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INVITED REVIEW

History of scurvy and use of vitamin C in critical illness: A narrative review

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Abstract

In 1747, an important milestone in the history of clinical research was set, as the Scottish surgeon James Lind conducted the first randomized controlled trial. Lind was interested in scurvy, a severe vitamin C deficiency which caused the death of thousands of British seamen. He found that a dietary intervention with oranges and lemons, which are rich in vitamin C by nature, was effective to recover from scurvy. Because of its antioxidative properties and involvement in many biochemical processes, the essential micronutrient vitamin C plays a key role in the human biology. Moreover, the use of vitamin C in critical illness—a condition also resulting in death of thousands in the 21st century—has gained increasing interest, as it may restore vascular responsiveness to vasoactive agents, ameliorate microcirculatory blood flow, preserve endothelial barriers, augment bacterial defense, and prevent apoptosis. Because of its redox potential and powerful antioxidant capacity, vitamin C represents an inexpensive and safe antioxidant, with the potential to modify the inflammatory cascade and improve clinical outcomes of critically ill patients. This narrative review aims to update and provide an overview on the role of vitamin C in the human biology and in critically ill patients, and to summarize current evidence on the use of vitamin C in diverse populations of critically ill patients, in specific focusing on patients with sepsis and coronavirus disease 2019.

KEYWORDS
antioxidant, COVID-19, critical illness, scurvy, sepsis, vitamin C

Abbreviations: ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; DGEM, German Society for Nutritional Medicine; EN, enteral nutrition; ESPEN, European Society for Clinical Nutrition and Metabolism; GPP, good practice point; HAT, combination of hydrocortisone, ascorbic acid, and thiamin; IL-6, interleukin-6; I/R, ischemia-reperfusion; IV, intravenous; N/A, not applicable; PN, parenteral nutrition; RCT, randomized controlled trial; ROS, reactive oxygen species; RR, relative risk; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; SOFA, sequential organ failure assessment; SRMA, systematic review and meta-analysis; SVCT1, sodium-dependent vitamin C transporter 1; SVCT2, sodium-dependent vitamin C transporter 2.

INTRODUCTION

The year 2022 marks the 275th anniversary of the first planned randomized controlled trial (RCT). In 1747, the Scottish surgeon James Lind was interested in scurvy, which caused the death of thousands of British seamen per year. He randomized 12 seamen with scurvy, two at a time, to six dietary interventions and found oranges and lemons produced the most sudden and visible effect, with one patient who had taken them for 6 days being deemed fit for duty. Unfortunately, the idea of dietary cause of scurvy did not gain traction and it was not until 1794 that the British Admiralty allowed Lind to repeat his experiment—this time on an entire fleet of ships. The results in favor of vitamin C were so dramatic that in 1795, the Admiralty made lemon juice a required part of the standard diet of British seamen and scurvy disappeared.[1,2]

Akin to scurvy in the 18th century, critical illness defining conditions in the 21st century, like sepsis, kill thousands of people each year. The bidirectional relationship between vitamin C deficiency and dysregulated inflammatory and immune responses has been recognized for years—with deficiency associated with both altered immune responses and worse clinical outcomes and inflammation, themselves promoting depletion of vitamin C in a vicious circle.[3]

As an essential micronutrient with antioxidant properties, the use of vitamin C in critical illness has gained significant interest in recent years[4,5] and represents an inexpensive, safe, and promising therapeutic option to improve clinical outcomes.[6]

This narrative review aims to update and provide an overview on the physiological functions of vitamin C in general, its specific role in critically ill patients, and potential properties of (intravenous [IV]) supplementation in diverse patient cohorts, such as cardiac surgery, trauma, burn, septic patients, and patients with coronavirus disease 2019 (COVID-19).

MECHANISMS OF ACTION: THE ROLE OF VITAMIN C IN THE HUMAN BIOLOGY

Vitamin C is an essential, water-soluble micronutrient predominantly found in citrus fruits and diverse vegetables (eg, pepper, potatoes, and cabbage), which acts as cofactor of diverse enzymes and as an antioxidant.[7,8] In the human biology, vitamin C plays a key role in the synthesis of catecholamines, collagen, cortisol, neurotransmitters, and peptide hormones, the immune cell functions, the maintenance of endothelial vasodilation and barrier, and the iron and folic acid metabolism. Moreover, because of its antioxidative potential, vitamin C acts as scavenger of reactive oxygen species (ROS) and inhibits proinflammatory cytokines (Figure 1).[4,6] In detail, vitamin C may neutralize the formation of ROS by inhibiting pro-oxidative enzymes such as nicotinamide adenine dinucleotide phosphate oxidase and inducible nitric oxide synthase. Furthermore, as vitamin C directly acts as scavenger or quencher of radicals, it may regenerate other antioxidants, such as alpha-tocopherol (vitamin E) from alpha-tocopheroxyl radicals (generated through binding of fat peroxyl radicals). Moreover, as a substrate of the ascorbate peroxidase (conversion of hydrogen peroxide into water) vitamin C may prevent the adhesion of phagocytes and concomitant ROS-mediated endothelial damages.[9,10]

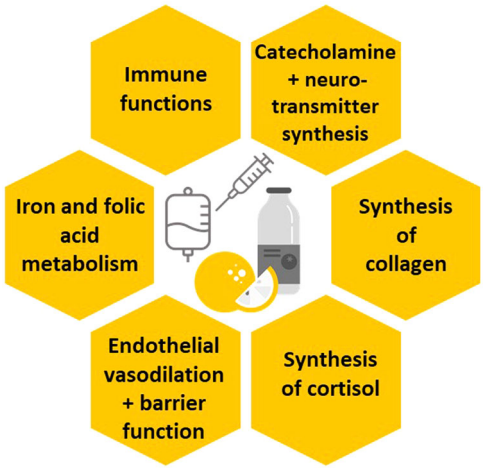

FIGURE 1 Physiological functions of vitamin C. In the human biology, vitamin C plays a key role in the functionality of the immune system, the synthesis of catecholamines, neurotransmitters, collagen, and cortisol, the endothelial vasodilation and barrier function, and the metabolism of iron and folic acid.

Vitamin C homeostasis is regulated by the interplay of diverse mechanisms: (1) uptake in the intestine by the sodium-dependent vitamin C transporter 1 (SVCT1), (2) free filtration in the kidneys and reabsorption in the proximal tubule via SVCT1, (3) uptake to the cells mediated by the sodium-dependent vitamin C transporter 2 (SVCT2), and (4) urinary excretion.[11,12] Because of active transport mechanisms as well as differences in the capacity and sensitivity of SVCT1 and SVCT2 in transporting vitamin C, intracellular vitamin C concentrations—especially in leukocytes and neuronal cells—are manifold higher than in plasma.[13] However, vitamin C uptake in the intestine and further distribution to cells is influenced by plasma levels and intake dosages.

Although the urinary vitamin C excretion is restricted in the case of deficiencies, the intestinal absorption and tubular reabsorption rates are reduced following high vitamin C intake and in the case of elevated plasma concentrations.[6,9]

As endogenous synthesis of vitamin C is not possible in humans, adequate dietary intake via fruits and vegetables is essential to maintain physiological functions. Thus, a reference value for vitamin C intake of 95–110 mg/day is recommended for healthy adults to keep an adequate status defined as plasma level of ≥50 μmol/L.[8] However, in the case of inadequate dietary intake, vitamin C deficiency, also known as scurvy, when clinically significant, may occur.[13] Clinically manifested scurvy goes along with vitamin C serum concentrations of ≤10 μmol/L.

ROLE OF VITAMIN C IN CRITICAL ILLNESS

Even though vitamin C deficiency is only rarely reported in developed countries in the 21st century, there still exist diverse (patient) populations at risk for inadequate vitamin C status. Besides smokers, individuals with limited variety in diet, and individuals with malabsorption and chronic diseases (eg, cachexia and cancer), low vitamin C levels have been frequently observed in critically ill patients, for example, in patients with sepsis and after cardiac surgery, which are associated with inflammation and oxidative stress.[9,13–15] In general, vitamin C may affect the functionality of various organs and systems, such as heart, lung, kidneys, brain, blood, and immune defense (Figure 2), which may be impaired during low vitamin C levels and critical illness.[16] In addition to its role as effective antioxidant in humans,[17] vitamin C has anti-inflammatory effects and may optimize immune defense mechanisms. Furthermore, vitamin C is involved in the synthesis of different mediators and hormones. As such it can influence the norepinephrine and collagen synthesis, which is important for the hemodynamic regulation and to limit the endothelial and ischemia-reperfusion (I/R) injury in critically ill patients.[4,10,18]

However, vitamin C levels are depleted in critical illness.[15,19,20] For example, in a study of 44 critically ill patients, 68% were found to have hypovitaminosis C (<23 μmol/L) and 32% were deficient in vitamin C (<11 μmol/L), despite receiving the recommended amount of nutrition support.[15] Vitamin C level is even lower in patients with sepsis and is associated with multiple organ failure.[15,20] As humans cannot synthesize and store vitamin C, supplementation to replete the plasma concentration is imperative.[21] During critical illness, vitamin C concentrations rapidly decrease due to increased metabolic needs for antioxidative and anti-inflammatory processes. However, in this context it must be noted that especially in the presence of inflammation, recirculation of vitamin C to other organs and redistribution to other compartments may also contribute to the commonly observed low plasma levels. Thus, low plasma levels observed during inflammation may not necessarily indicate states of depletion or deficiencies, and concomitant measurement of inflammatory markers such as C-reactive protein (CRP) is indicated (CRP >10 mg/L

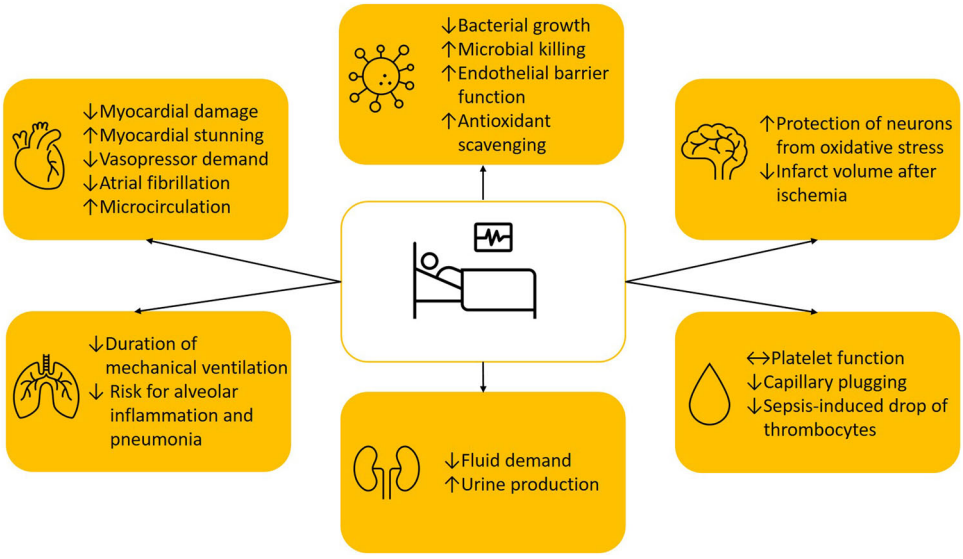

FIGURE 2 Potential influences of vitamin C on various organs and system. During critical illness, vitamin C may affect the functionality of various organs and systems, such as the heart, lung, kidneys, brain, blood, and immune defense.

TABLE 1 Current clinical nutrition guideline recommendations on the use of vitamin C in critically ill patients

Guideline	Recommendation	Grade—consensus
ESPEN micronutrient guideline, 2022[23]	PN should provide 100–200 mg vitamin C per day	GPP—strong consensus 97%
	In patients with chronic oxidative stress (diabetes mellitus, smoking, heart failure, alcoholism, severe COPD, and chronic dialysis) or malabsorption, a dose of 200–500 mg per day may be provided	GPP—strong consensus 92%
	During critical illness, a higher vitamin C repletion dose of 2–3 g per day should be given IV during the acute phase of inflammation	B—consensus 84%
Guidelines for the provision of nutrition support therapy in the adult critically ill patient: The American Society for Parenteral and Enteral Nutrition, 2021[27]	N/A	N/A
Surviving sepsis campaign: international guidelines for management of sepsis and septic shock, 2021[28]	For adults with sepsis or septic shock, we suggest against using IV vitamin C	Weak recommendation, low quality of evidence
Clinical nutrition in critical care medicine—guideline of DGEM[29]	A patient should receive vitamins and trace elements, if EN cannot meet daily needs, and if supplemental PN is required to ensure the desired calorie and protein intake according to the disease phase and individual metabolic tolerance	Strong consensus 100%
	Vitamins and trace elements should ever be substituted in the case of total PN	Strong consensus 100%
	A pharmacotherapy with the micronutrients zinc, alpha-tocopherol, vitamins A and C, and their combination should not be applied routinely	Strong consensus 93.75%
ESPEN guideline on clinical nutrition in the intensive care unit, 2019[30]	To enable substrate metabolism, micronutrients (ie, trace elements and vitamins) should be provided daily with PN	B—strong consensus 100%
	We recommend the repletion of micronutrients in conditions of chronic and acute deficiency	N/A
	Antioxidants as high-dose monotherapy should not be administered without proven deficiency	B—strong consensus 100%

Abbreviations: COPD, chronic obstructive pulmonary disease; DGEM, German Society for Nutritional Medicine; EN, enteral nutrition; ESPEN, European Society for Clinical Nutrition and Metabolism; GPP, good practice point; IV, intravenous; N/A, not applicable; PN, parenteral nutrition.

may affect vitamin C status).[22,23] In addition, vitamin C may decrease because of increased loss resulting from the necessity of specific medical treatments (eg, drainages, medication, renal-replacement therapy, and extracorporeal membrane oxygenation) and impaired redistribution.[9] Low vitamin C status at intensive care unit (ICU) admission and impaired delivery within the medical nutrition therapy during the ICU stay may further affect the vitamin C depletion.[23] Overall, there occurs an imbalance between antioxidants and oxidants, which may lead to oxidative stress characterized by fat peroxidation, inactivation of enzymes, and DNA modifications.[9] In consequence, these adverse reactions may lead to damages in cells, tissues, and organs. Overall, low vitamin C levels are associated with oxidative stress, inflammation, organ dysfunctions, and mortality.[6,23] Therefore, higher dosages than recommended for healthy adults might be needed to counteract disease-related vitamin C depletion and deficiencies. In this context, enteral supplementation of vitamin C is ineffective in restoring plasma concentration to normal levels due to the saturable intestinal uptake via the SVCT1,[21] and vitamin C absorption may also be impaired as cause of the critical illness. In addition, vitamin C concentration in the plasma and tissue are tightly controlled by the absorption, tissue accumulation, and renal reabsorption mechanisms when administered

through the gastrointestinal tract.[24] These tight controls can be bypassed by IV injection of vitamin C.[24] Studies have shown that at least 2 g/day administered by IV for ~2–3 days is needed to restore plasma vitamin C concentrations to normal values in critically ill patients, and the supplementation needs to be given continuously to prevent decline to hypovitaminosis C.[25,26] Nevertheless, overall evidence on the optimal dosage of vitamin C supplementation to replenish physiological serum levels and to achieve supraphysiological levels to antagonize the overwhelming oxidative and inflammatory responses during critical illness is still low. In consequence, current international clinical nutrition guidelines differ markedly regarding their recommendations on vitamin C supplementation during critical illness and in diverse patient cohorts, e.g. patients with sepsis (Table 1).

CURRENT EVIDENCE ON THE USE OF VITAMIN C TREATMENT IN DIVERSE PATIENT COHORTS OF CRITICAL ILLNESS

Even though oxidative stress, inflammation, and concomitant damages of essential biofunctional structures (eg, mitochondria) represent interesting targets of clinical research, there is still limited evidence about the optimal dosage and timing of vitamin C supplementation that might be beneficial to counteract depletion and deficiencies in critically ill patients and especially in specific patient populations (eg, cardiac surgery, sepsis, burn, and COVID-19) and, thus, to improve the patient outcomes. Overall, available studies show a great variance in methodological aspects, such as the use of vitamin C either as high-dose IV monotherapy or as an "antioxidant mixture" (eg, the combination of high-dose IV vitamin C, hydrocortisone, and thiamin, also known as the HAT therapy). Furthermore, the timing of administration, the dosage used, the duration of application, the patient population, and the outcome measures used[31] have to be considered cautiously for the interpretation of received findings. A detailed overview about the methodology of available studies on the use of vitamin C in critically ill patients has been summarized in previously published articles.[32-36]

Patients with sepsis

The seminal article on a safety and dose-finding study of high-dose IV vitamin C monotherapy was published by Fowler et al.[37] In this study, 26 patients with severe sepsis with at least one organ dysfunction were enrolled within 48 h of ICU admission and randomly assigned into three groups: placebo with 5% dextrose water, low-dose vitamin C (50 mg/kg/day), or high-dose vitamin C (200 mg/kg/day). The dosage of IV vitamin C were divided into four equal doses and administered over 30 min every 6 h for up to 96 h. Compared with placebo, sequential organ failure assessment (SOFA) score decreased significantly faster in the high-dose vitamin C group. In addition, the vitamin C groups showed a greater decline in CRP (inflammatory markers) and procalcitonin (infections marker) levels, and a stable thrombomodulin (endothelial injury marker) level compared with the placebo group. No study-related adverse events were detected.[37]

The antioxidant mixture was popularized by Marik et al in 2016.[38] In a retrospective before-after study, patients with severe sepsis or septic shock were randomly assigned to receive either IV hydrocortisone (50 mg every 6 h for up to 7 days followed by a taper over 3 days), vitamin C (1.5 g every 6 h for up to 4 days) and thiamin (200 mg every 12 h for up to 4 days within 24 h of ICU admission) (intervention group), or hydrocortisone at the discretion of the attending physician (control group). The sepsis mixture was found to have a large treatment effect favoring the intervention group for hospital mortality (8.5% vs 40.4%), time on vasopressor, and improvement in the SOFA score at 72 h.[38] However, subsequent RCTs were unable to demonstrate these beneficial effects.[39-41] In a recent systematic review and meta-analysis (SRMA) of RCTs, no effect on mortality was demonstrated for studies that used the antioxidant mixture (relative risk [RR], 1.00; 95% CI, 0.85-1.18; $P = 0.99$; $I^2 = 0.0\%$).[32] Given the positive effects observed in SRMAs, when high-dose vitamin C was given as single intervention, compared with trials which used an antioxidant mixture, neutralizing effects of this combined supplementation strategy were supposed.[31]

For vitamin C monotherapy, the beneficial effect was further strengthened by the CITRIS-ALI trial, a multicenter trial among 170 patients with sepsis and acute respiratory distress syndrome (ARDS) who were administered IV vitamin C at 50 mg/kg every 6 h for up to 96 h vs placebo.[42] Although no significant difference was found for the primary outcome (change in modified SOFA score from baseline to 96 h), a significant reduction in 28-day mortality was found for the treatment group (29.8% vs 46.3%).[42] This beneficial effect was further supported by a recent SRMA of RCTs that demonstrated significant benefits in the IV vitamin C monotherapy subgroup (RR, 0.64; 95% CI, 0.49-0.83; $P = 0.0006$; $I^2 = 0\%$; 6 studies) but not for the combination (antioxidant mixture) therapy (test for subgroup differences; $P = 0.004$).[32]

However, the most recent landmark trial (the LOVIT trial) on IV vitamin C monotherapy found results, which were in apparent contrast to previous findings.[43] In this international trial, IV vitamin C or matched placebo were given at the same dose of 50 mg/kg every 6 h for up to 96 h to patients with sepsis within 24 h of ICU admission. The incidence of the primary outcome, a composite of death or persistent organ dysfunction (need for vasopressors, invasive mechanical ventilation, or renal-replacement therapy) on day 28 was significantly higher in the vitamin C group than in the control group (44.5% vs 38.5%; $P = 0.01$). Although the incidence of the components of the primary outcome was not statistically different between groups, the vitamin C group consistently demonstrated a higher incidence of these outcomes.[43] The most recent SRMA including the LOVIT trial still demonstrated that the IV vitamin C monotherapy subgroup was associated with significant reduction of 30-day or hospital mortality (RR, 0.67; 95% CI, 0.55-0.82; $P = 0.04$; $I^2 = 44\%$; 16 studies).[34] However, the rather high statistical heterogeneity reduces the certainty of this finding. In the five high quality studies reporting 90-day mortality ($n = 2$ monotherapy and $n = 3$ antioxidant therapy), the authors speculated that high-dose vitamin C was associated with increased 90-day mortality with moderate certainty (RR, 1.07; 95% CI, 0.94-1.21; $P = 0.29$; $I^2 = 0\%$). In addition, there was also moderate certainty that high-dose vitamin C increased the risk of hypoglycemia (RR, 1.20; 95% CI, 0.69-2.08).[34] Notably, the authors of the LOVIT trial were unable to provide potential explanations for the received surprising findings.[43] Potential explanations may have been small imbalances in the baseline characteristics. In the treatment group, patients' lactate levels were about 10% higher and more patients had signs of shock and were already mechanically ventilated at baseline and, thus, appeared to be sicker, which overall may have contributed to the received findings. Furthermore, a recently published nationwide cohort study from Korea demonstrates the importance of a treatment duration of at least 5 days,[44] thus the treatment period used here may have been too short to translate into clinically meaningful differences.

Patients with COVID-19

Severe COVID-19 seems to be driven by a massive cytokine release (ie, interleukin-6 [IL-6]), delayed cytotoxic immune response, and dysregulation of the coagulation system.[45,46] Depending on the variant of the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), patients may require critical care due to fulminant ARDS, vasoplegic shock, and multiorgan failure with high mortality rates.[47,48] Especially in the early phases of the pandemic, the huge workload overwhelmed the existing healthcare systems around the world. To date, there are only few effective therapies despite huge international research efforts.[49] In this context, vitamin C is considered as an attractive treatment option, as it is readily available, cheap, and has a favorable and well-studied risk profile. Its anti-inflammatory, antiviral, and immunomodulating properties might be of importance for a targeted and balanced immune response against SARS-CoV-2.[50] Furthermore, critically ill patients may particularly benefit from supplementation, as endogenous catecholamine and cortisol synthesis highly depends on adequate vitamin C levels.[18] In addition, vitamin C can restore glucocorticoid receptor function, whereas glucocorticoids mediate upregulation of the sodium-dependent vitamin C transporter and increase cellular vitamin C uptake.[51] Although high-dose IV vitamin C failed to improve 28-day mortality and ventilator-free days in a RCT in critically ill patients with COVID-19, improved partial pressure of oxygen and fraction of inspired oxygen ratios and a significant decrease in IL-6 have been observed.[52] Majidi et al even reported improved survival rates in the vitamin C group, although using a lower dose supplementation strategy.[53] As for patients with moderate COVID-19, Zhao et al conducted a retrospective before-after study and observed a shorter duration of systemic inflammation and smaller likelihood of progression toward severe disease in the high-dose vitamin C supplementation group.[54] In contrast, ambulatory outpatients with COVID-19 did not benefit from vitamin C supplementation with regards to the duration of symptoms.[55] Meta-analyses on the topic did not reveal clinical benefits for vitamin C supplementation in patients with COVID-19.[56,57] However, the validity of these meta-analyses is currently limited, as they only analyze low numbers of trials with medium quality and a heterogenous patient collective including severe and nonsevere cases and a great variety of supplementation strategies. Therefore, evidence remains unclear and further research is needed, especially regarding new emerging virus variants and altered courses of disease.

Further patient cohorts

In general, as a strong antioxidant, vitamin C is expected to play a key role in patient populations who suffer from oxidative stress. One typical cause for acute oxidative stress is I/R injury. Examples in which benefits of vitamin C administration have been shown after I/R-injury are patients undergoing open heart surgery using cardiopulmonary bypass,[58-64] patients with ischemic stroke,[65-67] after cardiopulmonary resuscitation, or after organ surgery requiring to temporarily clamp large arteries.[16] Patients experiencing chronic oxidative stress causing organ damage are suggested to benefit from

vitamin C as well, for example, in chronic obstructive pulmonary disease[68,69] or coronary artery disease.[16] Another patient group who may benefit from vitamin C are patients undergoing a systemic inflammatory reaction, for example, patients with polytrauma, burn trauma, and shock, and critically ill patients in general, as they frequently have suboptimal vitamin C levels.[15,25,70] During these systemic reactions, vitamin C restores vasopressor sensitivity, increases vasopressor synthesis, and improves endothelial function and microperfusion, which leads to reduced extravasation and edema as well as fluid demands.[16,38,71]

A further mechanism of vitamin C is protection from drug-induced toxicity. It has been shown that patients receiving vitamin C have a lower risk for contrast induced-acute kidney injury,[72] decreased drug toxicity,[73] as well as attenuated apoptosis and DNA damage while undergoing radiotherapy and/or chemotherapy.[74]

OUTLOOK

Currently, still recruiting and further planned clinical trials in patients with ARDS (LOVIT ARDS, NCT04404387), COVID-19 (LOVIT-COVID, NCT04401150; REMAP-CAP, NCT02735707), severe burn injuries (VICToRY, NCT04138394), and after cardiac surgery (advanceCSX, EudraCT-Number: 2019-001086-32) will provide more answers about the potential benefits of high-dose vitamin C in specific critically ill subpopulations.

CONCLUSION

The administration of vitamin C has gained significant interest since its discovery as an effective strategy against scurvy. Given its antioxidative functions and its involvement in many biochemical and biological processes, it is reasonable to compensate severe vitamin C deficiencies in critically ill patients. Regarding the potential effects of high-dose vitamin C in critically ill patients, recent aggregated evidence indicated beneficial effects across different SRMAs, whereas the use of high-dose vitamin C as monotherapy cannot be recommended in patients with sepsis and septic shock. Further research is urgently warranted to determine the optimal timing, dosage, duration, and target population among critically ill patients who most significantly benefit from such a high-dose vitamin C administration.

AUTHOR CONTRIBUTIONS

Ellen Dresen and Christian Stoppe equally contributed to the conception and design of this manuscript; Ellen Dresen, Zheng-Yii Lee, Aileen Hill, Quirin Notz, and Jayshil J. Patel drafted the manuscript; and Ellen Dresen, Zheng-Yii Lee, Aileen Hill, Quirin Notz, Jayshil J. Patel, and Christian Stoppe critically revised the manuscript and agree to be fully accountable for ensuring the integrity and accuracy of the work.

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CONFLICT OF INTEREST

None declared.

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