, 1.2, and 0.4 days less than the control group, respectively).[22] The aforementioned CITRIS-ALI trial noted improved outcomes over the placebo group comprised of more days free of mechanical ventilation at day 28 (13.1 vs. 10.6), days free of the ICU at day 28 (10.7 vs. 7.7), and days free of being in the hospital at day 60 (22.6 vs. 15.5).[23] A retrospective study of veteran ICU patients with sepsis by Mitchell et al. had mixed results. This study found a statistically significant improvement in length of ICU stay in the vitamin C treatment group compared to the control group (7.1 versus 15.6 days, respectively) however, there were no improvements to the overall length of the hospital stay.[24]

Adverse events are a concern in any sort of medication or intervention, and vitamin C is not exempt from this. Hypernatremia is an adverse event researchers are concerned about developing in study participants receiving vitamin C infusion.[9,11] Preparations of vitamin C infusions typically have a minor sodium load, and corticosteroids tend to cause sodium retention, so development of hypernatremia is an intuitive and reasonable concern with this intervention.[9,25] A randomized controlled trial utilizing combination therapy indicated the treatment group had a greater incidence of participants developing hypernatremia compared to the control group (13 vs. 3, respectively).[25]

Additionally, there is concern for the development of nephrolithiasis via formation of calcium oxalate kidney stones, particularly in those with renal failure being given high doses of vitamin C.[10,14,18,26] High doses of vitamin C increases oxalate production, which crystallizes in dysfunctional kidneys to form kidney stones.[10,16] However, a study by Padayatty et al. assessed the adverse events of high dose vitamin C administration in 9,328 patients. Out of the thousands of patients in this study, only three developed kidney stones (1 being calcium oxalate, 2 being unspecified).[16] Although there is reason to be concerned for development of adverse events in the administration of vitamin C, numerous studies have reported little to no occurrence of these events.

Vitamin C in Combination Therapy

Recent novel approaches utilizing vitamin C in sepsis are going beyond its use as a sole additional intervention to current standards of care by additionally including a steroid (primarily hydrocortisone) and thiamine (Vitamin B_1). This combination utilizes components that are affordable, readily available, relatively safe, and thought to work in conjunction with multiple overlapping pathways to better regulate the body's immune response to sepsis and thus prevent

sequela such as organ failure and death.[5,10] Taking the low-cost and accessibility of this combination into consideration, if a benefit in sepsis is proven, the burden of sepsis could be dramatically reduced around the world.

The addition of a corticosteroid is primarily due to its anti-inflammatory effects for shock control and acclaimed synergistic effects when paired with ascorbic acid.[2,5] Corticosteroids work to attenuate inflammation via numerous mechanisms, but most significantly by repressing genes encoding for pro-inflammatory pathways.[5] Corticosteroids are also thought to improve catecholamine function targeting vascular smooth muscle.[27] Hydrocortisone was introduced into the SSC 2004 guidelines, and has remained the corticosteroid of choice through the latest guidelines released in 2016.[2,27] Current standard of care recommends the addition of hydrocortisone in patients with shock refractory to fluids and vasopressor administration.[16] Tangible results of the effects of hydrocortisone have been reported in recent studies in 2018 on patients with septic shock.[5] One of these is the ADRENAL study, a randomized controlled trial following 3,658 septic shock patients undergoing mechanical ventilation, which were separated into a hydrocortisone treatment group and placebo group.[28] Although no statistically significant differences in 90-day all-cause mortality were found, those receiving hydrocortisone treatment came out of shock sooner (median duration 3 vs. 4 days), a finding that was deemed statistically significant.[28] The other study, dubbed APROCCHSS, is a randomized controlled trial that utilized two corticosteroids, hydrocortisone combined with fludrocortisone, in septic shock patients. This study also found the treatment group to have more days free of vasopressors than the placebo group by day 28 (17 vs. 15).[29] The findings from these studies, along with the recommendations put forth by the SSC, have provided a basis for the addition of corticosteroids to sepsis combination therapy.

Patients with critical illnesses, such as sepsis, have progressively declining thiamine levels, and patients with a thiamine deficiency may have an increased risk of death due to this deficiency.[10,11] Considering thiamine deficiency is not uncommon in patients that present with sepsis, it is intuitive to hypothesize that thiamine supplementation could prove beneficial to these patients.[11] In addition to having some anti-inflammatory effects, thiamine has many functions throughout the body where it acts to reduce oxidative stress and also plays a role in proper brain function via nerve tissue repair, neuronal communication, serotonin uptake, and myelin sheath synthesis.[5] Thiamine has been implicated in causing less oxalate to form from the metabolism of vitamin C, which helps to prevent calcium oxalate stones from forming in the kidneys.[4,14,16] Further, thiamine deficiency is believed to be a cause of elevated serum lactate levels.[11,16] Elevated serum lactate is not exclusive to sepsis, but is often seen in sepsis and was a common laboratory finding in septic patients amongst the studies reviewed.[5,10,11,24,29,30] Serum lactate is used as a marker for tissue perfusion, with elevated levels indicating hypoperfusion, so serially measuring lactate can help guide resuscitative efforts.[13] The effects of thiamine in septic shock have been studied; treatment groups exhibited significantly reduced 24-hour serum lactate levels, were less likely to need renal replacement therapy, and had improved 30 day mortality outcomes compared to placebo.[5] Since septic patients are often deficient in thiamine and turnaround time for tests on serum levels takes a few days, including thiamine as part of the early treatment initiation bundle for sepsis may be of benefit.[16] No major adverse effects have been documented with administration of thiamine, and considering its affordability, supplementation in sepsis patients could make this a low-risk yet high-reward addition to combination sepsis therapy.[11]

Current research suggests the combination of ascorbic acid, thiamine, and steroids (ATS) shows promise in being an effective addition to sepsis management. In a retrospective before and

after study by Marik et al., 47 patients were followed in each arm of the study. The treatment group was reported as having an in-hospital mortality rate of 8.5%, compared to the placebo group with a rate of 40.4%.[10] The benefits of ATS did not end there, however. In comparison to the control group, the treatment group also exhibited a rapid reduction in procalcitonin levels (median clearance 86.4% vs. 33.9%) and change in SOFA scores (4.8 +/- 2.4 vs. 0.9 +/-2.7) with zero participants in this group developing progressive organ failure.[10] The treatment group also spent less time requiring the use of vasopressors than the control group (Figure 3).[10] On the other hand, the control group in this study saw relatively no improvement in procalcitonin levels, and those that survived were slow to see improvements to their SOFA scores.[10]

Another study, called the ORANGES trial, was completed in June 2019 by Iglesias et al. in which ATS was used as an intervention in 137 septic and septic shock patients. This was a double-blind randomized controlled trial that showed patients in the intervention group exhibiting a statistically significant improvement in shock recovery time compared to the placebo group.[26] This outcome could normally be questioned as a result of the use of corticosteroids, however, the team realized this and adjusted for corticosteroid use, meaning ATS combination therapy was in fact found to decrease the amount of time patients were using vasopressors from 54 hours in the control group to 34 hours in the treatment group.[26] The ORANGES trial, however, found no statistically significant secondary outcomes, which included SOFA scores, mortality, ventilator-free days, and procalcitonin biomarkers.[26]

One last study, a randomized controlled trial, found the beneficial effects of combination therapy to be greatest in those that started combination therapy within 48 hours of diagnosis. This study took place in a tertiary academic hospital in China that enrolled patients in various stages of sepsis. The prespecified 48-hour patient subgroup exhibited 28-day mortality rates

superior to the control group (13.6% vs. 47.6%).[25] Procalcitonin clearance rates at the 72-hour mark were also greater in this subgroup (75.6% vs. 58.9%).[25] Other outcomes that were improved in this subgroup but not considered statistically significant included less time spent in the ICU, less time on vasopressors, 72-hour lactate clearance rate, and 72-hour change in SOFA scores.[25]

Despite several studies claiming benefit to using vitamin C in the management of septic patients, alone or in ATS combination therapy, other studies conclude otherwise. A randomized controlled trial looking at vitamin C alone by Fowler et al. concluded that there are no statistically significant differences between vitamin C and placebo regarding reduction in SOFA scores and inflammatory markers.[23] The VITAMINS trial, conducted by Fujii et al., has also documented results that clash with the purported benefits of vitamin C. The VITAMINS randomized controlled trial utilized ATS combination therapy and found no difference between groups in time alive, duration of septic shock, or all-cause mortality at 28 days, among various other secondary outcomes.[30] A final study, this one being retrospective, also concluded no statistically significant differences in outcomes between the ATS treatment group and the standard care group.[27] Outcomes measured in this study were hospital and ICU mortality, hospital and ICU length of stay, and requirements for vasopressors and renal replacement therapy.[27]

Conflicting evidence amongst studies demonstrates a need for further research regarding the effects of vitamin C in sepsis. According to the U.S. National Library of Medicine's ClinicalTrials.gov website, there are currently over a dozen randomized controlled trials recruiting participants to further investigate the potential role of vitamin C in sepsis and septic shock, either alone or in combination therapy. There are numerous other trials awaiting to

publish results. One such study is the LOVIT (Lessening Organ dysfunction with VITamin C) Trial, which began recruiting participants (with a goal of up to 800) for the study in November 2018 and is scheduled to conclude in November 2021. The LOVIT Trial is a phase III randomized controlled trial taking place in up to 25 ICU's throughout various countries to determine superiority of vitamin C as an isolated adjunct intervention in septic patients to reduce mortality compared to placebo.[31] Another trial that just completed in January 2020 is the Vitamin C, Thiamine and Steroids in Sepsis (VICTAS) study, which enrolled 501 participants into its phase III, multicenter, double-blind, randomized controlled trial.[4] Once published, the results of each of these studies, amongst the many others in progress, with their larger sample size and well-defined study design, will provide valuable insight into ATS combination therapy's currently unclear role in sepsis management.

Methods

The electronic database PubMed was used to search literature that addressed the research question. Key terms used in the search were "Vitamin C", "Ascorbic Acid", "Sepsis", "Physiology", "Post-Sepsis", "SOFA Score", "Complications", and "Intensive Care Unit". The literature search was completed between June 1st and July 12th, 2020. Search results yielded peer-reviewed articles filtered within the past 10 years, with the majority of articles used being published within the last 5 years. One exception to this filtered timeframe is the article "The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure" by Vincent et al., as it provides the definition of the SOFA score, which was created in 1994. One other notable exception is the 2002 article by Nathens et al. titled "Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients", which was one of the earlier studies testing vitamin C, amongst other antioxidants, in critically ill patients. In addition,

relevant studies cited within the peer-reviewed articles from the search results were identified from the references list and reviewed. Utilization of the references list in the initial articles reviewed was done for multiple reasons, the first being to find additional studies for use in the literature review. Reviewing the sources of each article used in this review also prevented overreporting of the same study results cited in two or more articles. Finally, reviewing original studies allowed for a personal analysis of that study to verify accuracy of reported results. For articles in which the full text versions could not be obtained from PubMed, Augsburg University's interlibrary loan system was utilized. Finally, expert interviews were conducted with practicing physicians and physician assistants that have experience caring for septic patients. The goal of the interviews was to learn more about current sepsis management and to see if the use of vitamin C in sepsis patients has made its way into these provider's practices. Potential interviewees were contacted via email, and the providers interested in participating were sent a follow-up email with the six interview questions as shown in Table 3. Participants were asked to consider reaching out to colleagues known to manage septic patients that may have interest in completing the interview questions.

Discussion

Sepsis, a life-threatening inflammatory disease process, has ravaged intensive care units worldwide. With staggering mortality and rehospitalization rates, paired with the serious complications of post-sepsis syndrome, sepsis dominates as one of the most expensive hospital stays a person could experience.[2-6,14,26,32] Current standard of care protocols and early treatment bundles recommended by the Surviving Sepsis Campaign have reduced the mortality rate and improved patient outcomes substantially, however, despite the improvements, the mortality rate continues to range between 20-35% and as high as 50% in those that present with septic

shock.[3,8,26] For these reasons an effective treatment for sepsis is so desperately needed, which has led to many potential therapies being tested over the years.[3,5,8,16,27] Vitamin C is among one of the newest prospective treatments, and promising results from early studies have garnered much attention from the medical community. Vitamin C has been studied both as a solo adjunct to current standard of care sepsis protocols in addition to a more recently proposed triple therapy with a corticosteroid (namely hydrocortisone) and thiamine (vitamin B1). This combination has been tested in a few studies already, with many more in progress or currently awaiting results and publishing. Some providers, particularly in the ICU, have already adopted its use in practice. Ryan MacDougall, an internal medicine MD at Delaware County Memorial Hospital in Pennsylvania, frequently manages septic patients. In his response to the interview questions, he said that when using vitamin C in septic patients, he has only ever used it in combination with corticosteroids and thiamine. Doctor MacDougall mentions that some providers opt to use vitamin C without the remaining triple therapy components, however, he has seen good patient outcomes with triple therapy administration within 12 hours of admission. The components in this proposed triple therapy are thought to work synergistically with each other in attenuating the pathophysiologic process of sepsis and septic shock.[5,14,16]

Understanding the physiology of vitamin C, hydrocortisone and thiamine in the body provides a sound basis for the plausible use of each of these interventions in attenuating the complex, not yet fully elucidated pathophysiology behind a septic disease state. Critically ill patients, such as those that are in a septic state, are documented to have deficient levels of vitamin C.[3,9,10,20] Exogenous administration of vitamin C resolves the deficiency in these patients. Doses used in the literature were typically split into divided doses every 6 hours and found to range from 50 mg/kg/day on the low end to 200 mg/kg/day on the high end.[9,20,22,23,31]

Significant improvement or normalization of serum levels of vitamin C was seen within 12 to 24 hours after initiation, whereas serum levels in the control or placebo groups continued to trend downward.[9,20,22,23] Researchers opting for combination therapy have consistently reported the addition of 50 mg hydrocortisone every 6 hours and 200 mg thiamine every 12 hours.[4,10,14,24-27,30] The improvement in serum levels of vitamin C amongst the intervention groups then begs the question: did those treated with vitamin C with or without hydrocortisone and thiamine have improved outcomes over the placebo or control groups? Researchers attempt to answer this question by assessing various outcomes, including patients' hemodynamic profile, serum biomarker levels, SOFA scores, mortality rate, resource allocation and adverse events.

Due to various pathophysiologic processes, septic patients are prone to becoming hemodynamically unstable, meaning their blood pressure drops, and patients are deemed hypotensive at a blood pressure of 90/60. Intravenous fluids are given as first-line management to improve blood pressure, however, is often not enough to correct the hypotension.[2,20] At this point, vasopressors are given, with norepinephrine being the recommended first-line agent.[2,20] As the hypotension progresses, septic patients are defined as being in septic shock if vasopressors are required to maintain a mean arterial pressure (MAP) greater than 65 mmHg with a serum lactate level $\geq$ 2 mmol/L, and hypovolemia has been excluded as an underlying cause.[12] Various studies have looked at vitamin C's effects on improving the condition of septic shock, typically by measuring patients' needs for vasopressors. Vitamin C has been shown to reduce the dose of vasopressors required by patients to maintain an adequate mean arterial pressure.[20] In addition to reducing required doses, vitamin C appears to decrease the duration septic patients require vasopressors.[19,20] There is evidence that combination therapy also helps to improve patient hemodynamics, primarily in the time to shock resolution.[10,25,26] The idea behind this mechanism

is the hydrocortisone working in unison with the vitamin C by improving the vitamin's uptake into cells.[16] Additionally, hydrocortisone works to decrease inflammation, improve catecholamine function, and increase serum volume via sodium and water retention, all of which help stabilize a patient's blood pressure.[2,5,16,27-29] During her interview, Doctor Robbins agreed that although she has not utilized vitamin C or its combination therapy agents in unison within the emergency department, steroids are occasionally used while managing shock patients and are started with the second administration of vasopressors. These findings, along with the extensive prior research on hydrocortisone, support the potential for vitamin C and combination therapy to improve hemodynamic stability among septic patients.

Research into biomarkers involved with sepsis is becoming more and more prevalent. Procalcitonin and C-reactive protein are biomarkers that have been well-established as being elevated in sepsis, with procalcitonin being trended most commonly throughout the literature. Research suggests exogenous administration of vitamin C reduces procalcitonin and C-reactive protein in septic patients.[9] These findings have been echoed in some studies on ATS combination therapy, where a prompt reduction in procalcitonin levels occurred in the intervention group, but did not occur in the control groups.[10,25] However, this conclusion was not supported in several studies reviewed, one employing vitamin C alone and the other employing combination therapy.[23,26] The administration of ascorbic acid causing an overall downward trend in serum levels of these biomarkers builds upon ascorbic acid being a promising adjunct treatment to sepsis. Research into novel biomarkers is ongoing as two more, known as cell-free DNA and mitochondrial DNA, were recently implicated in being elevated in sepsis and showing subsequent attenuation in serum levels with vitamin C administration.[21] Further evidence defining the efficacy of new and old biomarkers alike, along with their responses to vitamin C

administration, is much anticipated. It is important to note that the use of biomarkers should always be looked at in conjunction with the clinical picture, as these tests are not perfectly sensitive nor specific. For example, a septic patient that has significantly improved clinically yet has an elevated serum procalcitonin should not be immediately deemed as having a poor prognosis. An example of this point being used in practice was identified by Meredith Wold, PA-C. During the interview, Meredith mentioned that a mildly elevated lactate is not necessarily bad, and that aggressively trying to normalize that lactate level with IV fluids may in fact be worse for the patient.

Once organ dysfunction occurs, a patient is said to have severe sepsis.[12] The extent of organ dysfunction is readily estimated via the SOFA score, which was created in the 1990's as a tool to identify mortality risk in ICU patients but is now commonly used in the diagnosis of sepsis.[17] A patient must have an increase in SOFA score by two or more points to be considered to have organ dysfunction.[12] As the score increases, the associated mortality rate also increases.[12,15,17] Its use also extends to monitoring patient improvement, particularly in the many clinical trials taking place to find adjunct treatments for sepsis.[17] Therefore, quantification of organ dysfunction is often done in clinical trials to assess whether an intervention is capable of reducing the organ dysfunction at hand. SOFA scores are typically obtained at baseline in studies and then participants are scored again at prespecified time intervals. Intervention and control groups are shown to have similar SOFA scores at baseline upon hospital admission and study enrollment.[9,10,20,22-27,33] This helps to ensure quality in the conclusions made based on any differences found between groups thereafter. Despite one study finding no improvement, vitamin C as a solo adjunctive sepsis therapy appears to improve SOFA scores in septic patients compared to control and placebo groups.[9,22,23] Research focused on combination therapy boasts

similar findings. Again, one study found no significant differences, however, studies as a whole report SOFA scores are improved in patients receiving vitamin C, hydrocortisone, and thiamine in conjunction.[10,25] The literature currently available favors vitamin C and ATS combination therapy as being capable of reducing organ dysfunction, a finding that supports its use in septic patients.

Of course, a major primary outcome that research on vitamin C is centered around is that of patient mortality. Given the intimidating mortality rate associated with a sepsis diagnosis, it is imperative further interventions capable of reducing this burden are discovered.[6,14] Current studies indicate improvements in 28-day mortality rates when vitamin C is used in addition to standard treatment.[20,23] One of the randomized controlled trials published found no difference between groups in mortality rates, however.[30] Adding hydrocortisone and thiamine into the vitamin C intervention group appears to lessen mortality rates as well, however, one study claimed this finding was not considered statistically significant.[10,25,26] Although a reduction in mortality rate has not been a unanimous finding in each of the studies published, it is important to note that none of the studies reviewed found a statistically significant increase in mortality rate in those receiving vitamin C or combination therapy.

Currently, results vary on whether vitamin C lessens the time spent using hospital resources. The resources consistently documented throughout the literature include time spent in the ICU, hospital, and on mechanical ventilation. Overall, conclusions on the use of hospital resources are variable. Reduction in the time spent utilizing these resources is supported by various studies.[22-24] On the other hand, several other studies report there being no superiority in length of ICU or hospital stay in treatment groups, a finding noted in both vitamin C and combination therapy interventions.[20,27,30] Septic patients face extraordinary hospital costs, so any

improvement in lessening resources required to manage these patients, no matter how minute, will lessen the financial burden on patients and hospitals alike. Less time utilizing hospital resources also frees up mechanical ventilators and creates more room in the ICU and general wards for other patients in need of these resources.

There is always a risk to using any designated intervention in patient care. In the case with vitamin C infusion, the literature consistently agrees there are two of primary concern: hypernatremia and calcium oxalate nephrolithiasis. There is a sound physiologic basis for these concerns. Vitamin C infusion preparations have an additional sodium load, so when coupled with the sodium from intravenous fluids and the sodium retentive effects of hydrocortisone, hypernatremia may very well develop.[9,11,25] Kidney stone formation is also an established complication with excessive vitamin C.[10,14,18,26] This is particularly evident in those with renal dysfunction, which is not an uncommon finding in septic patients. Despite legitimate concerns for the development of these adverse events, an overwhelming amount of the studies conducted thus far have failed to show adverse events in critically ill patients due to vitamin C infusion, and it would appear the potential benefit outweighs the potential risk.[9,10,14,16,20,22-24,26,30]

Several implications exist with applying vitamin C therapy to the standard protocol of sepsis management. If vitamin C therapy is concluded to be ineffective in providing benefit to septic patients, there will be disheartening effects induced by the failure of yet another novel sepsis therapy. Further, implementing a therapy that lacks definitive patient benefit, no matter how affordable, would increase the already insurmountable costs associated with sepsis, correct? As it turns out, implementing vitamin C combination therapy may in fact save money. A cost-analysis was performed by Blythe et al. to determine the economic impact if the treatment bundle proposed in the study by Marik et al. were to be implemented before more definitive studies are

finished.[32] The cost-analysis took into consideration expected costs from the available literature and spanned the analysis over five years to account for long-term impact. Three scenarios were used in the analysis to model the intervention as being either effective as described in the Marik et al. study, less effective than described, and ineffective. The analysis found that implementing vitamin C combination therapy, even in the less effective scenario, would save the United States billions of dollars and millions of life-years.[32] This analysis was completed in 2017, so considering that the studies completed since then overall provide further support for implementing this intervention, it can be anticipated that the benefits to costs and lives as described are still applicable today.

However, health systems must consider the risks of implementing new treatment standards that may have to be rescinded if the more recent trials soon to be published have evidence largely against the use of vitamin C in sepsis. For these reasons, the use of vitamin C and its combination therapy has not been widely adopted into everyday practice, particularly in academic medical centers bound by organizational protocols. This sentiment was echoed during the interview with Doctor Bester, who noted that a "ground-breaking study or new published guidelines" are typically required to change practice in this often guideline-based setting unless a clinical trial that involves a specific treatment (i.e. vitamin C) is in progress at that medical center.

There are limitations to the studies done thus far that make drawing conclusions difficult. One key conclusion that was practically unanimous throughout each article of the literature review is that studies with larger, multi-center populations and well-defined protocol need to be done before routine utilization of vitamin C (or ATS combination therapy) in sepsis management is considered. As of writing, the studies published have utilized small population sizes, making it

difficult to draw any conclusions with extreme certainty. Regarding combination therapy, there are numerous articles defining the physiologic basis of using vitamin C, hydrocortisone, and thiamine in conjunction, yet only a few completed studies that have tested this intervention in clinical trials. A few of the studies published are retrospective trials, so an emphasis on the need for prospective trials is warranted. Fortunately, initial results have sparked widespread interest and enthusiasm for the use of vitamin C in sepsis management, so research into this novel therapy is ongoing.

Another important point worth noting is that one must exercise caution when drawing conclusions on individual components in combination therapy trials, as the effects of each individual component are at risk of being confounded by the others. This is particularly true with hydrocortisone in ATS combination therapy, as hydrocortisone has already been well documented to reduce the time patients require vasopressors in septic shock.[33] The issue presented in this example is that the efficacy of combination therapy to reduce vasopressor requirements could be overestimated, when perhaps hydrocortisone alone would have been just as effective. Careful study design and interpretation is necessary to help mitigate these effects.

Conclusion

Despite having such prevalence throughout the world, public awareness of sepsis is inadequate. Even providers may find it difficult to identify sepsis, as it can have a multitude of presentations given its systemic manifestations. Improved outcomes are associated with early identification and initiation of treatment. Ensuring clinicians are well-versed in the definitions and how to promptly recognize sepsis is the first step to reducing the associated global burden. Fortunately, groups such as the Surviving Sepsis Campaign and the Sepsis-3 Task Force have taken it upon themselves to define what constitutes sepsis and are continuing to improve upon its

management recommendations. The use of these recommendations has become and remains the standard protocol for sepsis management, which was a consistent response in the healthcare provider interviews conducted. For patients that survive an encounter with sepsis, it is imperative that their healthcare team prepare them for a possible change in quality of life, namely due to post-sepsis syndrome, re-hospitalization risks, and financial consequences.

In agreement with the hypothesis, analysis of the literature review suggests the addition of vitamin C to standard sepsis therapy has beneficial patient outcomes. The potential benefits and relative affordability of vitamin C seem to outweigh the limited risk of adverse effects and the potential risk of no actual benefit. Despite the promising results from initial findings, until more conclusive studies are published, vitamin C's role as an adjunctive treatment in sepsis remains uncertain and experimental before widespread implementation into practice is adopted. This is supported by the fact that the majority of the providers interviewed have yet to utilize vitamin C in their management of septic patients. Numerous studies are underway to better determine the efficacy of both vitamin C and its combination therapy adjuncts. A recommendation for future studies is to determine the presence of any discrepancies between early administration and late administration of vitamin C (and combination therapy) relative to sepsis onset to establish a timeline distinguishing when this therapy is most effective. In the meantime, as vitamin C and other adjunctive therapies are explored, providers must utilize the strategies known to improve patient outcomes: hemodynamic stabilization, early administration of broad-spectrum antibiotics, and source control measures.

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Appendices

Table 1: SOFA Score Components[15]

SOFA score	1	2	3	4
Respiration PaO_2/FiO_2, mmHg	<400	<300	<200	<100
			with respiratory support	
Coagulation Platelets $\times 10^3/mm^3$	<150	<100	<50	<20
Liver Bilirubin, mg/dl (μmol/l)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (<204)
Cardiovascular Hypotension	MAP < 70 mmHg	Dopamine ≤5 or dobutamine (any dose)[a]	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central nervous system Glasgow Coma Score	13–14	10–12	6–9	<6
Renal Creatinine, mg/dl (μmol/l) or urine output	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440) or <500 ml/day	>5.0 (>440) or <200 ml/day

[a] Adrenergic agents administered for at least 1 h (doses given are in μg/kg·min)

Table 2: Dose and Duration of Norepinephrine in Ascorbic Acid versus Control[20]

Characteristics	Ascorbic acid group (*n*=14)	Control group (*n*=14)	*P*
Mean dose of norepinephrine (mcg/min) during the study period (72 h)	7.44±3.65	13.79±6.48	0.004
Mean dose of norepinephrine (mcg/min) during first 24 h (mcg/min)	6.51±3.53	12.58±5.99	0.003
Total dose of norepinephrine during the first 24 h (mcg)	156.42±84.81	302.14±143.85	0.003
Duration of norepinephrine administration (h)	49.64±25.67	71.57±1.60	0.007
Length of ICU stay (days)	21.45±10.23	20.57±13.04	0.85
28-day mortality	2 (14.28)	9 (64.28)	0.009

Data presented as mean±SD or *n* (%). SD=Standard deviation, ICU=Intensive Care Unit

Table 3: Questions Utilized in Expert Interviews

1) Have you managed septic and/or septic shock patients in your practice before?
2) What is included in your workup?
3) What is considered routine standard therapy in your practice?
4) Have you ever utilized vitamin C as an adjunct treatment in the management of sepsis? If so, was this initiated early in treatment or not until later in patients when standard therapy was not improving the patient's status? Do you recall the patient outcomes?
5) Have you ever utilized combination therapy of vitamin C, hydrocortisone, and thiamine in the treatment of sepsis? If so, was this initiated early in treatment or not until later in patients when standard therapy was not improving the patient's status? Do you recall the patient outcomes?
6) Any other experience you would like to share that was not covered in one of the previous questions?

Figure 1: Cell Free-DNA Levels in Placebo, Low- and High-Ascorbic Acid Infusion Groups[21]

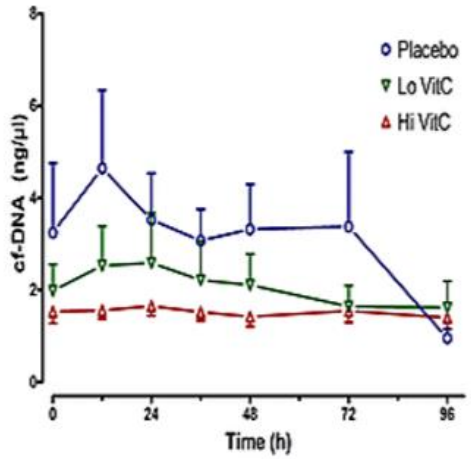


Figure 2: Delta SOFA Scores in Placebo, Low- and High-Ascorbic Acid Infusion Groups[9]

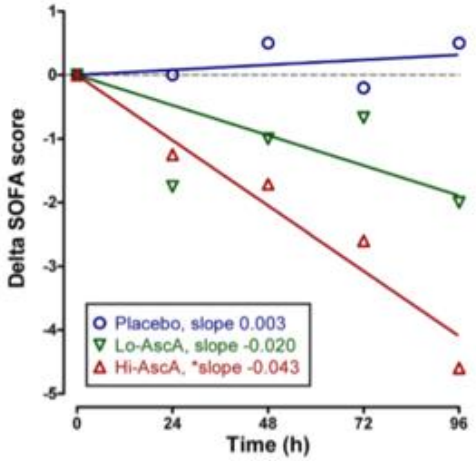
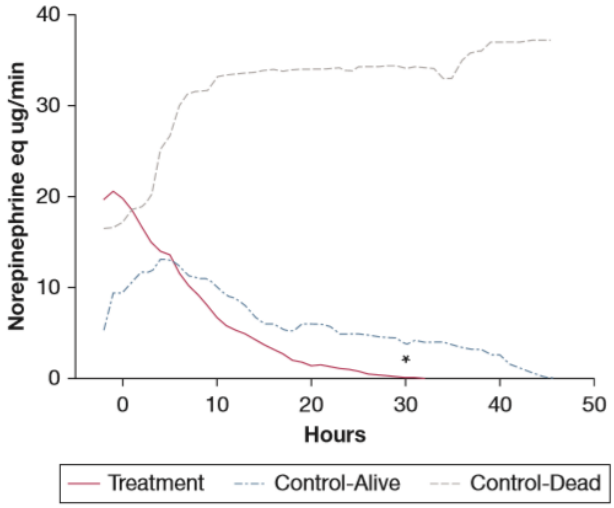


Figure 3: Time Course of Vasopressor Dose in Treatment vs. Control Survivors and Non-Survivors[10]



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