Nutrition 60 (2019) 185–190

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Review article

# Vitamin C for the critically ill: Is the evidence strong enough?

Pascal L. Langlois M.D., R.D. [a,*], François Lamontagne M.D., Ph.D. [b]

[a] *Department of Anaesthesiology and Reanimation, Faculty of Medicine and Health Sciences, Sherbrooke University Hospital, Sherbrooke, Québec, Canada*
[b] *Department of Intensive Care Medicine, Faculty of Medicine and Health Sciences, Sherbrooke University Hospital, Sherbrooke, Québec, Canada*

ARTICLE INFO

*Article History:*
Received 16 July 2018
Received in revised form 3 September 2018
Accepted 7 October 2018

ABSTRACT

Vitamin C exhibits interesting properties in the context of critical illness, with benefits described in neurologic, cardiovascular, renal, and hematologic systems, both in in vitro and in animal models. Through direct effects on bacterial replication, immunomodulation, and antioxidant reserve of the organism, vitamin C directly affects the pathophysiological process of sepsis, trauma, burn, and systemic inflammation. Even if several observational trials have linked vitamin C deficiency to worse outcomes, the evidence is not such as to provide us with a distinction between causality effects or simple epiphenomenon, and the current focus is on interventional trials.

Pharmacokinetic data suggest that a minimal supplementation of 3 g/d intravenously is required to restore normal serum values in critically ill patients with known deficiency. According to these data, only five trials, including a retrospective analysis, studied pharmacologic dose: three as an antioxidant cocktail and two as monotherapy. The largest trial, conducted in 2002, reported reduced incidence of multiorgan failure and duration of mechanical ventilation. Recently a retrospective analysis reported impressive results after administration of vitamin C, thiamine, and hydrocortisone. The two most recent trials reported improved clinical outcomes, including improved mortality, but contained significant methodological limitations. A recent systematic review did not find clinical benefits with the most-studied low-dose oral supplementation, potentially because of suboptimal or insufficient repletion.

Current guidelines do not support the administration of high-dose vitamin C in critically ill patients. Future larger trials are required to support any therapy, but the low cost and safety profile can justify supplementation in the meantime. Metabolomics study will further help understand biological effect.



## Introduction

Adequate intake of vitamin C is of uttermost importance in humans considering that, similarly to most other mammals, humans lack the L-gluconolactone oxidase required for its production. Adequate plasma levels are therefore dependent on sufficient vitamin C intake and adequate absorption by the intestinal sodium-dependent vitamin C transporter (SVCT1) [1]. As a water-soluble vitamin, it is filtrated in the kidneys by the glomerulus and is reabsorbed in the proximal tubule. This reabsorption is critical in case of deficiency to minimize renal loss. Definitions of normal vitamin C levels vary depending on references, but it is recognized that levels $<23$ µmol/L define hypovitaminosis, whereas $<11$ µg/L defines deficiency. The active transport into cells by the SCVT2 explains why serum content is only a small fraction of body content, but plasma concentration and dietary intake have been correlated to the tissue concentration, notably for granulocytes, platelets, and erythrocytes [2]. Human skeletal muscles also appeared highly responsive to vitamin C intake despite having levels relatively lower than other tissues [3].

The severe deficiency was originally well described by our ancestors, travelling oceans and at risk of developing scurvy because of a severe lack of intake. Although inadequate intake is not anymore a common cause of deficiency, today, modern laboratory analysis has confirmed that as many as 30% of the critically ill patients do present significantly low plasmatic levels of vitamin C. Septic patients are particularly at risk, with an incidence rate of 40% [4]. Nonetheless, it is clinically hard to document this deficiency because of sparse availability of high-performance liquid chromatography. The deficiency must therefore be suspected and treated even if not objectively measured, and a higher severity of disease score, such as the Sequential Organ Failure Assessment score, should increase the suspicion and prompt the clinicians to initiate supplementation [5]. Considering that most patients had normal dietary intake before intensive care unit (ICU) admission, there is a clear association between development of critical illness and decreasing vitamin C levels. Patients in multiorgan

* Corresponding author. Tel.: 819-346-1110; fax: 819-820-6413.
*E-mail address:* Pascal.laferriere-langlois@usherbrooke.ca (P. L. Langlois).

https://doi.org/10.1016/j.nut.2018.10.009
0899-9007/

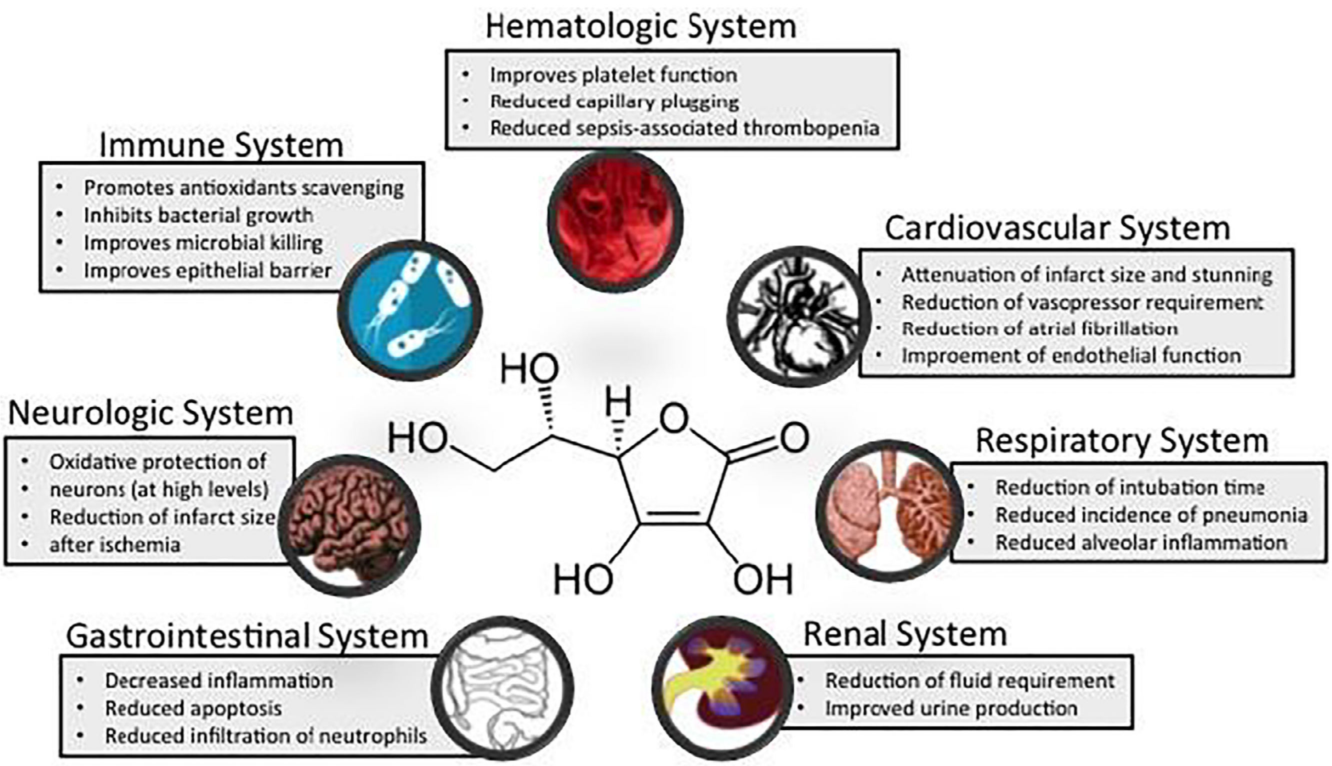


**Fig. 1.** Systemic effects of vitamin C.

failure exhibit even lower levels, sometimes reported as low as 3.8 μmol/L despite enteral nutrition [6].

## Biological plausibility and ascorbate deficiency

Many theories exist to explain the association between severity score and vitamin C deficiency, but none have been sufficiently studied to discern true causal effect from a simple epiphenomenon. During critical illness, elevated oxidative stress caused by microcirculatory defects, ischemia-reperfusion, and mitochondrial dysfunction increase the consumption and reduce the recycling of antioxidants, including vitamin C. Although other mammals increase their synthesis of vitamin C during such stress situation, humans are unable to raise serum levels as occurs for other stress hormones. This deficiency theoretically affects the various biological functions of vitamin C.

First, vitamin C modulates immune response by inhibiting nuclear factor κB activation, which is responsible for cascade development of the proinflammatory cytokine storm, and by enhancing leucocytes phagocytic activities and reducing superoxide production in macrophages [7,8]. Second, vitamin C is a primary circulating antioxidant, neutralizing reactive oxygen and nitrogen species. Endothelial dysfunction leads to the formation of $O_2^-$ and associated reduction of nitric oxide. $O_2^-$ further activates inducible nitric oxide synthetase to form the very reactive oxygen species $ONOO^-$ [9,10]. Ascorbate scavenges these reactive oxygen species, preventing damage, and reduces oxidized scavengers, α-tocopherol, glutathione, and urate while generating ascorbyl radicals. This oxidized form of vitamin C is a less damaging radical and will easily react with itself because of the position of its free electron. Two ascorbyl radicals will create one ascorbate and one dehydroascorbate. Third, vitamin C inhibits bacterial replications, and fourth, it increases endogenous vasopressor synthesis and sensitivity, including dopamine, norepinephrine, and vasopressin. Vitamin C also promotes wound healing through its role as a cofactor for collagen synthesis [11], and its adequate levels positively affect psychological mood [12]. For further details, refer to a recent in-depth review of biological effects in the critically ill [7,8].

Considering these biological functions and the observed depletion in critically ill patients, it seems plausible that restoring normal circulating levels could improve these patients' outcomes. Figure 1 details the various benefits found in both preclinical and clinical trials according to the different systems. Nonetheless, current data remain conflicted regarding the clinical benefits of supplementing ascorbic acid, sometimes to reach supraphysiological serum levels.

## Preclinical trials

One of the first arguments to support benefits of supplementing ascorbic acid came from various animal models of sepsis and ischemia reperfusion. With doses varying from 10 mg/kg to 200 mg/kg administered either prophylactically or after injury, vitamin C administration in sepsis murine model improved microvascular perfusion, blood flow, and mortality [13,14]. Acute lung injury and hepatic injury were also improved after high-dose administration [15,16].

Similarly, ischemia injury after arterial clamping was significantly improved. The administration of 50 to 100 mg/kg intravenously at start of cardiopulmonary resuscitation after cardiac arrest in murine models increased the survival at 72 h in a dose-dependent manner [17]. A reduction of infarct size after middle cerebral artery clamping in mice was found in addition to reduced neurologic deficits and mortality [18]. Similar clinical improvements were found in lung, renal, and hepatic ischemia models [19–21].

## Clinical trials in the broad ICU population

In humans, most results were not as conclusive, and many factors might explain this discrepancy. Apart from obvious differences regarding pharmacokinetic and pharmacodynamics profile between animal models and humans, the variability and complexity in the patients' pathologic conditions, especially when hospitalized in the ICU, do not allow the investigation of an isolated model of infarct in a homogeneous cohort. Moreover, the strategies of administration of vitamin C have varied greatly across the multiple trials (Table 1), with posology usually significantly inferior to those found effective in animal model and onset of supplementation usually delayed from the insult or hyperacute phase. Moreover, most trials addressing ascorbic acid supplementation administered antioxidants as cocktails and therefore created potential interactions between the investigated molecules.

Recent pharmacokinetic trials concluded that intravenous administration of 2 to 3 g/d is required only to normalize plasma levels, whereas many of the trials administered inferior doses [5], and even superior doses are required to obtain the supraphysiological levels described by the concept of pharmaconutrition. De Grooth et al. [22] randomly allocated 20 patients in four groups receiving either 2 g or 10 g of intravenous vitamin C, either twice daily as infusion or as continuous perfusion. Similar to previous findings, 2 g was sufficient to normalize serum levels, whereas 10 g was required to maintain serum levels constantly >40 mg/L, with a maximum at 295 mg/L. Interestingly, after 48 h of discontinuation, 15% of patients developed hypovitaminosis.

**Table 1**
Randomized clinical trials evaluating vitamin C supplementation in critically ill patients

| Study | Population | Intervention | Main findings |
|---|---|---|---|
| | | **Dose >2 g/d** | |
| **Nathens 2002** [45] | General surgical/trauma ICU<br>$n$ = 595 | IV vit C 1000 mg in 100 mL $D_5W$ every 8 h + α-tocopherol 1000 IU every 8 h via nasogastric or orogastric tube for duration of ICU stay, maximum 28 d. First dose of vit C given intravenously. | Reduced incidence of multiorgan failure. Reduction in duration of mechanical ventilation and ICU length of stay. No changes in pulmonary morbidities. |
| **Berger 2008** [26] | Mixed ICU<br>$n$ = 200 | Standard EN or PN + antioxidant continuous supplementation started within 24 h of ICU admission for 5 d. IV selenium (540 µg) + IV zinc (60 mg) + IV vit C 2700 mg + IV vit B 305 mg + vit E enteral 600 mg + vit E 12.8 mg IV daily for 2 d followed by half the dose of all. | Improvement of inflammation biomarkers (C-reactive protein). No effect on clinical outcomes, including mortality, organ function and SOFA score, length of hospitalization and infectious complications. |
| **Fowler 2014** [5] | Sepsis/septic shock<br>$n$ = 26 | Two experimental groups: 1) low-dose ascorbic acid (Lo-AscA): 50 mg/kg/24 h ($n$ = 8); 2) high-dose ascorbic acid (Hi-AscA): 200 mg/kg/24 h ($n$ = 10). Ascorbic acid dosage divided into 4 equal doses and administered over 30 min every 6 h for 96 h in 50 mL of $D_5W$. | Improvement in SOFA score and inflammation biomarkers (C-reactive protein, procalcitonin, thrombomodulin). No clinical benefits but not powered to find any. |
| **Zabet 2016** [28] | ICU patients with septic shock<br>$n$ = 28 | 25 mg/kg ascorbic acid in 50 mL $D_5W$ every 6 h for 72 h administered as IV infusion over 30 min. | Reduced 28-d mortality. Reduction in dose and duration of norepinephrine administration. No effect on length of hospitalization. |
| | | **Dose <2 g/d** | |
| **Maderazo 1991**[48] | Blunt trauma<br>$n$ = 46 | Standard EN or oral intake + 200 mg vit C, increased to 500 mg + 50 mg α-tocopherol given as 2 h infusions from day 0 to 7. | Improvement of the polymorphonuclear locomotory abnormality. No effect on infectious complications. |
| **Preiser 2000** [49] | Mixed ICU<br>$n$ = 51 | Antioxidant-rich formula via EN (133 µg/100 mL vit A, 13 mg/100 mL vit C & 4.9 mg/100 mL vit E + free arginine (0.63 g/dL) administered continuously at 30 mL/h for day 0–1 and 60 mL/h for days 0–7. | Improvement in LDL resistance to oxidative stress. No difference on clinical outcomes. |
| **Crimi 2004** [23] | Mixed ICU<br>$n$ = 224 | Standard EN + enteral vit C 500 mg, vit E 400 IU, started within 72 h of admission for 10 d. | Reduction in 28-d mortality. Improved ventilator-free days. Improved LDL resistance to oxidative stress. No effect on hospital LOS, severity score, and incidence of MOF. |
| **Beale 2008** [27] | Septic patients<br>$n$ = 55 | Intestamin (300 µg selenium, zinc 20 mg, vit C 1500 mg, vit E 500 mg) within 24 h after enrollment starting at 20 mL/h and increasing to 25 kcal/kg, via nasogastric tube, for up to 10 d. From day 2 patients also received a complete EN formula according to the ICU's feeding regimen. Patients randomly assigned to Intestamin received immunonutrient-containing Reconvan. | Faster recovery of organ function, assessed by SOFA score. |
| **Schneider 2011** [25] | ICU patients with sepsis or SIRS<br>$n$ = 58 | Intestamin (300 µg selenium, zinc 20 mg, vit C 1500 mg, vit E 500 mg) delivered via duodenal tube and initiated within the first 48 h. No specific length of intervention mentioned. | No changes in clinical outcomes, including mortality, infectious complications, duration of mechanical ventilation, and hospital and ICU LOS. |
| **Nogueira 2013** [46] | ICU patients requiring EN (80% postoperative, 20% medical)<br>$n$ = 34 | Hospital routine EN + 10 000 IU retinol acetate, 400 mg vit E, 600 mg vit C administered enterally, initiated within 48 h of ICU admission. | No improvement on inflammation biomarkers and clinical outcomes. |
| **van Zanten 2014** [47] | Mixed ICU patients<br>$n$ = 301 | High-protein EN enriched with antioxidants (vitamin C 690 mg/L; vit 3 266 mg, selenium 285, zinc 30 mg), glutamine, ω-3, and fiber initiated within 48 h and continued during ICU stay for maximum 28 d. | No effects on infectious complications, duration of mechanical ventilation. Increased 6-mo mortality rate after intervention in medical subgroup. |

$D_5W$, dextrose 5% in water; EN, enteral nutrition; ICU, intensive care unit; ITT, intention to treat; IV, intravenous; LDL, low-density lipoprotein; LOS, length of stay; MOF, multiorgan failure; PN, parenteral nutrition; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment; TBSA, total body surface area; vit, vitamin.

Recent clinical trials have found very interesting results and restored a significant interest in this pharmaconutrition strategy, but the idea has been investigated for decades. In 2004 Crimi et al. [23] had found a significant reduction in 28-d mortality after vitamin C and vitamin E were supplemented in critically ill patients, with doses as low as 500 mg/d and 400 IU/d, respectively. Four years later, Collier et al. [24] conducted a before and after analysis and administered vitamin C and vitamin E 1000 IU three times a day, plus 200 μg of intravenous selenium [24]. The authors reported an association with reduced mortality, with an impressive odds ratio of 0.32 and reduced ICU and hospital length of stay (LOS). Many randomized controlled trials (RCTs) investigated similar doses and failed to find a positive effect on clinical outcomes in a heterogeneous population of critically ill patients [25–27]. The recent pharmacokinetic data supporting administration of higher dose could explain these negative findings. The timing of initiation might also influence the conclusions, considering the results found after prompt initiation of treatment by Collier et al.

Four trials administered a dose higher than 2 g/d, the theoretical minimum for repletion. The first RCT was conducted in early 2002 by Nathens et al. [45] in which 1000 mg of vitamin C and 1000 IU of α-tocopherol were given each hour by nasogastric or orogastric route, except for the first dose of vitamin C, which was given intravenously. After randomly allocating 595 critically ill patients in a surgical ICU, the authors found a significantly reduced incidence of multiple organ failure (relative risk [RR] 0.43; 0.19–0.96) as well as reduced duration of mechanical ventilation (weighted mean difference [WMD] −0.9; −0.6 with −1.2) and ICU LOS (WMD −1.2; −0.81 with −1.5). No difference was found regarding mortality. In 2008 Berger et al. [26] randomly assigned 200 patients to receive 2700 mg of ascorbate in cocktail with selenium (540 μg), zinc (60 mg), vitamin B (305 mg), and vitamin E (600 mg enteral and 12.8 mg parenteral) or a control. Apart from improvement on C-reactive protein, an inflammation biomarker, no effect was found on clinical benefits in the overall analysis. Only the trauma subgroup had a significant improvement in hospital LOS (26 ± 19 versus 39 ± 24; $P = 0.045$). The two recent RCTs, by Zabet et al. [28] and Fowler et al. [5], during which a high dose of intravenous vitamin C was administered as a monotherapy, have set the table for future investigation despite major methodological limitations. In the former, the 28 patients recruited did not initially grant sufficient power to evaluate 28-d mortality, but the authors found impressive results. In the placebo group, 9 (64%) of 14 patients died, and 2 (14%) of 14 died after receiving 100 mg/kg/24 h intravenously [28]. Considering the small sample size, the 50% absolute reduction of mortality is probably overestimated, but a signal seems to exist. The trial conducted by Fowler et al. [5] was designed as a phase 1 trial to evaluate safety of ascorbic acid administration with a small number of patients: 8 patients received a placebo, 8 patients received 50 mg/kg per 24 h for 96 h and 10 patients received 200 mg/kg per 24 h for the same duration. A significant reduction in the Sequential Organ Failure Assessment score, C-reactive protein, and procalcitonin was found. However, from these 10 patients, one was withdrawn by family members and transferred to another institution, and another was withdrawn after diagnosis of sepsis and hemophagocytic syndrome. The analysis was conducted per protocol and therefore did not include these patients, which would have counted for 20% of patients in an intention-to-treat analysis. Results should therefore be interpreted with caution.

Finally, an important and recently conducted study cited to support vitamin C benefits, by Marik et al. [29], also stimulated interest in the field. In a before and after study, the authors analyzed 47 septic patients before intervention and 47 patients after initiating the treatment. The treatment consisted in administration of vitamin C 1.5 g every 6 h for 4 d, thiamine 200 mg every 12 h for 4 d, and hydrocortisone 50 mg every 6 h for 7 d. Although predicted mortality was similar in both cohorts, the observed relative risk reduction was 87%. These impressive results must nonetheless be interpreted with caution, considering the small number of patients, the retrospective aspect, and the biological implausibility of such a strong treatment effect.

## Systematic review, meta-analysis, and current guidelines

A recent systematic review and meta-analysis conducted by our group aggregated the data of 11 RCTs (1322 patients) reporting clinical outcomes in a heterogeneous population of critically ill patients [30]. Overall analysis did not report any effect of vitamin C administration on mortality (RR 0.72, 0.43–1.20, $P = 0.21$), incidence of new infections, ICU and hospital LOS, or duration of mechanical ventilation. Interestingly, from the 11 included trials, nine administered vitamin C in an antioxidant cocktail, five administered parenteral supplementation, and seven investigated doses <1.5 g/d [30]. The only trials investigating high-dose intravenous ascorbic acid as a monotherapy were the trials by Zabet et al. [28] and Fowler et al. [5] presented earlier. When these two trials were aggregated, the RR was 0.21 (0.04–1.05), with a non-significant but interesting *P* value of 0.06. This systematic review and meta-analysis has many limitations, and clinicians should be careful when interpreting the results. Intravenous administration was mixed with oral supplementation and the trials covered a wide range of doses. Very few trials addressed intravenous high-dose regimens, and these results are therefore more applicable to low-dose vitamin C supplementation. A systematic review conducted on an insufficient dose of antibiotic for infection treatment would also have yielded negative results even if adequate regimen had been found effective. Current ASPEN guidelines do not separate vitamin C from other antioxidant strategies and recommend the administration of an antioxidant cocktail comprising vitamin C and vitamin E, in addition to selenium, zinc, and copper, when specialized nutrition therapy is started. A specification of particular benefit is mentioned regarding trauma, burn, and critical illness requiring mechanical ventilation.

## Subgroups of critically ill patients

The cardiac surgery population is an interesting group to investigate considering that the onset of systemic inflammation and ischemia reperfusion injuries are known to the investigators. Recent trials addressed how supplementing vitamin C, both before and after cardiopulmonary bypass, affected clinical outcomes, including incidence of atrial fibrillation because of its burden on duration of hospitalization and the need for anticoagulation [31]. Its incidence rate has been correlated to the extent of oxidative stress and is therefore of much interest in the investigation of antioxidants administration [32]. An old trial by Dingchao et al. [33] compared 45 patients receiving a dose as high as 250 mg/kg of intravenous ascorbic acid before cardiopulmonary bypass to 40 controls and found a reduction of hospital LOS, ICU LOS, and post-bypass defibrillation [33]. More recently, Papoulidis et al. [34] administered 2 g of vitamin C 3 h before the bypass to 85 patients and intravenous saline to 85 controls and found both a reduction of the time to sinus rhythm conversion and a reduction of ICU and hospital LOS. In recent trials a commonly used regimen of administration included 2 g on the day before the surgery and 1 g twice a day from postoperative days 1 to 5. Although two trials failed to identify benefits of this strategy in 185 [35] and 304 patients [36], respectively, a recent trial by Sadeghpour et al. [37] found a significant reduction of atrial fibrillation (RR 0.63; 0.48–0.84) and hospital LOS (10.17 ± 4.63 d versus 12 ± 4.51 d; $P = 0.01$). In the last 2 years, various meta-analyses confirmed reduction of atrial fibrillation after cardiac surgery both in overall analysis and trial sequential analysis, with secondary improvement in ICU and hospital LOS [38,39]. Interestingly, some subgroup analyses proposed that because of a variable intake, effect might be more pronounced in non-US countries [39].

In burn patients the iconic trial conducted by Tanaka et al. [40] in 2000 found reduced requirements of fluid repletion, an improved $PaO_2/FiO_2$ (PF) ratio, and reduced duration of mechanical ventilation after starting administration in the first 2 h of admission of a massive dose of ascorbic acid at 66 mg/kg per h, resulting in 110 g/d in an average 70-kg adult. However, even if this study claimed to be an RCT, the process of random allocation was predictable and therefore created a significant selection bias. More recent data issued from a retrospective analysis of patients receiving a similar administration strategy also found reduced fluid requirements by improved endothelial function, but the results are yet to be confirmed by stronger data [41]. Literature on this subject remains very scarce. A recent systematic review of literature concerning antioxidants in burn patients [42] reported only one RCT conducted in 32 children during which a cocktail of vitamin C, vitamin E, and zinc improved wound healing [43].

## Conclusions

Investigation regarding administration of vitamin C in the heterogeneous population hospitalized in the intensive care units has been recently invigorated by three small trials using pharmacologic dose of vitamin C [5,28,29]. Although still questionable because of bias and a small number of patients, the signal obtained prompts future investigation. The phase 2 trial conducted by Fowler et al. (NCT02106975) is expected to be published soon and will hopefully enlighten clinicians. Although the vitamin C deficiency often found in ICU patients clearly needs prompt supplementation, a recent systematic review and meta-analysis reported that small doses of oral vitamin C might not be the optimal strategy considering the absence of clinical impact [30]. In the specific population of cardiac surgery patients, trials have reported a reduction on the incidence of atrial fibrillation and the duration of hospitalization. Unfortunately, the transposition of these results to American populations is questionable because these positive results have not been reproduced. Future larger trials are required to support any therapy, but the low cost and positive safety profile can justify supplementation in the meantime. Finally, new emerging sciences, including metabolomics and proteomics, will allow a better understanding of biological effects of antioxidants administration [44].

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