European Review for Medical and Pharmacological Sciences 2019; 23: 7703-7712

Oxidative stress in critical care and vitamins supplement therapy: "a beneficial care enhancing"

C. ZANZA[1,2], J. THANGATHURAI[1], A. AUDO[4], H.A. MUIR[1], M. CANDELLI[2], G. PIGNATARO[2], D. THANGATHURAI[1], S. CICCHINELLI[2], F. RACCA[4], Y. LONGHITANO[1,3], F. FRANCESCHI[2]

[1]Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA
[2]University Hospital IRCCS-Fondazione Policlinico Gemelli, Rome, Italy
[3]S. Giovanni Battista Molinette Hospital, Turin, Italy
[4]SS. Antonio e Biagio Hospital, Alessandria, Italy

Abstract. – OBJECTIVE: Critical illnesses are a significant public health issue because of their high rate of mortality, the increasing use of the Intensive Care Units and the resulting healthcare cost that is about 80 billion of dollars per year. Their mortality is about 12% whereas sepsis mortality reaches 30-40%. The only instruments currently used against sepsis are early diagnosis and antibiotic therapies, but the mortality rate can also be decreased through an improvement of the patient's nutrition. The aim of this paper is to summarize the effects of vitamins A, B, C and E on the balance between pro-oxidants and anti-oxidants in the critical care setting to confirm "a beneficial care enhancing".

MATERIALS AND METHODS: The peer-reviewed articles analyzed were selected from PubMed databases using the keywords "critical care", "intensive care", "critical illness", "sepsis", "nutritional deficiency", "vitamins", "oxidative stress", "infection", and "surgery". Among the 654 papers identified, 160 articles were selected after title and abstract examination, removal of duplicates and of the studies on pediatric population. Finally, only the 92 articles relating to vitamins A, C, E and the B complex were analyzed.

RESULTS: The use of vitamins decreased morbidity and mortality in perioperative period and critically ill patients, especially in ICU. Among the most encouraging results, we found that the use of vitamins, both as monotherapy and in vitamins combinations, play a crucial role in the redox balance. Vitamins, especially vitamins A, C, E and the B complex, could help prevent oxidative damage through the breakdown of the oxidizing chemical chain reaction.

CONCLUSIONS: Even if the results of the studies are sometimes discordant or inconclusive, the current opinion is that the supplementation of one or more of these vitamins in critically ill patients may improve their clinical outcome, positively affecting the morbidity and the mortality. Further, randomized studies are required to deeply understand the potentiality of a vitamin supplementation therapy and develop homogeneous and standardized protocols to be adopted in every critical care scenario.

Key Words:
Critical care, Sepsis, Vitamins, Oxidative stress, Infection.

Introduction

Before introducing the "starring vitamins", we have preferred to summarize the principal critical care settings where the physicians can meet oxidative stress; concurrently, the aim of this review is to regroup the principal activity of some vitamins that are "a beneficial care enhancing" the human body during critical illness. Over the past years many studies on critical illnesses demonstrated an imbalance between prooxidant and antioxidant factors, resulting in oxidative stress [1,2].

Pathophysiology of the Reactive Species

The main prooxidant molecules are the Reactive Oxygen Species (ROS) and the Reactive Nitrogenous Species (RNS). ROS include superoxide anion ($\cdot O2^-$), hydroxyl radical ($\cdot OH$) and hydrogen peroxide (H_2O_2); RNS include nitric oxide ($NO\cdot$) and peroxynitrite ($ONOO^-$)[3,4]. These reactive species,

Corresponding Author: Christian Zanza, MD; e-mail: christian.zanza@gmail.com

also known as free radicals, contain an unpaired electron that makes them highly reactive with other molecules like proteins, lipids and DNA [5-7]. The cell reacts to the damage of these molecules by activating apoptosis and autophagy that lead to the death of the cell and consequently to tissue damage and organ dysfunction[8]. ROS and RNS are formed through many physiological processes, like cellular respiration, immune response, apoptosis, proliferation and gene expression[4,9-15]. ROS and RNS are produced by enzymes clusters such as nicotinamide adenine dinucleotide phosphate oxidase (NOX), xanthine oxidase (XO) and nitric oxide synthase (NOS)[16-18]. NOX is an enzymatic complex that can be found in the cellular membrane lipid double layer, in peroxisomes and inside mitochondria (Figure 1). It uses cytosolic oxygen (O_2) and nicotinamide adenine dinucleotide phosphate (NADPH) to produce hydrogen peroxide (H_2O_2), which damages lipidic membranes and the DNA[16]. Under physiological conditions the human redox network produces free radicals through endothelial nitrogenous oxide syntetase (eNOS)[18] that generates nitrogenous oxide (NO), which is involved in many physiological activities like neuronal transmission, vasodilatation and immunity[19-21]. During the infections, phagocytes release NO and produce peroxynitrite that can spontaneously decompose into hydroxyl radicals and nitrogen dioxide[19].

Natural Antioxidant Enzymatic Pathways

Antioxidants are substances that prevent the transfer of electrons from an organic molecule to another and to oxygen[22]. The main antioxidant enzymes of the human body are glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT) and thioredoxin (TRX). Reduced Glutathione (GSH) is the core molecule of an antioxidant system found in the cytoplasm and in the mitochondria; GPx produces glutathione disulfide (GSSH) and water through hydrogen peroxide. GSSH is reduced to GSH by the glutathione reductase (GR)[23] (Figure 1).

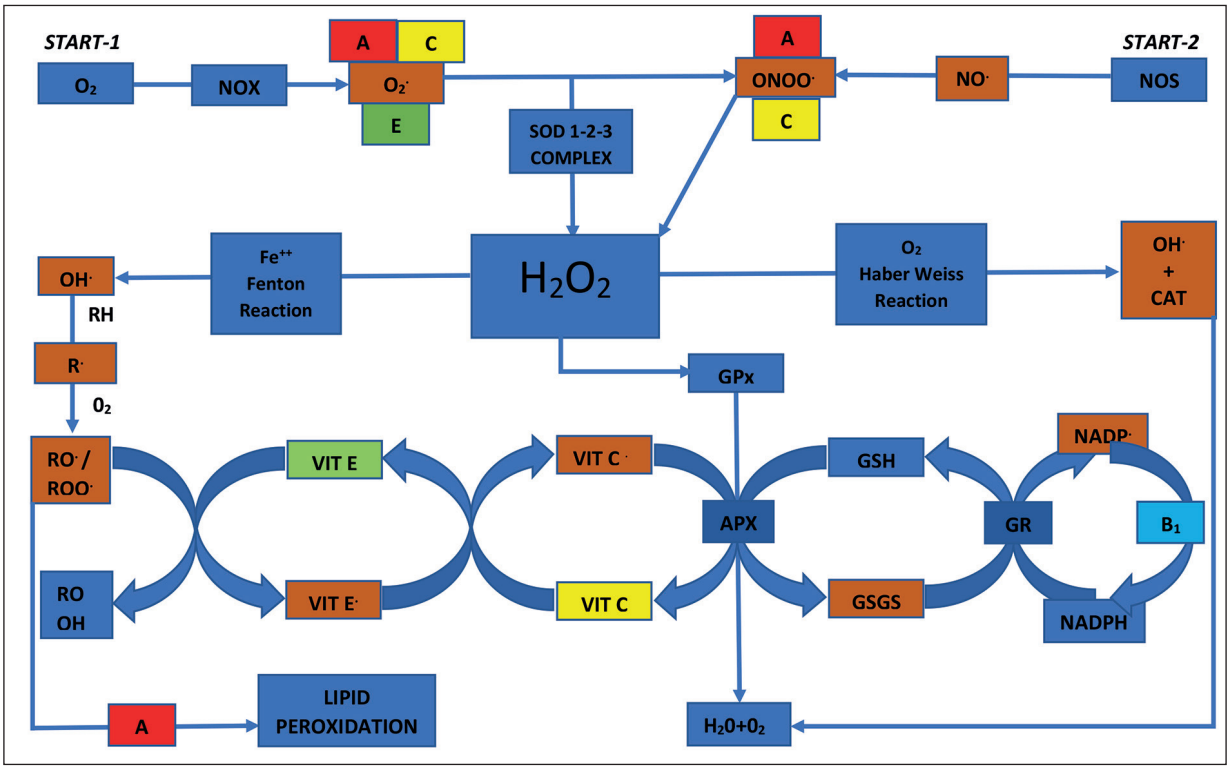

Figure 1. Vitamin human antioxidant network (*simplified scheme*). The brown boxes contain oxidizing compounds. Vitamins surround oxidizing compounds to deactivate them. CAT, catalase; Fe2+, iron(II); GPx, glutathione peroxidase; GR, glutathione reductase; GSH, reduced glutathione; GSSG, oxidized glutathione; H_2O, dihydrogen monoxide ("water"); H_2O_2, hydrogen peroxide; NADP, nicotinamide adenine dinucleotide phosphate; NADPH, reduced nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; NOS, nitric oxide synthase; NOX, nicotinamide adenine dinucleotide phosphate oxidase; O2-, superoxide; O, hydroxyl radical; ONOO, peroxynitrite; R, alkyl radical; RH, radical-hydrogen; RO, alkoxy radical; ROO, peroxy radical; ROOH, hydroperoxide; SOD, superoxide dismutase; Vit A, vitamin A; Vit C, vitamin C; Vit C, Vitamin C radical; Vit E, vitamin E; Vit E , Vitamin E radical; Vit B_1, vitamin B or TTP.

SODs are metalloproteins that catalyze the splitting of superoxide to hydrogen peroxide and oxygen. They can be found in all living cells with 3 subtypes: subtype 1 is cytosol-copper-zinc (Cu-Zn) dependent; subtype 2 is mitochondrial-manganese (Mn) dependent; subtype 3 is extracellular-Cu-Zn dependent[24]. The CAT is a cluster of enzymes in the membrane double layer that converts hydrogen peroxide in oxygen and[25]. The TRX catalyzes reactions from hydrogen peroxide into water and oxidized TRX which is reduced into TRX by a NADPH-dependent reductase[26,27]. Reduced TRX can reduce ascorbate-using selenium as a cofactor[28].

Oxidative Stress in the Critical Care Setting and Measuring Methods

Since 1990 many studies in intensive care medicine have described the increase of ROS and RSN and the concomitant decrease of the antioxidants in sepsis, acute respiratory distress syndrome (ARDS), multiorgan dysfunction syndrome (MODS), diaphragm fatigue, acute heart failure (AHF) and other conditions related to ischemia-reperfusion injury syndrome.

Sepsis is the major cause of death in Intensive Care Units (ICU)[29,30] and part of its pathological core is the imbalance between prooxidant and antioxidant factors. This imbalance depends on the overregulation of some enzymes, like NOX, XO and eNOS[7]. Oxidative stress triggers an inflammatory response through the activation of the NF-κb (Nuclear Factor-κb)[31-34] and the increase of circulating proinflammatory cytokines[35-37]. Those cytokines recall leukocytes in order to maintain an inflammatory state and phagocytize the cells with a peroxided membrane[38]. Besides, oxidative injuries are responsible of the mitochondrial membrane peroxidation that causes irreversible alteration of the Krebs' Cycle, leading to MODS[39,40]. The concentration of ROS and RSN (mainly peroxynitrite) also increases during a strong immune response against microorganisms[10,11] and during tissue hypoperfusion, because of the decreased washout of these molecules. In normal conditions the glutathione system counterbalances the excess of radicals but when it is completely consumed and no longer replaced, radicals accumulate and cells are damaged. On top of that, blood vessels become hyporeactive to catecholamines and more permeable, thus leading to septic shock, despite adequate fluid resuscitation[41].

Acute respiratory distress syndrome (ARDS) is a massive uncontrolled inflammation mediated by neutrophil granulocytes that infiltrate the alveolus and produce ROS and RNS[42]. Particularly, peroxynitrite induces the nitration of the surfactant proteins leading to lung epithelium alterations, causing oedema[43]. When O_2 is administered to patients with ARDS, the production of ROS and RSN is enhanced and is not counterbalanced by natural antioxidant systems, such as the glutathione, which is lacking in patients affected by this condition[44]. Many investigations show that patients with ARDS have increased levels of prooxidant molecules in the bronchoalveolar lavage fluid and in the plasma[45]. The hydrogen peroxide concentration is increased in the exhaled breath as well[44].

Ischemia-reperfusion injury syndrome is a very common complication in vasculopathy and in heart, lung and kidney transplantation[46]. During ischemia, hypoxia compromises the mitochondrial ATP genesis and switches the metabolism from aerobic to anaerobic, leading to cellular death and subsequent tissue damage due to hyperlactacidemia with acidosis, intracellular calcium overload, mitochondrial changes and cytokine excess[47]. A prolonged anaerobic metabolism and the aerobic metabolism restoration can lead to negative consequences that define the ischemia-reperfusion injury syndrome[46]. The most important radical involved is super oxide (SO), which is formed by two main pathways:

1. Xanthine dehydrogenase (XD), that is constitutively present in the endothelium and is converted into xanthine oxidase (XO) in case of hypoxia. XO catalyzes the production of superoxide from hypoxanthine – largely synthesized during ischemia – and the molecular oxygen provided by the reperfusion[48];
2. NADPH-oxidase (NOX) and eNOS catalyze the production of both SO and NO. Low concentrations of NO have a positive effect on the tissue perfusion as they cause vasodilatation and prevent leukocytes and platelets adhesion on the endothelium; instead, high concentrations of NO react with superoxide, producing peroxynitrite radicals. Furthermore, SO can induce eNOS uncoupling with additional production of SO instead of NO: this leads to an endothelial dysfunction and subsequent extravasation and activation of leukocytes, with ROS production and inflammatory response[49]. Moreover, the leukocytes accumulation in the microvasculature creates obstruction thereby avoiding reperfusion[50].

Oxidative stress measuring methods are useful to reveal a prooxidant or an antioxidant status. The direct determination of ROS and RNS is almost impossible due to their ultra-short half-life that is why it is more common to use indirect methods[51-53]. The antioxidant status is assessed by measuring the consumption of antioxidant compounds and observing the kinetics of the involved enzymes. For instance, the Total Antioxidant Capacity (TAC) is an *in-vitro* method that measures the variation of concentration of a biological antioxidant compound when added in a solution containing free radicals[54]. However, the limit of this technique is not to consider the production of prooxidants that takes place *in vivo*. The main method used in the clinical practice to detect a prooxidant status is the quantification of the stable products of lipid peroxidation, like malondialdehyde and isoprostanes, and those of DNA oxidation like 8-oxo-2'-deoxyguanosine[52,53]. But also this method shows some limits: most of the markers are evaluated in the plasma and many studies demonstrate that there is a poor correlation between their plasmatic and the tissue concentration[52].

Materials and Methods

Original articles published in peer-reviewed journals, with no limitations on year of publication, were electronically collected in Medline and PubMed databases by matching the following keywords: "critical care", "intensive care", "critical illness", "sepsis", "nutritional deficiency", "vitamins", "oxidative stress", "infection", and "surgery". This led to the selection of 553 articles. In order to avoid omissions, all biographies were analyzed one by one and double-checked. In this way, further 101 articles were found, with 654 papers in total. An initial title examination determined the exclusion of 420 of them. Of the remaining 234, only 160 were finally selected, after the examination of abstracts and the removal of duplicate results and of papers regarding pediatric intensive care. Of these 160 papers, solely 92 focusing on the main antioxidant vitamins (vitamin A, C, E and a vitamin of the B complex) were considered in this review.

Discussion

The antioxidant network is formed by many different molecules like vitamins, endogenous antioxidant compounds – such as ubiquinone, α-lipoic acid, bilirubin, serum albumin, ferritin, metallothionein, L-carnitine, uric acid, glutathione, melatonin – and micronutrients like zinc, selenium, iron, manganese and copper. These antioxidants trap the ionized metals in inactive complexes, scavenge or quench free radicals, interrupt the free radical chemical reaction and repair damaged molecules.

Vitamin A (all-trans-retinol) is a fat-soluble acid molecule that belongs to the group of retinoids together with its natural and synthetic derivatives[55]. Vitamin A cannot be synthesized by vertebrates and, therefore, it must be introduced with the diet. It can be found in food both as preformed vitamin A (e.g. retinyl esters and retinol) and as provitamin A. The term "provitamin A" refers to some carotenoids, the most important of which is the β-carotene that is converted in the active form in the intestinal mucosa or in peripheral cells like adipocytes and macrophages[56,57]. About 60% of vitamin A is absorbed in the small intestine and is then transferred to the liver, where it can be stored or excreted in the bile[58]. It is essential for many physiological functions like vision, cellular proliferation and differentiation, immune function, reproduction, gene transcription and antioxidant activity[59]. β-carotene has more antioxidant properties than retinol, while retinol enhances the antioxidant effect of ascorbic acid[60]. β-carotene is able to scavenge the hydroxyl radical, the superoxide anion and the peroxynitrite and to prevent these radicals from binding with transition metals[61]; moreover, β-carotene and retinol completely block the lipid peroxidation. In clinical practices vitamin A cannot be directly measured, that is why it is needed to dose serum β-carotene and plasmatic retinol. The normal range is 0.74-3.72 μmol/L for the former and > 0.70 μmol/L for the latter[58]. Hypervitaminosis A can occur after an acute intake (> 0.2 g) or a chronic intake (> 0.01 g/day), while deficiency occurs, especially in critical illness, because of poor intake, increased use or massive excretion of the vitamin or in case of acute renal failure zinc deficiency[62]. Zinc deficiency inhibits the production of retinol binding protein (RBP) in the liver and consequently the plasmatic retinol concentration decreases. Moreover, zinc is a cofactor of the enzyme photoreceptor retinol dehydrogenase, whose dysfunction leads to night blindness[62]. The importance of Zn is emphasized in the research of Matos et al[63], in which two groups of patients received vitamin A supplements before cardiac surgery. The first

group had normal plasmatic zinc levels and the second one suffered from zinc deficiency. The study demonstrated that the levels of prooxidants were lower in the group with a normal zinc level. During a critical illness, especially in acute infections, the metabolism of vitamin A could be altered with the excretion of significant amounts of retinol and RBP in the urine[64]. Because of this alteration the availability of vitamin A and its derivatives decreases. Stephensen et al[65] showed that about 40% of patients with an acute infection excreted half of the recommended daily dietary intake of vitamin A with the urine, whereas only traces were found in the urine of healthy people. Doise et al[66] and Ribero et al[67] observed the antioxidant capacity of retinol and β-carotene in patients with sepsis and septic shock compared to healthy patients, concluding that retinol and β-carotene levels were significantly lower in the first group than in the control group. Also Goode et al[40] showed the decrease in antioxidant levels and the increase of lipid peroxidation in patients with septic shock and MODS. Metnitz et al[42] evaluated the levels of retinol, β-Carotene and ROS in a very small number of patients with ARDS. In the ARDS group, the plasmatic concentrations of retinol and β-carotene at day 0 of the diagnosis were 0.77 and 0.08 μmol/L, respectively, while they were 1.19 and 1.22 μmol/L (p <.001) in the healthy controls. Retinol level normalized in 6 hours, whereas β-carotene plasmatic level remained low in patients affected by ARDS. Many other previous studies showed that in critical ill patients both vitamin A and β-carotene should be supplemented: in particular, since the β-carotene is a more potent antioxidant, one of these researches suggests that β-carotene should be supplemented in case of a vitamin A deficiency[68,69]. Moreover, β-carotene is safer than retinol, as retinol can quickly accumulate during supplementation. Matos et al[63] investigated the role of vitamin A in 90 patients with a primary diagnosis of angina pectoris and undergoing a coronary bypass grafting surgery. Patients were assigned to a control group, receiving a standard diet, or to an intervention group, which received a daily supplementation of 5,000 IU of vitamin A as retinol palmitate. A reduction in the mortality (3.3% *vs.* 8.3%) and in the ICU length of stay (4.6 *vs.* 8.5 days) was reported in the intervention group, while no significant differences between the two groups were reported in terms of invasive support ventilation. Corcoran et al[70] evaluated the association between serum β- and α-carotene concentrations and mortality of 67 patients, performing daily measurements from admission in ICU until discharge or death. They concluded that there is no correlation between the serum β- and α-carotene levels and mortality (p = .5).

Vitamin C or ascorbic acid is a natural, water-soluble antioxidant and cofactor of many enzymatic reactions in some crucial metabolic pathways like those of iron, folic acid, collagen, cortisol, catecholamines and carnitine; moreover, it plays an important role in several immune system pathways[71]. Its absorption takes place mostly in the small intestine, while It is mostly excreted through urines. The normal plasmatic concentration is > 23 μmol/L[71]. Vitamin C deficiency occurs in conditions of insufficient intake, increased loss or acute consumption because of oxidative stress. Low plasma concentrations of this vitamin are associated with inflammation, organ failure and mortality[72]. The ascorbic acid limits the production of ROS and RSN both directly and indirectly. The direct limitation depends on the inhibition of nitric oxides (NOx) and of inducible nitric oxide synthase (iNOS) which prevents the formation of superoxide, hydroxyl, peroxyl and nitroxide radicals; as an alternative, the ascorbic acid can act as a substrate for ascorbate peroxidase, which converts the hydrogen peroxide into water. The production of free radicals can be indirectly inhibited through the restoration of antioxidant systems such as the production of the α-tocopherol from α-tocopheroxyl radical or of glutathione from the glutathione disulfide (Figure 1)[71]. Furthermore, vitamin C is a very strong protector against the adhesion of phagocytes to the endothelium[73]. Several investigators observed low circulating levels of vitamin C in critically ill patients, particularly in sepsis and after cardiac arrest. Moreover, critically ill patients show low vitamin C concentration in plasma (< 10 μmol/L) and urines, despite intravenous (IV) supplementation according to daily-recommended dose[74]. These data suggest that a dose of 3 g/day – which is 30 times higher than the recommended daily dose – for several days is required to obtain benefits in critically ill patients[72]. Sadeghpour et al[75] carried out a randomized case *vs.* control trial, dividing 290 patients in two groups; the case group received 2 grams of vitamin C one hour before a cardiac surgery and 1 gram/day for 4 days after the surgery. This report did not show any differences between the two groups. Fowler et al[76] studied the effect of the administration of low doses (50 mg/kg/24 h) or high doses (200 mg/

kg/24 h) of ascorbic acid *vs.* placebo in patients with sepsis. At the time of admission, the plasmatic levels of the ascorbic acid were subnormal (normal range 50-70 μM) in all the septic patients with no significant differences among the three groups. The Sequential Organ Failure Assessment (SOFA) score improved in patients receiving ascorbate; the 28-day mortality rate was of 38.1% for the low-dose group, 50.6% for the high-dose group and of 65.1% for the placebo group; no differences were found for the ICU-LOS and for the ventilator-free days among the three groups.

Vitamin E identifies a family of lipid soluble compounds made up of four tocopherols and four tocotrienols. The α-tocopherol is the most studied member of this family since the human body uses subtle regulatory mechanisms to retain α-tocopherol and excrete non-α-tocopherol forms[77]. Vitamin E is involved in antioxidant activities, in the stabilization of cellular membranes and in the empowerment of the immune response during infections[78]. Being a lipid, it follows the lipid metabolism pathway: it is embedded in chylomicrons after enteral adsorption and then it binds an alpha-tocopherol transfer protein and is secreted in the bloodstream[78]. As an antioxidant, it prevents cell damage due to superoxide and hydroxyl radicals and protects the cell against lipid peroxidation and breaking radical chain reactions[78]. In healthy subjects with a normal lipid profile, vitamin E should be higher than 11.5 μmol/L (4.95 mg/mL)[77]. Alterations in the plasmatic concentration of cholesterol and triglycerides can influence the plasmatic tocopherol values that is why some authors suggest that the best method to determine the real α-tocopherol levels is to measure its concentration inside red blood cells (RBC)[79]. The plasmatic range in critical diseases is unclear, but many investigators have assessed a decrease of the α-tocopherol levels in critically ill patients[80-82]. However, Vasilaki et al[83] demonstrated that RBC α-tocopherol concentration corrected for the hemoglobin level is the same of healthy subjects. Corcoran et al[70] performed daily measurements of α-tocopherol levels from the time of ICU admission until the discharge and did not find any correlation between them and the mortality (p = .23). In most studies about the use of vitamin E in critical care settings it is not used as monotherapy but in combination with other antioxidant compounds; moreover, there are few studies about its use in the preoperative period. Bartels et al[81] administered an IV solution, containing 1,800 IU of vitamin E, in 68 patients the day before elective partial liver resection; Lassnigg et al[80] administered 4 IV doses of 270 mg of vitamin E in the time between 16 hours before and 48 hours after elective cardiac surgery. A significant reduction of the ICU-LOS was observed in the first investigation but not in the second one; no difference was observed in SAPS II (Simplified Acute Physiology Score II), in H-LOS or in 30-day mortality in any of the studies. In patients with ARDS, the administration of 1 gram/day of vitamin E for 5 days slightly increased its serum level; patients with sepsis have a higher production of superoxide and a decrease in the vitamin E/lipids ratio compared to non-septic subjects[82].

Vitamin B_1, also known as thiamine, is a water-soluble vitamin that is very important for carbohydrate metabolism. It serves as a junction between glycolysis and Krebs' Cycle because it is the cofactor of pyruvate dehydrogenase, the enzyme responsible for the conversion of pyruvate to acetyl-coenzyme A (acetyl-CoA)[84]. Thiamine also plays a role in the metabolism of branched-chain amino acids and is a critical component of the pentose phosphate pathway, which is essential for the generation of NADPH and hence for the glutathione cycling[84] (Figure 1). Thiamine is passively absorbed in the small intestine at high concentrations or actively absorbed through thiamine transporter proteins at lower concentrations[84]. Approximately 90% of the thiamine contained in the blood is in the erythrocytes; of the outstanding part is contained in serum thiamine where it is bounded to proteins, mainly albumin. A specific binding protein called thiamine-binding protein (TBP) has been identified in the serum of rats in which it is supposed to be a hormone-regulated carrier protein that is important for the distribution of this vitamin in the tissues; anyway a human counterpart of this binding protein has not been identified yet[85]. The recommended daily intake of thiamine is between 0.9 and 1.4 mg, and a human adult can store about 30 mg of thiamine in the muscles, liver, and kidneys. The thiamine reserves can be depleted in about 18 days after the cessation of the intake[84]. A thiamine deficiency syndrome, the beri beri, shows some similarities with the sepsis, including peripheral vasodilation, cardiac dysfunction and elevated lactate levels in the blood[86]. Thiamine deficiency is not rare in critically ill populations and may be associated with increased mortality[86], therefore, the supplementation may mitigate organ

dysfunction[87]. Thiamine supplementation does not seem to be associated with significant adverse effects, even at high doses[87]. In a research in mice, the prophylactic administration of thiamine before the induction of a cardiac arrest improved the histologic signs and the neurologic outcomes[87]. There is little evidence to support or reject the supplementation of thiamine in the treatment and prevention of sepsis and septic shock. A retrospective investigation by Marik et al[88] on the use of vitamin C with thiamine and hydrocortisone for the treatment of sepsis and septic shock showed a significant difference in the mortality between the group of treated patients (n=47) and the control group (n=47), that was higher in the second one. This suggests that the intervention may reduce mortality in severe sepsis and septic shock. Donnino et al[87] observed no differences in the lactate levels, in the severity of illness or in the mortality rate between the thiamine treated group (n=43) and the control group (n=45). However, a subpopulation of patients showing a baseline thiamine deficiency displayed a significant reduction in the lactate levels after 24 hours. A post-hoc analysis by Moskowitz et al[89] aimed at identifying whether thiamine supplementation reduces the severity of the renal injury in the septic shock. A significant difference was detected for the requirement of renal replacement therapy between the control and the intervention group ($p=0.04$), thus indicating that supplementation of thiamine may reduce the risk of sepsis associated kidney injury. However, no difference was observed between the groups for in-hospital mortality ($p=0.45$).

Vitamin D is included among the liposoluble vitamins. The active forms in human body are the D_2-ergocalciferol and D_3-colecalciferol. They are important for calcium and phosphates balance that influences the bone metabolism and the immune system function. Vitamin D has anti-inflammatory, anti-neoplastic properties and prevents depression[90]. The important role of the vitamin D metabolism has been deeply investigated in the critical care and its deficiency has been found to be a strong predictor of MOF, sepsis and mortality[91,92]. However, since only one study has investigated the role of vitamin D as an antioxidant compound, it has not been considered in this review. Iqbal et al[90] analyzed the antioxidant role of this vitamin and concluded that it has an antioxidant property in mice with alloxan-induced diabetes, in which antioxidant levels are increased and prooxidant levels decreased.

Conclusions

Currently early diagnosis and antibiotic treatment are the most important and, sometimes, the only weapons that can be used against critical illnesses like sepsis, acute respiratory distress syndrome and ischemia-reperfusion syndrome. Since all these conditions are associated with impairment between the prooxidant and the antioxidant status, great interest is addressed towards antioxidant vitamins, like vitamin A, B_1, C and E. Many studies proved that the supplementation of a single class of these vitamins causes a decrease in the mortality and morbidity in critically ill patients. When used in combination, their benefit seems to be exponential Data about the benefits of vitamin B_1 supplementation are discordant as few reports suggest that it would have an impact on morbidity but not on the mortality; an exception is given by Marik et al[88] that highlighted a reduction in the mortality when the thiamine is administered together with corticosteroids.

Some studies have shown results in favor of a supplementation of thiamine in refeeding syndrome, probably connected to its crucial role in glucose metabolism. Since these studies are not numerically strong, further, large, randomized researches are needed to confirm these data. Even if the results of the investigations are sometimes discordant or inconclusive, the current opinion is that the supplementation of one or more of these vitamins in critically ill patients may improve their clinical outcome, positively affecting the morbidity and the mortality. Further, randomized trials are required to deeply understand the potentiality of a vitamin supplementation therapy and develop homogeneous and standardized protocols to be adopted in every critical care scenario.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Pisoschi AM, Pop A. The role of antioxidants in the chemistry of oxidative stress: a review. Eur J Med Chem 2015; 97: 55-74.
2) Bernal ME, Varon J, Acosta P, Montagnier L. Oxidative stress in critical care medicine. Int J Clin Pract 2010; 64: 1480-1488.
3) Betteridge DJ. What is oxidative stress? Metabolism 2000; 49: 3-8.

4) Thannickal VJ, Fanburg BL. Reactive oxygen species in cell signaling. Am J Physiol Lung Cell Mol Physiol 2000; 279: L1005-1028.
5) Gebicki JM. Oxidative stress, free radicals and protein peroxides. Arch Biochem Biophys 2016; 595: 33-39.
6) Ramana KV, Srivastava S, Singhal SS. Lipid peroxidation products in human health and disease 2016. Oxid Med Cell Longe 2017; 2017: 2163285.
7) Dizdaroglu M, Jaruga P. Mechanisms of free radical-induced damage to DNA. Free Radic Res 2012; 46: 382-419.
8) Kaminskyy VO, Zhivotovsky B. Free radicals in cross talk between autophagy and apoptosis. Antioxid Redox Signal 2014; 21: 86-102.
9) D'Autréaux B, Toledano MB. ROS as signaling molecules: mechanisms that generate specificity in ROS homeostasis. Nat Rev Mol Cell Biol 2007; 8: 813-824.
10) Knight J. Review: free radicals, antioxidants, and the immune system. Ann Clin Lab Sci 2000; 30: 145-158.
11) Yang Y, Bazhin AV, Werner J, Karakhanova S. Reactive oxygen species in the immune system. Int Rev Immunol 2013; 32: 249-270.
12) Burdon RH, Rice-Evans C. Free radicals and the regulation of mammalian cell proliferation. Free Radic Res Commun 1989; 6: 345-358.
13) Ito F, Yamada Y, Shigemitsu A, Akinishi M, Kaniwa H, Miyake R, Yamanaka S, Kobayashi H. Role of oxidative stress in epigenetic modification in endometriosis. Reprod Sci 2017; 24: 1493-1502.
14) Martin LD, Krunkosky TM, Voynow JA, Adler KB. The role of reactive oxygen and nitrogen species in airway epithelial gene expression. Environ Health Perspect 1998; 106 Suppl 5: 1197-1203.
15) Greiber S, Müller B, Daemisch P, Pavenstädt H. Reactive oxygen species alter gene expression in podocytes: induction of granulocyte macrophage-colony-stimulating factor. J Am Soc Nephrol 2002; 13: 86-95.
16) Chuong Nguyen MV, Lardy B, Paclet MH, Rousset F, Berthier S, Baillet A, Grange L, Gaudin P, Morel F. NADPH oxidases, nox: new isoenzymes family. Med Sci (Paris) 2015; 31: 43-52.
17) Battelli MG, Polito L, Bortolotti M, Bolognesi A. Xanthine oxidoreductase-derived reactive species: physiological and pathological effects. Oxid Med Cell Longev 2016; 2016: 3527579.
18) Hancock JT, Neill SJ. Nitric oxide: its generation and interactions with other reactive signaling compounds. Plants (Basel) 2019; 8(2). pii: E41.
19) Bogdan C. Nitric oxide and the immune response. Nat Immunol 2001; 2: 907-916.
20) Steinert JR, Chernova T, Forsythe ID. Nitric oxide signaling in brain function, dysfunction, and dementia. Neuroscientist 2010; 16: 435-452.
21) Bohlen HG. Nitric oxide and the cardiovascular system. Compr Physiol 2015; 5: 808-823.
22) Yang CS, Ho CT, Zhang J, Wan X, Zhang K, Lim J1. Antioxidants: differing meanings in food science and health science. J Agric Food Chem 2018; 66: 3063-3068.
23) Brigelius-Flohé R, Maiorino M. Glutathione peroxidases. Biochim Biophys Acta 2013; 1830: 3289-3303.
24) Sheng Y, Abreu IA, Cabelli DE, Maroney MJ, Miller AF, Teixeira M, Valentine JS. Superoxide dismutases and superoxide reductases. Chem Rev 2014; 114: 3854-3918.
25) Glorieux C, Zamocky M, Sandoval JM, Verrax J, Calderon PB. Regulation of catalase expression in healthy and cancerous cells. Free Radic Biol Med 2015; 87: 84-97.
26) Léveillard T, Aït-Ali N. Cell signaling with extracellular thioredoxin and thioredoxin-like proteins: insight into their mechanisms of action. Oxid Med Cell Longev 2017; 2017: 8475125.
27) Mustacich D, Powis G. Thioredoxin reductase. Biochem J 2000; 346: 1-8.
28) Sofo A, Scopa A, Nuzzaci M, Vitti A. Ascorbate peroxidase and catalase activities and their genetic regulation in plants subjected to drought and salinity stresses. Int J Mol Sci 2015; 16: 13561-13578.
29) Winters BD, Eberlein M, Leung J, Needham DM, Pronovost PJ, Sevransky JE. Long-term mortality and quality of life in sepsis: a systematic review. Crit Care Med 2010; 38: 1276-1283.
30) Herring AA, Ginde AA, Fahimi J, Alter HJ, Maselli JH, Espinola JA, Sullivan AF, Camargo CA Jr. Increasing critical care admissions from U.S. emergency departments, 2001-2009. Crit Care Med 2013; 41: 1197-1204.
31) Tóbon-Velasco JC, Cuevas E, Torres-Ramos MA. Receptor for AGEs (RAGE) as mediator of NF-kB pathway activation in neuroinflammation and oxidative stress. CNS Neurol Disord Drug Targets 2014; 13: 1615-1626.
32) Jin H, Wang Y, Wang D, Zhang L. Effects of Qingshen granules on the oxidative stress-NF/kB signal pathway in unilateral ureteral obstruction rats. Evid Based Complement Alternat Med 2018; 2018: 4761925.
33) Turillazzi E, Neri M, Cerretani D, Cantatore S, Frati P, Moltoni L, Busardò F, Pomara C, Riezzo I, Fineschi V. Lipid peroxidation and apoptotic response in rat brain areas induced by long-term administration of nandrolone: the mutual crosstalk between ROS and NF-kB. J Cell Mol Med 2016; 20: 601-612.
34) Moldogazieva NT, Mokhosoev IM, Feldman NB, Lutsenko SV. ROS and RNS signalling: adaptive redox switches through oxidative/nitrosative protein modifications. Free Radic Res 2018; 52: 507-543.
35) Prasad KN. Oxidative stress and pro-inflammatory cytokines may act as one of the signals for regulating microRNAs expression in Alzheimer's disease. Mech Ageing Dev 2017; 162: 63-71.
36) Elmarakby AA, Sullivan JC. Relationship between oxidative stress and inflammatory cytokines in diabetic nephropathy. Cardiovasc Ther 2012; 30: 49-59.

37) Pereda J, Sabater L, Aparisi L, Escobar J, Sandoval J, Viña J, López-Rodas G, Sastre J. Interaction between cytokines and oxidative stress in acute pancreatitis. Curr Med Chem 2006; 13: 2775-2787.

38) Galley HF. Oxydative stress and mitochondrial dysfunction in sepsis. Br J Anaesth 2011; 107: 57-64.

39) Crouser ED. Mitochondrial dysfunction in septic shock and multiple organ dysfunction syndrome. Mitochondrion 2004; 4: 729-741.

40) Goode HF, Cowley HC, Walker BE, Howdle PD, Webster NR. Decreased antioxidant status and increased lipid peroxidation in patients with septic shock and secondary organ dysfunction. Crit Care Med 1995; 23: 646-651.

41) De Backer D, Orbegozo Cortes D, Donadello K, Vincent JL. Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock. Virulence 2014; 5: 73-79.

42) Metnitz PG, Bartens C, Fischer M, Fridrich P, Steltzer H, Druml W. Antioxidant status in patients with acute respiratory distress syndrome. Int. Care Med 1999; 25: 180-185.

43) Zhu S, Ware LB, Geiser T, Matthay MA, Matalon S. Increased levels of nitrate and surfactant protein a nitration in the pulmonary edema fluid of patients with acute lung injury. Am J Respir Crit Care Med 2001; 163: 166-172.

44) Kietzmann D, Kahl R, Müller M, Burchardi H, Kettler D. Hydrogen peroxide in expired breath condensate of patients with acute respiratory failure and with ARDS. Intensive Care Med 1993; 19: 78-81.

45) Lenz AG, Jorens PG, Meyer B, De Backer W, Van Overveld F, Bossaert L, MaierKL. Oxidatively modified proteins in bronchoalveolar lavage fluid of patients with ARDS and patients at-risk for ARDS. Eur Respir J 1999; 13: 169-174.

46) Kalogeris T, Baines CP, Krenz M, Korthuis RJ. Ischemia/reperfusion. Compr Physiol 2016; 7: 113-170.

47) Kalogeris T, Baines CP, Krenz M, Korthuis RJ. Cell biology of ischemia/reperfusion injury. Int Rev Cell Mol Biol 2012; 298: 229-317.

48) Nishino T. The conversion of xanthine dehydrogenase to xanthine oxidase and the role of the enzyme in reperfusion injury. J Biochem 1994; 116: 1-6.

49) Förstermann U, Sessa WC. Nitric oxide synthases: regulation and function. Eur Heart J 2012; 33: 829-837.

50) Coito AJ. Leukocyte transmigration across endothelial and extracellular matrix protein barriers in liver ischemia/reperfusion injury. Curr Opin Organ Transplant 2011; 16: 34-40.

51) Lemineur T, Deby-Dupont G, Preiser JC. Biomarkers of oxidative stress in critically ill patients: what should be measured, when and how? Curr Opin Clin Nutr Metab Care 2006; 9: 704-710.

52) Bar-Or D, Bar-Or R, Rael LT, Brody EN. Oxidative stress in severe acute illness. Redox Biol 2015; 4: 340-345.

53) Grune T, Berger MM. Markers of oxidative stress in ICU clinical settings: present and future. Curr Opin Clin Nutr Metab Care 2007; 10: 712-717.

54) Miftode AM, Stefanache A, Spac AF, Miftode RF, Miron A, Dorneanu V. In vitro measurement of total antioxidant capacity of crataegus macracantha lodd leaves. Rev Med Chir Soc Med Nat 2016; 120: 452-456.

55) McLaren DS, Kraemer K. Vitamin A in nature. World Rev. Nutr Diet 2012; 103: 7-17.

56) Lobo GP, Amengual J, Li HNM, Golczak M, Bonet M, Palczewski K, von Lintig J. β,β-carotene decreases peroxisome proliferator receptor γ activity and reduces lipid storage capacity of adipocytes in a β,β-carotene oxygenase 1-dependent manner. J Biol Chem 2010; 285: 27891-27899.

57) Zolberg Relevy N, Bechor S, Harari A, Ben-Amotz A, Kamari Y, Harats D, Shaish A. The inhibition of macrophage foam cell formation by 9-cis β-carotene is driven by BCMO1 activity. PLoS One 2015; 1: e0115272.

58) D'Ambrosio DN, Clugston RD, Blaner WS. Vitamin A metabolism: an update. Nutrients 2011; 3: 63-103.

59) Tanumihardjo SA. Vitamin A: biomarkers of nutrition for development. Am J Clin Nutr 2011; 94: 658S-665S.

60) Bouvier D, Sapin V, Bonnard-Gougeon M, Marceau G. Retinol potentiates the inhibitory effect of ascorbic acid on uric acid assay. Clin Chem Lab Med 2010; 48: 693-695.

61) Sies H, Stahl W. Vitamins E and C, beta-carotene, and other carotenoids as antioxidants. Am J Clin Nutr 1995; 62: 1315S-1321S.

62) Christian P, West KP. Interactions between zinc and vitamin A: an update. Am J Clin Nutr 1998; 68: 435S-441S.

63) Matos AC, Souza GG, Moreira V, Ramalho A. Effect of vitamin A supplementation on clinical evolution in patients undergoing coronary artery bypass grafting, according serum levels of zinc. Nutr Hosp 2012; 27: 1981-1986.

64) Gavrilov V, Weksler N, Ahmed A, Gorodischer R. Urinary excretion of vitamin A in critically ill patients complicated with acute renal failure. Ren Fail 2004; 26: 589-590.

65) Stephensen CB, Alvarez JO, Kohatsu J, Hardmeier R, Kennedy JI Jr, Gammon RB Jr. Vitamin A is excreted in the urine during acute infection. Am J Clin Nutr 1994; 60: 388-392.

66) Doise JM, Aho LS, Quenot JP, Guilland JC, Zeller M, Vergely C, Aube H, Blettery B, Rochette L. Plasma antioxidant status in septic critically ill patients: a decrease over time. Fundam Clin Pharmacol 2008; 22: 203-209.

67) Ribero Nogueira C, Borges F, Lameu E, Franca C, Ramalho A. Effects of supplementation of antioxidant vitamins and lipid peroxidation in critically ill patients. Nutr Hosp 2013; 2: 1666-1672.

68) Koekkoek WA, van Zanten AR. Antioxidant vitamins and trace elements in critical illness. Nutr Clin Pract 2016; 31: 457-474.

69) Quasim T, McMillan DC, Talwar D, Sattar N, O'Reilly DS, Kinsella J. Lower concentrations of carotenoids in the critically ill patient are related to a systemic inflammatory response and increased lipid peroxidation. Clin Nutr 2003; 22: 459-462.

70) Corcoran TB, O'Neill MP, Webb SA, Ho KM. Inflammation, vitamin deficiencies and organ failure in critically ill patients. Anaesth Intensive Care 2009; 37: 740-747.

71) Oudemans-van Straaten HM, Spoelstra-de Man AM, de Waard MC. Vitamin C revisited. Crit Care 2014; 18: 460.

72) Berger MM, Oudemans-van Straaten HM. Vitamin C supplementation in the critically ill patient. Curr Opin Clin Nutr Metab Care 2015; 18: 193-201.

73) May JM, Harrison FE. Role of vitamin C in the function of the vascular endothelium. Antioxid Redox Signal 2013; 19: 2068-2683.

74) De Grooth HM, Spoelstra-de Man AME, Oudemans-van Straaten HM. Early plasma vitamin C concentration, organ dysfunction and ICU mortality. Intensive Care Med 2014; 40: S199.

75) Sadeghpour A, Alizadehasl A, Kyavar M, Sadeghi T, Moludi J, Gholizadeh F, Totonchi Z, Ghadrdoost B. Impact of vitamin C supplementation on post-cardiac surgery ICU and hospital length of stay. Anesth Pain Med 2015; 5: e25337.

76) Fowler AA III, Syed AA, Knowlson S, Sculthorpe R, Farthing D, DeWilde C, Farthing CA, Larus TL, Martin E, Brophy DF, Gupta S; Medical Respiratory Intensive Care Unit Nursing, Fisher BJ, Natarajan R. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. J Transl Med 2014; 12: 32.

77) Niki E, Traber MG. A history of vitamin E. Ann Nutr Metab 2012; 61: 207-212.

78) Azzi A. Molecular mechanism of alpha-tocopherol action. Free Radic Biol Med 2007; 43: 16-21.

79) Antosik A, Czubak K, Cichon N, Nowak P, Zbikowska H. Vitamin E analogue protects red blood cells against storage-induced oxidative damage. Transfus Med Hemother 2018; 45: 347-354.

80) Lassnigg A, Punz A, Barker R, Keznickl P, Manhart N, Roth E, Hiesmayr M. Influence of intravenous vitamin E supplementation in cardiac surgery on oxidative stress: a double blinded, randomized, controlled study. BJ Anaesth 2003; 90: 148-154.

81) Bartels M, Biesalski HK, Engelhart K, Sendlhofer G, Rehak P, Nagel E. Pilot study on the effect of parenteral vitamin E on ischemia and reperfusion induced liver injury: a double blind, randomized, placebo-controlled trial. Clin Nutr 2004; 23: 1360-1370.

82) Bulger EM, Maier RV. An argument for vitamin E supplementation in the management of systemic inflammatory response syndrome. Shock 2003; 19: 99-103.

83) Vasilaki AT, Leivaditi D, Talwar D, Kinsella J, Duncan A, O'Reilly DS, McMillan DC. Assessment of vitamin E status in patients with systemic inflammatory response syndrome: plasma, plasma corrected for lipids or red blood cell measurements? Clin Chim Acta 2009; 409: 41-45.

84) Collie JTB, Greaves RF, Jones OAH, Lam Q, Eastwood GM, Bellomo R. Vitamin B1 in critically ill patients: needs and challenges. Clin Chem Lab Med 2017; 55: 1652-1668.

85) Voskoboyev AI, Averin VA. Thiamine-binding protein from rat erythrocytes. Acta Vitaminol Enzymol 1983; 5: 251-254.

86) Attaluri P, Castillo A, Edriss H, Nugent K. Thiamine deficiency: an important consideration in critically ill patients. Am J Med Sci 2018; 356: 382-390.

87) Donnino MW, Andersen LW, Chase M, Berg KM, Tidswell M, Giberson T, Wolfe R, Moskowitz A, Smithline H, Ngo L, Cocchi MN; Center for Resuscitation Science Research Group. Randomized, double-blind, placebo-controlled trial of thiamine as a metabolic resuscitator in septic shock: a pilot study. Crit Care Med 2016; 44: 360-367.

88) Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. Chest 2017; 151: 1229-1238.

89) Moskowitz A, Andersen LW. Ascorbic acid, corticosteroids, and thiamine in sepsis: a review of the biologic rationale and the present state of clinical evaluation. Crit Care 2018; 22: 28.

90) Iqbal S. Khan S, Naseem I. Antioxidant role of vitamin D in mice with alloxan-induced diabetes. Canadian J Diabetes 2018; 42: 412-418.

91) Lee P, Eisman JA, Center JR. Vitamin D deficiency in critically ill patients. N Engl J Med 2009; 360: 1912-1914.

92) Braun A, Chang D, Mahadevappa K, Gibbons FK, Liu Y, Giovannucci E, Christopher KB. Association of low serum 25-hydroxyvitamin D levels and mortality in the critically ill. Crit Care Med 2011; 39: 671-677.