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**Vitamin C in the critically ill–indications and controversies**

Nabzdyk CS *et al*. Vitamin C in critical care

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**Abstract**

Ascorbic acid (vitamin C) elicits pleiotropic effects in the body. Amongst its functions it serves as potent anti-oxidant, co-factor in the collagen and catecholamine synthesis, and modulator of immune cell biology. Furthermore, an increasing body of evidence suggests that high dose vitamin c administration improves hemodynamics, end-organ function, and may improve survival in critically patients. This articles reviews studies that evaluate vitamin C in pre-clinical models and clinical trials with regards to its therapeutic potential.

**Key words:** Ascorbic acid; Vitamin C; Critical care medicine; Sepsis; Shock; Vasopressors; Cardiovascular

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**Core tip:** An increasing body of evidence suggests that high dose vitamin C administration improves hemodynamics, end-organ function, and may improve survival in critically ill patients. This article reviews studies that evaluate vitamin C in pre-clinical models and clinical trials with regards to its therapeutic potential.

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**INTRODUCTION**

Vitamin C is one of the most well-known essential nutrients and believed by many to confer a litany of health benefits (Figure 1). The Nobel Prize Winner Linus Pauling may have been the foremost ambassador to date suggesting the use of vitamin C would enhance cardiovascular health, the body’s immune function to overcome infections and even cancer[[1-4](#_ENREF_1)].These health claims created significant controversies that lasted for decades. While many of his “more is better” claims have not been supported by rigorous scientific investigation, a growing number of benefits of vitamin C administration have been identified for medical treatment including in the field of critical care. This mini-review will examine the evidence in support of vitamin C administration for critically ill patients and provide general recommendations for use by intensive care unit (ICU) practitioners.

**Vitamin C levels in the critically ill**

Vitamin C is water-soluble and it circulates in the plasma. It is freely filtered by the glomerulus and reabsorbed in the proximal tubule *via* the first sodium-dependent vitamin C transporter (SVCT1). In the setting of hypovitaminosis C its urinary excretion is minimal[[5](#_ENREF_5)]. While SVCT1 regulates whole-body homeostasis of vitamin C, a high affinity/low capacity a second sodium-dependent vitamin C transporter (SVCT2) protects metabolically active cells against oxidative stress facilitating vitamin C accumulation where it is needed[[6](#_ENREF_6)]. The recommended daily oral dose of vitamin C is 75 mg (adult female)/90 mg (adult male) and only ten milligrams of oral vitamin C daily is necessary to prevent scurvy (plasma level < 0.1 mg/dl; normal range 0.8-1.6 mg/dl). Despite meeting these recommended daily intakes many critically ill patients exhibit decreased vitamin C plasma levels. Carr *et al*[[7](#_ENREF_7)] reported hypovitaminosis C in forty-four critically ill patients receiving standard ICU nutrition, of which one third had vitamin C deficiency. The degree of vitamin C deficiency was more pronounced in the septic population as compared to the non-septic critically ill. Continuous renal replacement (CRRT) is commonly utilized in critically ill patients and is believed to lead to a depletion of water-soluble vitamins[[8-10](#_ENREF_8)]. A retrospective study of critically ill patients receiving CRRT revealed that 87% (13 of 15) had vitamin C deficiencies[[9](#_ENREF_9)].

**Biological effects of vitamin C**

Amongst vitamin C’s pleiotropic functions of relevance to critical illness are its immune enhancing effects, anti-oxidant properties as well as its potential antimutagenic effects[[11](#_ENREF_11),[12](#_ENREF_12)]. Vitamin C has been shown to enhance neutrophil chemotaxis, phagocytosis, and thus microbial clearance[[13](#_ENREF_13),[14](#_ENREF_14)]. In addition vitamin C promotes T-cell and NK-cell proliferation and modulates T- and NK-cell function[[13](#_ENREF_13),[15](#_ENREF_15)]. Studies on vitamin C’s effects on B-cells have revealed conflicting data with regard to proliferation and differentiation[[13](#_ENREF_13),[15](#_ENREF_15)]. Vitamin C appears to induce antibody production in human lymphocytes and guinea pigs[[16](#_ENREF_16),[17](#_ENREF_17)]. In a mouse model of abdominal sepsis induced by cecal-puncture-ligation, parenteral vitamin C administration improved sepsis outcomes through reversal of regulatory T-cell inhibitory function[[18](#_ENREF_18)]. Hypovitaminosis C in a sepsis model using guinea pigs was also associated with fewer macrophages in the peritoneal cavity and impaired macrophage migration[[19](#_ENREF_19),[20](#_ENREF_20)]. Interestingly adverse effects of vitamin C deficiency were more pronounced in the elderly guinea pigs[[19](#_ENREF_19)].

In cell culture and rodent experiments, vitamin C has been shown to decrease lipid peroxidation, prevented occludin dephosphorylation, and thus diminished loosening of tight junctions[[5](#_ENREF_5),[21-23](#_ENREF_21)]. Vitamin C also improves microcirculatory flow impairment by inhibiting tumor-necrosis-factor-induced intracellular adhesion molecule 1 (TNF induced ICAM 1) expression, thereby decreasing leukocyte adhesiveness[[5](#_ENREF_5),[24](#_ENREF_24),[25](#_ENREF_25)]. In smokers, a single bolus administration of vitamin C (3 g IV) was found to increase coronary flow reserve, which is an integrated parameter of endothelial function and vascular smooth muscle relaxation. This effect was not seen in healthy control patients[[26](#_ENREF_26)].

Vitamin C is a co-factor in collagen synthesis, a mitogen for fibroblasts, and is believed to positively modulate proinflammatory signaling and inflammation resolution that occur in wound beds[[27](#_ENREF_27),[28](#_ENREF_28)]. Vitamin C supplementation in deficient mice promotes wound healing through enhanced matrix deposition and fibroblast proliferation[[27](#_ENREF_27)]. In addition topical vitamin C increases dermal collagen biosynthesis in healthy volunteers[[29](#_ENREF_29),[30](#_ENREF_30)]. However, vitamin C supplementation does not consistently improve pressure ulcer healing in nursing home and hospitalized patients, and recent systematic reviews have concluded that vitamin C (often administered in conjunction with zinc and other nutrients) is ineffective for treatment for this condition[[31-35](#_ENREF_31)].

Vitamin C is a co-factor in carnitine synthesis, a molecule that facilitates fatty acid shuttling into mitochondria, reduces oxidative stress, and promotes endothelial sprouting[[36](#_ENREF_36),[37](#_ENREF_37)]. Its deficiency has been linked to cardiomyopathy and neurometabolic disease[[38](#_ENREF_38),[39](#_ENREF_39)]. Despite carnitine’s essential metabolic roles, clinical data to date have not yielded convincing evidence, that supplementation in critically ill patients will improve outcomes[[40-42](#_ENREF_40)].

 Vitamin C also is a cofactor in catecholamine synthesis and in adrenal steroidogenesis[[43](#_ENREF_43),[44](#_ENREF_44)]. Vitamin C contributes to the conversion of dopamine to norepinephrine by dopamine beta-hydroxylase[[45](#_ENREF_45)]. Vitamin C enhances norepinephrine synthesis both by recycling tetrahydrobiopterin, a critical cofactor in the catecholamine synthesis, and increasing tyrosine hydroxylase expression[[46](#_ENREF_46)]. Furthermore, vitamin C is a cofactor for the peptidylglycine α-amidating monooxygenase that is required for the endogenous synthesis of vasopressin[[47](#_ENREF_47)]. One study in cardiac surgical patients has suggested that pre-operative administration of vitamin C mitigated etomidate-induced adrenal suppression[[48](#_ENREF_48)]. Thus there has been significant interest in utilizing vitamin C for the management of hemodynamically unstable patients[[49](#_ENREF_49)].

**Vitamin C in cardiovascular patients**

While a recent review concluded that there is insufficient evidence to support the use of vitamin C to reduce cardiovascular disease risk or mortality in the general population, increasing evidence suggests that it may have a beneficial role in patients with acute coronary syndromes or undergoing cardiac surgical procedures[[50](#_ENREF_50)]. Cardiac surgery, extracorporeal membrane oxygenation and hemodialysis produce oxidative stress, which negatively impacts morbidity and mortality[[51](#_ENREF_51)]. Vitamin C’s ability to scavenge reactive oxygen species and increase nitric oxide production through induction of endothelial nitric oxide synthase have made it a focus of interest as a cardiovascular therapy adjunct[[52](#_ENREF_52)]. In one study of cardiac surgical patients undergoing cardiopulmonary bypass (CPB) statistically significant reductions in plasma levels of vitamin C were found intraoperatively compared to preoperative levels even prior to initiation of CPB (∆16.3% compared to baseline). The decrease in vitamin C plasma levels continued after CBP and lasted for at least six days[[53](#_ENREF_53)].

Perioperative vitamin C administration has also been shown to prevent post-operative atrial fibrillation in majority number of studies[[54-59](#_ENREF_54)]. Its effects further appear result in decreases in the duration of hospital and ICU stay of cardiac surgery[[54-57](#_ENREF_54)].

Other studies examining the effects of vitamin C administration on patients with acute myocardial infarction and undergoing coronary revascularization procedures have reported improved left ventricular ejection fraction (LVEF), microcirculation, and limited infarct size in patients with acute myocardial infarction[[60-62](#_ENREF_60)]. One recent randomized multicenter clinical trial of patients with myocardial infarction undergoing percutaneous coronary angioplasty did not show a significant improvement in infarct size or ejection fraction at the time of the intervention with vitamin C administration. However, a decline in the LVEF between 7-15 d and 2-3 mo noted in the control group was not seen in the vitamin C group[[63](#_ENREF_63)]. The authors of this study suggested that vitamin C may have ameliorated myocardial reperfusion injury[[63](#_ENREF_63)].

In addition to potential beneficial effects on microperfusion and myocardial protection, a growing body of evidence suggests that vitamin C administration may positively affect hemodynamic parameters and hasten freedom from vasopressors in critically ill patients[[64-67](#_ENREF_64)]. Interestingly some evidence suggests that vitamin C’s effects on hemodynamics may have a ceiling effect. A recently reported pharmacokinetic study by Grooth *et al*[[68](#_ENREF_68)] only found a minimal reduction in heart rate among critically ill patients randomized to receive 2 g/d *vs* 10 g/d of vitamin C. However, only the treatment group that received the 2 g/d of vitamin C, but not the 10 g/d treatment regimen had a clinically relevant decrease in norepinephrine requirements (delta from baseline of 4 µg/kg per minute) over 48 h[[68](#_ENREF_68)].

**Vitamin C in burn-injured patients**

Increased capillary leakage is a clinical hallmark of burn injury. It is associated with significant fluid and protein extravasation. The term “fluid creep” was coined to describe the phenomenon that burn patients often receive significantly more resuscitation fluid than anticipated based on Parkland formula calculations[[69](#_ENREF_69)]. This excess fluid resuscitation can be associated with edema-related complications[[70](#_ENREF_70)]. Endothelial damage leading to increased permeability in patients with burn injury may partly be mediated by reactive oxygen species-induced lipid peroxidation. As an antioxidant vitamin C has been evaluated as a therapy to decrease fluid resuscitation requirements[[71](#_ENREF_71),[72](#_ENREF_72)]. In a rodent model of burn injury high dose vitamin C appeared to improve microvascular barrier dysfunction, without affecting leukocyte activation[[73](#_ENREF_73)]. In a study of guinea pigs with 70% third degree burns given high dose vitamin C (170, 340 and 680 mg/kg per day) fluid requirements were significantly reduced while stable cardiac outputs were maintained[[74](#_ENREF_74)]. In a study of dogs with burn injuries vitamin C administration (14 mg/kg per hour) decreased lipid peroxidation and microvascular protein and fluid leakage[[75](#_ENREF_75)]. A burn study in sheep provided additional evidence that high dose vitamin C (250 mg/kg bolus plus 15 mg/kg per hour) could reduce fluid requirements and lipid peroxidation, and improved antioxidant status[[76](#_ENREF_76)]. Preliminary studies in humans have also been promising. In a study of thirty-seven patients with > 30% total body surface area burns (TBSA), vitamin C administration (66 mg/kg per hour) reduced fluid requirements, wound edema, and increased the ratio of PaO2 to fraction of inspired oxygen[[66](#_ENREF_66)]. In a retrospective review of 40 patients with greater than 20% TBSA, vitamin C (66 mg/kg per hour) was associated with increased urine output and decreased fluid requirements, but no changes in outcomes or incidence of acute kidney injury[[77](#_ENREF_77)]. In another small study (*n* = 30) of patients with second degree burns, topical vitamin C accelerated granulation tissue formation[[78](#_ENREF_78)].

**Vitamin C in septic patients**

Recently there has been a surge of interest in the use of vitamin C as a treatment of sepsis. This interest was stimulated by the findings of a cohort study by Marik *et al*[64] that administered a cocktail of vitamin C (1.5 g IV every 6 h), hydrocortisone (50 mg IV every 6 h) and thiamine (200 mg IV) to 47 septic patients and found a significant reduction in SOFA scores, dependence on vasopressors, and most importantly a reduction in hospital mortality to 8.5% in the treatment arm *vs* 40.4% in a historic control group. These findings were consistent with small phase I double-blinded placebo-controlled trial suggesting beneficial effects of vitamin C in patients with sepsis[[67](#_ENREF_67)]. This trial which randomized 24 septic patients with and documented hypovitaminosis C to receive placebo, low dose (50 mg/kg per day) or high dose (200 mg/kg per day) parental vitamin C for four days found significant reductions in SOFA scores and CRP plasma level reductions in the vitamin C treated groups[[67](#_ENREF_67)]. In another small trial of critically ill surgical patients Zabet *et al*[[65](#_ENREF_65)] reported a significant reduction in 28 d mortality in 14 patients with septic shock randomized to receive 25 mg/kg per day of ascorbic every 6 h for 72 h when compared to 14 patients with septic shock who received placebo. Despite these promising findings there are potential safety concerns worthy of consideration with vitamin C administration in the critically ill population. A recent study by De Grooth *et al*[68] evaluated four parenteral vitamin C repletion regimens (2 g/d *vs* 10 g/d; bolus *vs* continuous infusion) administered for 48 h to critically ill patients with multiple organ dysfunction. The patients receiving 10 g vitamin C per day had supraphysiologic vitamin C levels and hyperoxaluria, oxalate being a metabolite of vitamin C. These findings raise concern for an increased risk of oxalate nephropathy as has been reported with high dose vitamin C administration and more prolonged administration in the noncritically ill population[[68](#_ENREF_68),[79](#_ENREF_79),[80](#_ENREF_80)]. This theoretical risk of oxalate nephropathy stands in contrast with the mostly reassuring data about the safety of short-term high dose vitamin C administration[[64](#_ENREF_64),[65](#_ENREF_65),[67](#_ENREF_67)].

At present multiple ongoing randomized controlled trials including the VICTAS, ACTS, HYVCTTSSS trials are aimed at confirming the beneficial effects of vitamin C and adjuncts in critically ill patients with sepsis[[81-83](#_ENREF_81)].

**Vitamin C in hemorrhagic shock**

Trauma and hemorrhagic shock can lead to significant coagulopathy and inflammation and both are associated with increased mortality and morbidity. Given its antioxidant effects vitamin C has long been evaluated as a protective agent to mitigate effects on proinflammatory and procoagulant pathways caused by trauma and hemorrhagic shock[[84-88](#_ENREF_84)].

In a swine model of acute hemorrhagic shock, animals were randomized to receive either intravenous normal saline (NS), low-dose Vitamin C (50 mg/kg), or high-dose Vitamin C (200 mg/kg). The group of animals receiving normal saline (control) showed significantly greater histological end-organ damage including elevated acute lung injury scores, and increased mRNA levels of interleukin (IL)-1β, IL-8, TNF-α, plasminogen activation inhibitor-1 and tissue factor compared with the groups receiving vitamin C. Furthermore, only a modest correction of coagulopathy was observed in the vitamin C group when compared to the NS group[[88](#_ENREF_88)]. Similarly, in a rat model of hemorrhagic shock vitamin C administration (low 100 mg/kg or high 500 mg/kg) was shown to attenuate renal injury possibly *via* a SIRT1-mediated mechanism. Levels of serum creatinine, BUN, TNF-α, IL-1β were lower in the vitamin C group when compared to a sham group. Conversely, levels of hemeoxygenase-1 (HO-1), a stress-response protein which is believed to play key roles in mediating protection against oxidant-mediated lung injury, were higher in the kidneys treated with vitamin C. This effect appeared to occur irrespective of the vitamin C dose administered[[89](#_ENREF_89)]. Another study of the effects of vitamin C administration (100 mg/kg) on renal function found a decrease in the expression of induced dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN) in tubular epithelial cells of rat kidneys. DC-SIGN levels are believed to correlate with the occurrence of kidney injury. Vitamin C administration prior to resuscitation was also found to decrease proinflammatory cytokine production which mitigated renal injury[[90](#_ENREF_90)]. Another rat model of hemorrhagic shock found that vitamin C treatment induced HO-1 expression in a variety of tissues including kidney, lung, and liver with decreased organ injury and proinflammatory responses[[91](#_ENREF_91)]. Likewise, vitamin C pretreatment in the setting of hemorrhagic shock appears to protect the intestinal epithelium by decreased proinflammatory cytokine expression and neutrophil infiltration. This effect was also believed to be mediated by HO-1 and was abrogated by pharmacological HO-1 inhibition[[92](#_ENREF_92)]. Prior studies have suggested that pretreatment of rats with vitamin C (1 mg/100 g or 5 mg/100 g) decreases gastric mucosal bleeding after induction of hemorrhagic shock and retransfusion[[93](#_ENREF_93)]. Lastly, the combination of vitamin C administration (50 mg/kg per day for 3 d) prior to inducing hemorrhage together with intravenous infusion vitamin C (50 mg/kg) following hemorrhage improved cardiovascular parameters such as blood pressure and LV dp/dt, and decreased free radical production in a rat model of hemorrhagic hypotension[[94](#_ENREF_94)].

These beneficial effects of vitamin C stand in contrast with those obtained in a rat model of liver injury and hemorrhagic shock in which vitamin C preconditioning (10 mg/kg) did not improve recovery of animals after resuscitation[[95](#_ENREF_95)]. Likewise, a survival study of rats with hemorrhagic shock did not show a difference when lactated Ringer’s solution plus vitamin C (50 mg/kg) was administered for resuscitation compared with lactated Ringer’s solution alone[[96](#_ENREF_96)].

These preclinical studies point out multiple mechanisms by which vitamin C may serve as antioxidant in hemorrhagic shock and thus could provide organ protection, however evidence suggesting a vitamin C-mediated survival benefit is missing. To our knowledge there is thus far no human trial data available demonstrating a clinical benefit of vitamin C administration as an adjunct for the treatment of trauma and hemorrhagic shock.

**Vitamin C and pain**

Pain is a common problem in critically ill patients, be it due to injuries, secondary to infection, inflammation, trauma, surgery, cancer, or in the setting of reactivation of herpes zoster. Evidence suggests that vitamin C acts as a cofactor for the biosynthesis of opioid peptides and as potent anti-inflammatory agent[[97](#_ENREF_97),[98](#_ENREF_98)].

Several case reports and a cohort study have reported clinical improvement in relief for patients administered vitamin C with acute herpes zoster exacerbation[[99-101](#_ENREF_99)]. While, a recent randomized controlled trial of high dose intravenous vitamin C (5 g *iv* bolus per day on day 1, 3 and 5) failed to find a reduction in acute herpes zoster pain, there was a decrease in the incidence of post herpetic neuropathy (PHN)[[102](#_ENREF_102)]. A similarly designed study found lower plasma concentrations of vitamin C in patients with PHN than in healthy volunteers and a reduction in spontaneous PHN pain after high dose vitamin C treatment[[103](#_ENREF_103)].

Several trials have found reductions in the development of complex regional pain syndrome after wrist and ankle surgery with vitamin C[[104-107](#_ENREF_104)]. A study of patients with osteoarthritis-related hip or knee joint pain found that vitamin C administered enterally for 14 d provided modest pain relief, equivalent to approximately half the effect of nonsteroidal anti-inflammatory drugs[[108](#_ENREF_108)]. In a randomized controlled trial of vitamin C in patients undergoing single-level posterior lumbar interbody fusion, there was no difference in postoperative pain intensity between the 2 groups but vitamin C administration was associated with improved functional status[[109](#_ENREF_109)].

A majority of the prospective and case studies of vitamin C administration for cancer related pain have reported improvements in quality of life indicators such as pain, fatigue, insomnia, and nausea and vomiting[[110-115](#_ENREF_110)]. However, clinical trial data regarding vitamin C related opioid-sparing effects in cancer patients have yielded mixed results[[116-119](#_ENREF_116)].

**Vitamin C in cancer patients**

Perhaps more widely investigated than any other vitamin C related claim is the assertion of benefit for patients with cancer. In fact, a quick PubMed search of “ascorbic acid + cancer” yielded 4376 items, 247 of which were clinical trials (as of May 2018).

Cancer patients have been recognized to have low vitamin C levels compared with healthy controls[[120](#_ENREF_120)]. In a large randomized, placebo-controlled trial daily intake of antioxidants, vitamins and minerals, a combination of vitamin C (120 mg/d), vitamin E, zinc, beta carotene and selenium lowered total cancer incidence and all-cause mortality in men, but not in women at 7.5 years[[121](#_ENREF_121)]. A similar regimen of vitamin C and E supplementation, with beta carotene did not however prevent the formation of colon adenomas in a randomized trial of 864 patients[[122](#_ENREF_122)]. Another study of vitamin C and E supplementation for cancer prevention did not identify immediate or long-term effects on the risk of total cancers, prostate cancer, or other site-specific cancers[[123](#_ENREF_123)].

A randomized clinical trial examining different doses of vitamin C (1, 2 or 4 g/d) failed to find a dose-response relationship or an association between serum ascorbic acid levels and mutagen sensitivity, which has been described as a risk factor for tobacco-related epithelial cancers[[124](#_ENREF_124)]. Despite these clinical findings basic science data suggests that vitamin C may have a beneficial role in cancer progression through several different mechanisms. Vitamin C was recently found to restore Tet methylcytosine dioxygenase 2 function, one of the most frequently mutated genes in hematopoietic malignancies, and through this mechanism vitamin C may block aberrant self-renewal and leukemia progression[[125](#_ENREF_125)]. Vitamin C also facilitates DNA oxidation in leukemia cells rendering them more sensitive to poly ADP ribose polymerase inhibitors[[125](#_ENREF_125)].

In cholangiocarcinoma SVCT2 expression levels have been shown to correlate with susceptibility to vitamin C induced cancer cell death *in vitro* and *in vivo*[[126](#_ENREF_126)]. In separate experiments Vitamin C has been shown to increase methotrexate-mediated hepatocellular carcinoma cell death[[127](#_ENREF_127)]. Furthermore vitamin C enhances effectiveness of radiation therapy for glioblastoma and gemcitabine/epigallocatechin-3-gallate treatment for mesothelioma[[128](#_ENREF_128),[129](#_ENREF_129)]. These findings are in contrast to data showing that vitamin C interferes with chemotherapy drugs such as doxorubicin, methotrexate, and cisplatin[[128-131](#_ENREF_128)]. Furthermore vitamin C may enhance growth of some cancers. For example, plasmocytoma cell growth is dependent on the presence of vitamin C[[132](#_ENREF_132)]. Vitamin C exposure showed differential effects onan *in vitro* model ofcolony-forming bone marrow cell growth of patients with myelodysplastic syndrome. In this model Vitamin C responsiveness (both, growth enhancement or inhibition) was associated with shorter survival when compared to patients with no response to vitamin C[[133](#_ENREF_133)]. Adding to this complex picture is data derived from *in vitro* work that examined the response of HL-60 cells from an acute myeloid leukemia cell line to vitamin C. Vitamin C administration decreased oxidative stress and thus protected HL-60 cells from H2O2-induced cell-death[[134](#_ENREF_134)].

Curiously, high-dose vitamin C (0.5-5 mmol/L) has also been shown to increase procoagulant properties of freshly isolated red blood cells (RBC) *via* externalization of phophatidylserine; a mechanism known to lead to thrombus formation. Interestingly, this effect was more pronounced in RBC from cancer patients and could be confirmed in a rat model of thrombus formation[[135](#_ENREF_135)].

In one study in terminal cancer patients vitamin C was associated with increased quality of life and survival[[116](#_ENREF_116)]. In contrast, in two double-blinded randomized controlled trials that included patients with advanced cancers (stomach, colon, pancreas, lung, breast, and others) vitamin C (10 g/d) did not improve survival[[136](#_ENREF_136),[137](#_ENREF_137)].

Given the complexities of cancer biology and vitamin C, therisks and benefits of initiating high dose vitamin C therapy in critically ill oncology patients should be carefully weighed and discussed with the oncology consultant.

**Conclusion**

Vitamin C is once again a focus of intense interest for its role in the treatment of critically ill patients. Evidence suggest that vitamin C administration may have a variety of beneficial effects in patients undergoing cardiac surgical procedures, during resuscitation with acute burn injury, for treatment of sepsis, in reducing pain and in treatment of cancer. While many questions have yet to be answered, there is little data to suggest that short-term high dose vitamin C would elicit major harm except for the risk of oxalate nephropathy. In fact, evidence suggests, that in selected patients short-term high dose vitamin C may improve hemodynamic parameters, decrease fluid resuscitation requirements, reduce the incidence of perioperative atrial fibrillation, improve pain and potentially reduce sepsis-associated mortality. We eagerly await additions to the growing body of evidence which examine the role of vitamin C administration for improving outcomes for our sickest patients.

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Grade A (Excellent): A, A

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**Effects of vitamin C**

**Antioxidant**

* radical oxygen scavenger protecting cells from oxidative stress

**Steroid- and catecholamine synthesis**

* cofactor in the catecholamine, vasopressin and steroid synthesis
* improves hemodynamics may accelerate resolution of shock

**Immune cell function**

* increases neutrophil phagocytosis and chemotaxis
* affects macrophage migration
* enhances T- and NK-cell proliferation, modulates their function
* may increase antibody formation

**Endothelial cell function**

* decreases endothelial ICAM expression and leukocyte adhesion
* improves endothelial barrier mechanism
* decreases fluid requirements in burn patients
* improves microcirculation

**Carnitine production**

* modulates fatty acid metabolism
* may improve microcirculation and cardiac function

**Wound healing**

* co-factor of collagen production
* mitogen for fibroblasts

**Figure 1 Biological functions of vitamin C.** ICAM: intracellular adhesion molecule.