



Review Article

The role of oxidative stress in adult critical care

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Abstract

Oxidative stress defines an imbalance in production of oxidizing chemical species and their effective removal by protective antioxidants and scavenger enzymes. Evidence of massive oxidative stress is well established in adult critical illnesses characterized by tissue ischemia–reperfusion injury and by an intense systemic inflammatory response such as during sepsis and acute respiratory distress syndrome. Oxidative stress could exacerbate organ injury and thus overall clinical outcome. We searched MEDLINE databases (January 1966 to June 2005). For interventional studies, we accepted only randomized trials. Several small clinical trials have been performed in order to reduce oxidative stress by supplementation of antioxidants alone or in combination with standard therapies. These studies have reported controversial results. Newer large multicenter trials with antioxidant supplementation should be performed, considering administration at an early stage of illness and a wider population of critically ill patients.

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Keywords: Oxidative stress; Adult critical illness; Sepsis; Acute respiratory distress syndrome; Antioxidants; *N*-Acetylcysteine; Vitamins; Free radicals

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Abbreviations: ALI, acute lung injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; F_iO_2 , fraction of inspired oxygen; GSH-Px, glutathione peroxidase; ICU, intensive care unit; IL-8, interleukin-8; LDL, low-density lipoprotein; MEGX, monoethylglycinexylidide; MOF, multiple organ failure; NAC, *N*-acetylcysteine; NF- κ B, nuclear factor- κ B; P_aO_2 , arterial oxygen pressure; $PGF_{2\alpha}$, prostaglandin F $_{2\alpha}$; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; SIRS, systemic inflammatory response syndrome; TBARS, thiobarbituric acid-reactive substances; TRAP, total antioxidant capacity.

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Survival of critical illness depends on a complex carefully orchestrated immune response from all organ systems. Overall, a dysfunctional immune response presents in two different ways: (1) excessive activation of the cellular immune response, which is manifested clinically as the systemic inflammatory response syndrome, and (2) excessive down regulation of the cellular immune response leading to increased susceptibility to infection and overwhelming sepsis. An excessive production of free radicals contributes to an overwhelming inflammatory response and tissue injury. The immune system has evolved multiple “checks and balances” to ensure that the appropriate response falls in the physiologic middle ground. However, during severe sepsis or organ failure, the body response fails to protect itself. An intense study of oxygen radical-mediated mechanisms may lead to improved therapies in the treatment of critically ill patients.

Biochemistry of radicals

Oxygen metabolism continuously generates small amounts of reactive oxygen species (ROS) [1,2]. ROS are normally produced during physiologic processes such as cellular respiration and inflammatory defense mechanisms. Moreover, ozone is another recent source of ROS [3].

Scavenger systems include enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GSH-Px), a selenium-dependent enzyme, as well as nonenzymatic antioxidants such as vitamin E, vitamin C, β -carotene, and heme-binding proteins (ceruloplasmin, transferrin, haptoglobin, albumin) [1].

Massive increases in ROS and other radical species can lead to oxidative stress, promoting cell injury and death [4–6]. ROS could act as second messengers and have an effect on the signal transduction pathways, so influencing gene expression [7,8].

The radical nitric oxide and its derivative peroxynitrite are the main products of the reactive nitrogen species (RNS) variously involved in the mechanisms of oxidative injury [9–11]. Peroxynitrite is a powerful oxidizing agent, more cytotoxic than NO, and triggering a different proinflammatory process including the expression of intracellular adhesion molecule-1 and P-selectin, interleukin 8 (IL-8), and nuclear factor- κ B (NF- κ B) [12,13]. Moreover, peroxynitrite induces nitro(so)ation reactions, damage of proteins and lipids, depression of mitochondrial enzymes, depletion of glutathione, and DNA strand damage [14].

Several methods have been developed to monitor in vivo oxidative stress: direct quantification of reactive species by

electron spin resonance and indirect methods such as determination of antioxidants and total antioxidant capacity (TRAP) and detection of oxidized biological markers, the “biomarkers” of oxidative stress, including products of lipoperoxidation (malondialdehyde, 4-hydroxynonenal, isoprostanes, oxidized-LDL), protein oxidation (hydroxyl and carbonyls), and measurements of DNA damage (high-performance liquid chromatography, gas chromatography) [15]. However, each of these assays has limitations regarding sensitivity, specificity, and timing of analysis [16]. Therefore, a cluster of different methodologies (oxidized biological molecules and consumption of antioxidants) could be a better way to assess in vivo oxidative stress [17].

Free radicals and critical care

Oxidative stress during critical illness may be related to activation of phagocytes (neutrophils, monocytes, macrophages, eosinophils), production of NO, and release of iron and copper ions and metalloproteins [18]. Critical illnesses, such as sepsis or acute lung injury (ALI) acute respiratory distress syndrome (ARDS), are characterized by a severe production of ROS and other radical species with consequent oxidative stress [1]. Moreover, activation of xanthine oxidase represents a major source of ROS after burn trauma [19].

Clinical evidence demonstrates the role of severe oxidative stress in critical care (see below).

Search strategy

We reviewed clinical observational studies and clinical trials with antioxidants. For interventional studies, we accepted only randomized trials. We searched MEDLINE databases (January 1966 to June 2005), using text words.

Oxidative stress in human diseases

Cardiocirculatory shock

Biasi et al. [20] studied the occurrence of oxidative stress in shock patients with and without ischemic hepatitis. In all patients with circulatory shock, erythrocyte free malondialdehyde and total plasma lipoperoxides were increased and erythrocyte glutathione and plasma vitamin E concentrations were significantly reduced. Only patients with ischemic hepatitis, a condition of centrilobular necrosis with intense infiltration of polymorphonuclear cells and increase in serum transaminase and

lactate dehydrogenase, showed a selective increase in plasma aldehyde–protein adducts and a direct correlation of increase in aldehyde-modified proteins with extent of hepatic necrosis.

Sepsis

Oxidative stress has been studied in patients with systemic inflammatory response syndrome (SIRS), sepsis, and multi-organ failure (MOF).

Several studies confirm severe oxidative stress in patients with SIRS as demonstrated by reduced values of plasma total radical-trapping antioxidant parameter (TRAP) and its components (uric acid, protein SH groups, unconjugated bilirubin, vitamin C, vitamin E, and plasma unidentified antioxidants) [21,23]; elevated levels of thiobarbituric acid-reactive substances (TBARS), especially in patients who developed MOF [22]; and increased levels of malondialdehyde and 4-hydroxynonenal [23].

Patients with sepsis show an increase in lipid peroxides [24,25], malondialdehyde [25], TBARS [26], and xanthine oxidase activity [25]. Conversely, they present reduced levels of α -tocopherol [24,26], selenium [24], vitamin A, β -carotene, and lycopene [26] and ascorbic acid [27]. Higher levels of lipid peroxidation products [24,26] and lower plasma selenium [26] and ascorbic acid levels [27] were associated with higher incidence of MOF and worse prognosis. Moreover, plasma antioxidant potential values increased to normal or even supranormal values in patients who survived, whereas they did not in patients who died [28].

Xanthine oxidase activation in sepsis confirms the failure of microvasculature control, leading to underperfusion and ischemia. Patients with the highest xanthine oxidase levels showed better survival [25].

An increased plasma concentration of NO reaction products, nitrite plus nitrate, is present in patients with septic shock [29], and plasma concentrations of nitrotyrosine seem to relate to prognosis in human septic shock [30].

Increased xanthine oxidase activity and elevated NO synthesis with impaired arginine metabolism have been reported even in pediatric patients with sepsis [31–33].

These studies point out an antioxidant imbalance in pathologic processes involving neutrophil activation such as sepsis and MOF. The oxidant stress is more evident in patients with sepsis who develop MOF and die. If a causal relationship between the reduction of antioxidant capacity and outcome were clearly proven, early antioxidant supplementation would be strongly recommended.

ALI/ARDS

A disruption of oxidant–antioxidant balance is likely to be important in the pathogenesis of inflammatory conditions such as ALI/ARDS [34,35].

Decreased concentrations of water-soluble antioxidants (urate, glutathione, and ascorbate) are present in the distal air spaces in patients with ALI [36].

Elevated concentrations of hydrogen peroxide [37,38] as well as isoprostanes [39] and expression of peroxidation of

membrane phospholipids *in vivo* have been measured in the exhaled breath condensate of patients with ARDS.

Patients with ARDS showed a significant decrease in plasma levels of α -tocopherol, ascorbate, β -carotene, and selenium and elevated levels of lipid peroxidation products [40–43].

Kumar et al. [43] demonstrated that in patients with established ARDS, concentrations of lipid peroxides are significantly higher compared to control and patients who are at risk for ARDS. Moreover, patients at risk for ARDS or with established disease showed a significant decrease in polyunsaturated fatty acids, suggesting an essential fatty acid deficiency disease [44].

The results of the study of Kumar et al. showed a significant decrease in the levels of nitric oxide in patients with established ARDS. By contrast, other studies showed the deleterious effect of RNS by detection of nitrated proteins [45,46] and increased levels of nitrate and surfactant protein A nitration [47] in the bronchoalveolar lavage of patients with ALI/ARDS. In oxidant-induced lung injury such as ARDS, the actions of NO could be contemporarily beneficial and harmful [48], acting as either a protective species or a pro-oxidant as a precursor of peroxynitrite [49]. Pharmacological modulation of the NO pathway could be a logical therapeutic approach [50].

Accumulation of neutrophils plays a significant role in the development of acute lung injury [51]. The physiologic role of neutrophils in host defense is accomplished not only by production and release of ROS but also by release of proteases favoring pathogen translocation. Effective neutralization of neutrophil proteases and free radicals by lung antioxidants (glutathione) and antiproteases (α 1-antitrypsin, α 2-macroglobulin) prevents lung injury. A protease–antiprotease and oxidant–antioxidant imbalance can play an important role in the pathogenesis of ARDS [52].

Studies in mixed critically ill patients

Oxidative stress affects a wide spectrum of critically ill patients.

Lower levels of ascorbic acid in a mixed population of critically ill patients were associated with severity of the illness and were not prevented by parenteral nutrition with ascorbic acid [53]. Interestingly, the severity of illness by APACHE III was proportionally related to the degree of oxidative stress [54].

High protein carbonyl concentrations as a measure of protein oxidation were elevated early in severe sepsis and in major trauma patients both in plasma and in bronchoalveolar fluid [55].

Significantly lower levels of the carotenoids, vitamin A, and vitamin E were found in patients with acute pancreatitis compared to healthy control [56].

Plasma TBARS, protein carbonyls, and xanthine oxidase activity were elevated in patients with severe burn injury and associated with adverse outcome [57]. Patients with intracranial hemorrhage and head trauma showed lower plasma levels of ascorbic acid compared with healthy subjects. Ascorbic acid levels were inversely correlated with severity of neurological impairment and with extension of the lesions [58].

A characteristic reduction in muscle free glutamine and glutamate (glutamate, glycine, and cysteine are used for glutathione synthesis) and an increase in branched-chain amino acids, as well as a reduction in muscle protein synthesis, have been described in intensive care patients [59]. Critical illness is associated with decreased muscle glutathione concentrations and with decreased reduced/total glutathione ratio, evidence of oxidative stress. Low concentrations of glutathione may reduce muscle defense against oxygen free radicals and impair protein synthesis, negatively influencing amino acid transport [60]. In fact, glutathione is an endogenous scavenger and is involved in glutamyl amino acid transport across cell membranes and in protein degradation. These findings suggest potential benefits of glutamine supplementation with preservation of the glutathione redox state in ICU patients [61].

Antioxidant and scavenger therapy

Antioxidant therapy may be realized by restoring endogenous antioxidants (i.e., antioxidants or scavenger SOD or SOD mimetics) or supplementing exogenous agents with antioxidant properties (i.e., *N*-acetylcysteine) or administering drugs that reduce oxidant production (i.e., allopurinol, a xanthine inhibitor, or desferoxamine, an iron scavenger) [62–64].

Clinical trials in critically ill patients

Several antioxidants, alone or in combination, have been tested in different small randomized, double-blind, placebo-controlled trials (Table 1).

Table 1
Studies evaluating antioxidant supplementation in critically ill patients

Author	No. of patients	Pathology	Drug	Route	Main results
Jepsen (1992)	62	ARDS	NAC	iv	No clinical differences
Suter (1994)	61	ARDS	NAC	iv	Improvement P_aO_2/F_iO_2 ; reduction in length of ventilatory support
Laurent (1996)	16	ARDS	NAC	iv	Increased GSH in pulmonary granulocytes
Bernard (1997)	46	ARDS	NAC + procysteine	iv	Increased red blood cell GSH levels; accelerated recovery from ALI; increased cardiac index; reduced organ failure
Domenighetti (1997)	42	ARDS	NAC	iv	No clinical differences
Ortolani (2000)	36	ARDS	NAC	iv	Increased GSH in epithelial lining fluid; reduced expired ethane and MDA
Spies (1994)	58	Septic shock	NAC	iv	Increased tissue oxygenation and higher survival rate in responders (45%)
Peak (1996)	20	Septic shock	NAC	iv	Depression in cardiovascular performance
Spapen (1998)	22	Septic shock	NAC	iv	Improved P_aO_2/F_iO_2 and static lung compliance; reduction in IL-8; reduced length of ventilatory support and ICU stay
Ortolani (2000)	30	Septic shock	NAC + glutathione	iv	Decreased peroxidative stress; improved clinical scores (APACHE II, LOD)
Rank (2000)	60	Septic shock	NAC	iv	Increased hepatosplanchnic flow; improved liver function (MEGX test)
Heller (2001)	30	Sepsis/SIRS/ trauma	NAC	iv	Reduced respiratory burst; increased neutrophil phagocytosis
Paterson (2003)	20	Sepsis	NAC	iv	Reduced NF- κ B and IL-8
Hein (2004)	5	Septic shock	NAC	iv	Decreased hepatic lactate; increased liver perfusion and function (magnetic resonance spectroscopy)
Molnar (1998)	60	Mixed ICU patients	NAC	iv	No antioxidant or clinical difference
Angstwurm (1999)	42	SIRS	Selenium	iv	Improvement in organ dysfunction; reduced acute renal failure
Seeger (1987)	14	ARDS	Vitamin E	Enteral	No difference
Galley (1997)	30	Septic shock	NAC + ascorbic acid + α -tocopherol	iv	Transient increase in heart rate, cardiac index; decrease in systemic vascular resistance index
Gadek (1999)	146	ARDS	Vitamin C, β -carotene, and eicosapentaenoic and linolenic acid	Enteral	Reduction in length of ventilatory support, organ failure, and ICU stay
Preiser (2000)	51	Mixed ICU patients	Vitamins A, C, and E	Enteral	Increased vitamin concentrations, improved LDL resistance to oxidation; no clinical differences
Nathens (2002)	595	Surgical ICU patients	Vitamin C, α -tocopherol	iv; enteral	Reduced organ failure and ICU stay
Crimi (2004)	216	Mixed ICU patients	Vitamins C and E	Enteral	Reduced TBARS, isoprostanes; reduced 28-day mortality
Lopez (2004)	797	Septic shock	NOS inhibitor 546C88	iv	Increased mortality

N-Acetylcysteine

N-Acetylcysteine (NAC), the drug of choice in the treatment of paracetamol-induced hepatic failure, has various pharmacologic properties with potential benefits in critically ill patients [65,66]: restoration of cellular antioxidant potential by replenishing depleted glutathione stores, scavenging of ROS both directly and as a precursor of GSH, vasodilatation and inhibition of platelet aggregation by increasing cyclic guanosine monophosphate levels, and regenerating nitric oxide as sulfhydryl donor. Moreover, NAC can decrease NF- κ B activation with reduced proinflammatory cytokines production, such as IL-8 and tumor necrosis factor [67].

The role of NAC in the treatment of ALI/ARDS has been studied in several clinical trials [68–73]. NAC administration has demonstrated protective effects, replenishing GSH levels within pulmonary granulocytes ($n = 16$) [68] and in bronchoalveolar lavage fluid ($n = 36$) [69]. However, two different studies ($n = 66$; $n = 42$) [70,71] failed to demonstrate significant differences in clinical endpoints such as mortality, length of ventilatory support, or improvement in P_aO_2/F_iO_2 ratio in patients with established ARDS.

Bernard et al. [72], in a trial of NAC or procysteine vs placebo ($n = 46$), reported an increase in red blood cell GSH levels, a faster recovery from ALI, elevated cardiac index, and reduced development of organ failure (73% of the placebo group versus 39% of the treatment group; $p = 0.057$) but without any change in the mortality rate.

By contrast, Sutter et al. [73] showed, in a study of 61 patients, an improvement in arterial oxygenation and a reduction in ventilator days required but only in patients with mild to moderate acute lung injury and without any advantageous reduction in ARDS development. Currently, the clinical benefits of intravenous NAC in ARDS patients in a strong endpoint such as mortality have not clearly demonstrated [74].

Clinical trials of NAC in septic shock have also had mixed results.

Spies et al. ($n = 58$) [75] reported that 45% of patients given NAC (responders) showed increased oxygen consumption associated with an increase in gastric mucosal pH, improvement in cardiac function, and higher survival rate.

By contrast, Peak et al. ($n = 20$) [76] demonstrated significant depression of cardiovascular performance after 24 h associated with NAC infusion. In another study ($n = 22$) [77], NAC administration improved respiratory function and shortened ICU stay with no significant hemodynamic effects and, interestingly, attenuated production of IL-8. IL-8 is a chemokine, acting as an important mediator of septic lung injury [78], promoting recruitment and activation of neutrophils [79]. Administration of high doses of NAC added to GSH showed a decreased peroxidative stress and an improvement in clinical scores of patients in septic shock ($n = 30$) [80]. Intravenous infusion of NAC increased hepatosplanchnic blood flow, investigated by using indocyanine green, and improved liver function, determined by the monoethylglycineylidide (MEGX) test, within 24 h of the onset of septic shock ($n = 60$) [81]. Recently, Hein et al. reported that administration of NAC decreased hepatic

lactate production, increased liver perfusion, and improved liver function as shown by proton magnetic resonance imaging and spectroscopy in patients with septic shock [82].

A high dose of *N*-acetylcysteine (36 g for 3 days) increased phagocytic activity, with a reduced oxidative burst activity of neutrophils in patients with SIRS/sepsis [83].

A trial of NAC infusion in a mixed population of patients ($n = 50$) in ICU did not improve the total antioxidant potential, without any significant difference in clinical endpoints such as duration of inotropic support, mechanical ventilation, and ICU stay [84].

To date, monotherapy with NAC seems not change dramatically the natural history of complex diseases such as ARDS and sepsis. However, early timing of administration could be more useful, stopping the damage induced by oxidative stress. In a model of fluid-resuscitated endotoxic shock, administration of NAC before the endotoxin improved oxygen extraction, with an enhanced regional blood flow in mesenteric, renal, and femoral vasculature [85]. However, when NAC infusion was started after 12 h of endotoxin administration, there was no improvement in local and regional hemodynamics, metabolism, or oxygen exchange despite the increased glutathione concentration [86]. The lack of efficacy of delayed NAC administration highlights the importance of early antioxidant supplementation before the hemodynamic and metabolic effects induced by sepsis are fully established [87]. Thus, it is important to perform larger trials to establish populations of critical ill patients in which early NAC administration could have some beneficial effects.

Selenium

A novel therapeutic approach could be the administration of selenium with subsequent increase in selenium-dependent glutathione peroxidase. Accordingly, in patients with SIRS ($n = 42$), selenium replacement improved the resolution of organ dysfunction and reduced the incidence of acute renal failure requiring hemodialysis [88].

Vitamins

Only one very small clinical study evaluated the role of enteral administration of vitamin E in patients with ARDS ($n = 14$), with no significant response to vitamin E supplementation [89].

Because vitamins and minerals act in a synergistic and complementary way, several studies were performed using the replacement of combinations of antioxidants.

A study investigated the effect of intravenous antioxidant therapy (*N*-acetylcysteine, ascorbic acid, and α -tocopherol) in patients with septic shock, showing significant but transient beneficial hemodynamic changes ($n = 30$) [90]. More important, in another study [91], ARDS patients given a specialized formula containing vitamins C (844 mg/L) and E (317 IU/L) and β -carotene (5 mg/L) with eicosapentaenoic acid and linolenic acid required less ventilatory support and shorter stays in the ICU and had fewer new organ failures than control patients ($n = 146$); however, because of the

design of the study, it was not possible distinguish the anti-inflammatory properties of eicosapentaenoic acid and linolenic acid from the effects of antioxidants. In a retrospective analysis, in order to elucidate the potential mechanisms which lead to the clinical benefits of this diet, the authors showed, in patients fed with the special diet, a decreased level of IL-8 and leukotriene B₄, reduced neutrophil and protein levels in BALF [92], and restored plasma levels of β -carotene and α -tocopherol, without reduction of oxidative stress evaluated by lipid peroxide and TRAP [93].

In another small study ($n = 51$), the addition of antioxidant vitamins (133 μ g/dl vitamin A, 13.4 μ g/dl vitamin C, and 4.94 μ g/dl vitamin E) to enteral feeding solutions in critically ill patients was able to significantly increase plasma vitamin concentrations and to improve the resistance of LDL to oxidation, with no difference in clinical outcome [94].

A recent large clinical study ($n = 595$) showed that administration of vitamin C (3000 mg iv) and α -tocopherol (3000 IU/day enterally) reduced the incidence of organ failure and shortened ICU length of stay in critically ill surgical patients [95].

We have recently demonstrated in a large trial ($n = 216$) that antioxidant supplementation with vitamins C (500 mg/day) and E (400 UI/day) in enteral feeding for 10 days reduced oxidative stress as indicated by significant reduction in plasma TBARS and PGF_{2 α} isoprostanes [96]. Most importantly, antioxidant intervention was associated with a significantly reduced 28-day mortality (45.7% in the antioxidant group and 67.5% in the regular feeding group). High mortality, observed in the regular feeding group, was expected because this condition is relatively common, with frequent comorbidity, in elderly patients, as the recruited patients in this study were. Among patients older than 65 years of age, Knaus reported hospital mortality rates of 60% with one organ system failure, 90% with two organ system failures, and 100% with three or more organ system failures [97].

These two large studies were striking and convincing of a real protective effect.

Nitric oxide synthase inhibitor

Recently, a phase II study testing the efficacy of the nitric oxide synthase inhibitor *N*^G-methyl-L-arginine hydrochloride by intravenous infusion for up to 72 h in 312 patients with septic shock showed in treated patients an increase in vascular tone, a reduction in cardiac index and oxygen delivery [98], and a prompt resolution of shock at 72 h (40% of treated patients vs 24% placebo) [99]. However, a subsequent large (797 patients) double-blind, placebo-controlled phase III study was prematurely discontinued because of an increased mortality associated with treatment with the NOS inhibitor (59% treated group vs 49% placebo $p < 0.001$) [100]. There is no clear explanation of the adverse effect of this inhibitor in phase III of the study, but it is probably related to the complex actions of NO.

Pathophysiological basis for the failure of some clinical antioxidant trials

Although oxidative stress was initially considered only an “epiphenomenon” of the inflammatory response, there is increasing evidence that it represents an important pathway in the beginning and establishment of inflammatory diseases. Excessive oxidative stress may represent a common pathway for life-threatening critical illnesses such as septic shock and ARDS, increasing the probability of developing a MOF and death in the ICU [97]. Although supplementation with antioxidants seems to be the logical answer to reduced levels of antioxidants, the benefit of this therapy has not been clearly shown. Many variables can explain the discrepancies in the clinical results: class of drugs, dose and timing of administration, differences in patient population, and size of the samples.

Oxidant–antioxidant balance involves different pathways and, actually, there is no “ideal” drug able to affect all of them. Theoretically, a combination of antioxidants with different properties could be a better choice than monotherapy. Moreover, critical illnesses such sepsis and ARDS are not simply free radical-induced but show a complex pathophysiology with many involved inflammatory and noninflammatory pathways. It would be ingenuous to think of treating these diseases with only antioxidant therapy.

The most effective treatments rely on a combination of antioxidants and immunostimulants. Novel therapeutic approaches are based on newly developed antioxidant compounds [62] such as SOD [101], Tempol [102], and drugs modulating the NO pathway [50] as well as new pharmacologic compositions such as liposomal antioxidants [103].

Another important issue is the correct dose to use. There are no definitive guidelines, neither for intravenous (i.e., NAC) nor for enteral administration (i.e., vitamins C and E), and, mostly important, no pharmacokinetic studies have been performed in critically ill patients. The example of NAC administration emphasizes the importance of dosage and administration: whereas a bolus administration with a short continuous infusion of a low dose of NAC improves oxygenation and cardiovascular values, a long continuous infusion of a high dose, leading to the accumulation of the drug, induced cardiac depression with increased mortality. Therefore, supplementation with very high levels of antioxidants should be used carefully because of the risk of toxicity and, especially in case of enteral nutrition, the not well known nutrient interactions [59].

The appropriate time to start therapy is an important concern because antioxidants often lack an advantage when the tissue damage is irreversible [91]. Ideal therapy must be very early after admission to the critical care unit. Whereas therapy with antioxidants in established diseases did not show any clinical difference [70,71], the combination of early administration with high dose induced evident clinical benefits [95]. Ideally, the best choice should be a prophylactic administration of antioxidants, but it is not always possible in critical care, if not in specific groups of patients such as surgical patients.

Finally, clinical trials were often performed on small, specific populations, limiting the extension of the results to large groups of patients.

Conclusions

Critical illness is associated with massive oxidative stress that could exacerbate organ injury and thus overall clinical outcome. The lack of adverse effects, coupled with the minimal expense, supports the use of antioxidants in critically ill patients. Newer large multicenter trials with antioxidant supplementation should be performed, considering administration at an early stage of illness and a wider population of critically ill patients.

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