

Oxidative stress in critical care: Is antioxidant supplementation beneficial?

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ABSTRACT

Reactive oxygen species (ROS) are constantly produced in human beings under normal circumstances. Antioxidant systems help defend the body against ROS but may be overwhelmed during periods of oxidative stress, which can cause lipid peroxidation, damage to DNA, and cell death. Critical illness, such as sepsis or adult respiratory distress syndrome, can drastically increase the production of ROS and lead to oxidative stress. Sources of oxidative stress during critical illness include activation of the phagocytic cells of the immune system (the respiratory burst), the production of nitric oxide by the vascular endothelium, the release of iron and copper ions and metalloproteins, and the vascular damage caused by ischemia reperfusion. Only indirect measurements of ROS are available, but the presence of oxidative stress in critical illness is supported by clinical studies. In general, serum antioxidant vitamin concentrations seem to decrease and measures of oxidative stress seem to increase in critically ill populations. Oxidative stress has been associated with sepsis, shock, a need for mechanical ventilation, organ dysfunction, acute respiratory distress syndrome, disseminated intravascular coagulation, surgery, and the presence of an acute-phase response. In addition, higher levels of oxidative stress seem to occur in patients with more notable injuries. Dietary supplementation with antioxidant vitamins seems to be the logical answer to decreasing serum antioxidant concentrations, but antioxidants may have adverse effects. The benefit of supplementing antioxidants in critically ill populations has not been shown and requires further study. *J Am Diet Assoc.* 1998;98:1001-1008.

The cellular metabolism of oxygen in human beings continuously produces small amounts of reactive oxygen species (ROS). Tissue damage, whether from trauma, ischemia, or infection, leads to the increased production of ROS by many mechanisms. Large increases in the amount of ROS lead to oxidative stress, which is defined as a "disturbance in the prooxidant-antioxidant balance in favor of the prooxidants, leading to potential damage" (1, p xv-xvi). Because ROS can damage almost any molecule in the body, they have been investigated as a mechanism of injury in many diseases, including sepsis, multisystem organ failure (2,3), adult respiratory distress syndrome (ARDS) (3-5), fulminant hepatic failure (3), hepatitis (6), pancreatitis (7,8), cancer (9,10), cardiovascular disease (11,12), diabetes mellitus (13), Alzheimer's disease (14), asthma (15,16), cystic fibrosis (15,17), chronic obstructive pulmonary disease (16), rheumatoid arthritis (18,19), systemic lupus erythematosus (18,20), inflammatory bowel disease (21,22), ulcerative colitis (23), cataracts (24), and age-related macular degeneration of the retina (25).

WHAT ARE ROS?

ROS include not only oxygen-centered radicals but also nonradical derivatives of oxygen. Free radicals contain 1 or more unpaired electrons and are capable of independent existence (3). Free radicals can be formed by 3 methods: the loss of a single electron from a nonradical molecule, the addition of a single electron to a nonradical molecule, or the homolytic cleavage of the covalent bond of a nonradical molecule so that each fragment retains 1 of the electrons (26). This electron imbalance causes the radical to search for another electron to form a complete pair. ROS include the hydroxyl radical ($\bullet\text{OH}$), superoxide radical ($\bullet\text{O}_2^-$), nitric oxide radical ($\text{NO}\bullet$), and the nonradicals hydrogen peroxide (H_2O_2) and singlet oxygen (3).

Under normal circumstances, the major source of ROS produced in the body occurs from the leakage of electrons from the mitochondrial and microsomal electron transport chains.

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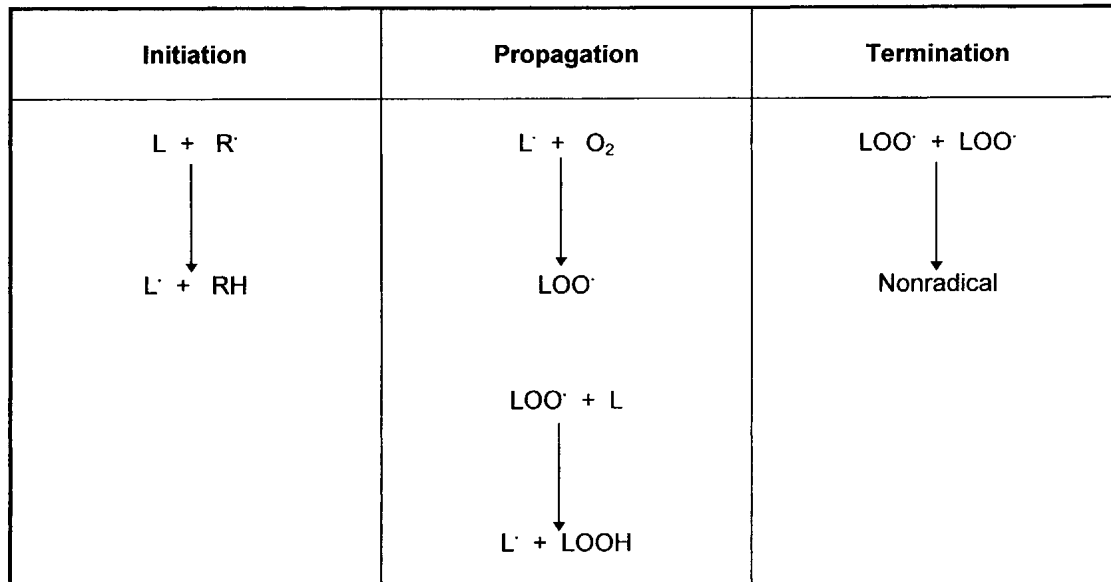


FIG 1. Stages of lipid peroxidation. In initiation, a polyunsaturated lipid molecule (L) is attacked by a radical (R•). The radical abstracts 1 of the hydrogen atoms at a double bond, producing a lipid radical (L•). In propagation, the lipid radical reacts with oxygen to form a peroxy radical (LOO•). This new peroxy radical can then react with another lipid molecule to yield another lipid radical and a peroxide (LOOH). This step repeats until termination, that is, when 2 peroxy radicals react to produce a nonradical product. Source: references 26,33,87.

All aerobically respiring cells reduce molecular oxygen to create $\cdot O_2^-$ (24,27-30). Electrons normally pass down a nonradical generating, cytochrome-catalyzed reduction of oxygen to water during oxidative phosphorylation (adenosine triphosphate [ATP] production). $\cdot O_2^-$ is formed when electrons do not complete the cascade (30). About 1% to 3% of the oxygen we consume generates $\cdot O_2^-$ (31).

HOW DOES THE HUMAN BODY DEFEND ITSELF AGAINST ROS?

Antioxidant systems have developed to defend the body against ROS. Halliwell et al (28) define the term antioxidant as "any substance that, when present at low concentrations compared to that of an oxidizable substrate, significantly delays or inhibits oxidation of that substrate" (p 601). These defenses either stop the radical chain reaction or divert the radical to a less deleterious target (32). The 3 main enzymes responsible for controlling ROS are superoxide dismutase, glutathione peroxidase, and catalase (33). Major nonenzymatic defenses include the tocopherols, the carotenoids, and ascorbic acid as well as free metal and heme-binding proteins (34). Because these defense systems are not 100% effective, the human body has also developed enzyme systems to repair the damage ROS inflicts on DNA, RNA, and proteins (24,28,29,32,35).

WHAT IS LIPID PEROXIDATION?

Polyunsaturated fatty acids in the cell membrane are oxidized in a process known as lipid peroxidation (Figure 1). Lipid peroxidation can cause damage to cell membranes directly by altering membrane fluidity, permeability, and integrity (30) or

can attack DNA and other molecules through self-perpetuating chain reactions and toxic byproducts (24,26,30,36). Lipid peroxides can form cyclic peroxides, which can decompose to highly cytotoxic products such as aldehydes and alkoxy radicals. These compounds can diffuse from the lipid membrane and damage other cells (3,26). The thiobarbituric acid reactive substances (TBARS) assay is commonly used to measure lipid peroxidation, although this assay has been criticized because it is not specific for lipid hydroperoxides and because several nonlipid molecules in the body produce false-positive results (37).

HOW DO ROS INDUCE DNA DAMAGE?

Several types of DNA damage are thought to be a result of ROS, which can attack DNA at the deoxyribose molecule or at any of the purine or pyrimidine bases. Attack at a sugar can lead to sugar fragmentation, base loss, and strand breaks. Attack at a base can lead to modification of the nucleotide bases (38). Mechanisms exist to repair the DNA damage (39), and water-soluble repair products have been measured in urine (40). However, the repair mechanisms are not error proof and may not be able to repair all of the damage. Evidence suggests that some ROS may alter the activity of DNA polymerases and decrease their fidelity. Oxidative damage to DNA appears to occur continuously at a low, steady state (41), with approximately 10,000 base oxidations taking place per cell per day (40). DNA damage secondary to oxidative stress has been shown to have mutagenic effects in bacteria (42) and various mammalian cells, and may even result in cell death (36). Other examples of the effect of DNA damage include decreased cell

proliferation caused by impaired DNA replication and decreased protein synthesis from transcription of modified DNA (43).

WHAT ROLE DOES THE IMMUNE SYSTEM PLAY IN OXIDATIVE STRESS?

The 3 main phagocytic cells of the immune system, neutrophils (polymorphonuclear leukocytes [PMNs]), eosinophils, and macrophages, require ROS to help destroy bacteria and other ingested materials (44). Phagocytic cells, whose resting metabolism is mainly anaerobic glycolysis, contain a membrane-bound enzyme complex called reduced nicotinamide-adenine dinucleotide phosphate oxidase, which is normally dormant. When the cell is activated, this highly efficient enzyme rapidly consumes oxygen in a "respiratory burst." Large amounts of $\cdot\text{O}_2^-$ are produced, which accounts for almost 90% of the oxygen consumed by the stimulated cells. H_2O_2 is produced via dismutation. A genetic deficiency of this oxidase causes the life-threatening condition known as chronic granulomatous disease, in which phagocytic cells cannot form $\cdot\text{O}_2^-$ and, therefore, have a seriously impaired ability to kill microorganisms (24,44). Neutrophils contain a bactericidal enzyme called myeloperoxidase; eosinophils contain a similar peroxidase. Both generate hypochlorous acid from H_2O_2 in the presence of chloride ions (9,35,44). Hypochlorous acid has been shown to damage cell membranes and induce cell lysis in vitro (45). Furthermore, activation of large numbers of phagocytic cells results in oxidative stress (27,28,30,32,35,46). Neutrophil-derived ROS have been shown to damage lung tissue in vitro and in animals (47). The release of $\cdot\text{O}_2^-$ also activates chemotaxis, causing neutrophils to attach to the endothelium and migrate into tissue, where these activated neutrophils cause tissue injury via oxidative and hydrolytic enzymes (48).

Trauma has been found to adversely affect immune function. Neutrophil locomotory dysfunction, with decreased rates of chemotaxis, has been associated with significantly increased infection rates in trauma patients (49). Auto-oxidation of PMN, caused by an increase in the production of ROS or a decrease in antioxidant defenses, is 1 reason for this defect. Because PMN locomotion and phagocytosis are membrane-dependent activities, α -tocopherol may improve this defect by stabilizing PMN membranes (50). Pharmacologic levels of α -tocopherol have been shown to decrease the production of H_2O_2 from PMN in vitro (51). Concentrations of antioxidants have been shown to be higher in the cells of the immune system compared with other cells (52) and supplementation with antioxidants has been shown to improve immune function, especially in the healthy elderly population. Meydani et al (53) gave healthy subjects over the age of 65 years α -tocopherol supplements (200 mg/day for 4 months) and found significant increases in indexes of cell-mediated immunity compared with a placebo. Cell-mediated immunity also increased in subjects given 60 or 800 mg/day, although not significantly.

HOW DOES THE VASCULAR ENDOTHELIUM CONTRIBUTE TO OXIDATIVE STRESS?

Many types of cells, especially vascular endothelial cells, produce $\text{NO}\cdot$ from the amino acid arginine and molecular oxygen by the enzyme nitric oxide synthase. $\text{NO}\cdot$ is normally produced at a basal rate to provide a vasodilator tone. Inhibitors of $\text{NO}\cdot$ synthesis cause an increase in blood pressure. $\text{NO}\cdot$ produces vasodilation by relaxing the smooth muscle cells in vessel walls and inhibits platelet aggregation and adhesion to endothelial cells (54,55). A second form of nitric oxide synthase is induced by cytokines and endotoxin and inhibited by glucocorticoids. This inducible form of nitric oxide synthase produces much

higher levels of $\text{NO}\cdot$ than the basal form and may be important in the pathogenesis of sepsis. The vasorelaxation caused by the induction of nitric oxide synthase results in the redistribution of blood flow and enhancement of oxygen delivery to target tissues in minor infections, but can be dangerous if carried too far and systemic hypotension develops (56). Physiologic concentrations of $\text{NO}\cdot$ also maintain intestinal epithelial integrity under normal conditions, but higher concentrations increase epithelial permeability (55). Macrophages and neutrophils also produce $\text{NO}\cdot$ for its cytotoxic properties. $\text{NO}\cdot$ shuts down cellular respiration by inactivating mitochondrial cytochromes and affects cellular proliferation by inhibiting ribonucleotide reductase (56). These cytotoxic effects may be responsible for the endothelial damage that occurs during sepsis (54). $\text{NO}\cdot$ rapidly reacts with $\cdot\text{O}_2^-$ to form peroxynitrite, which may be directly cytotoxic by oxidizing essential sulfhydryl groups on proteins (57), and can displace copper from ceruloplasmin (41). Peroxynitrite rapidly decays to form $\cdot\text{O}_2^-$ and nitrogen dioxide, which is highly toxic and capable of initiating lipid oxidation and nitrosylation of aromatic amino acids (58).

HOW DOES IRON CATALYZE OXIDATIVE DAMAGE IN CRITICAL ILLNESS?

Several metal ions are remarkably good promoters of free radical reactions in vitro. H_2O_2 can react with ferrous iron or copper to produce the hydroxyl radical by the Fenton or Haber-Weiss reaction (26,28,33). Because transition metal ions can be responsible for ROS production, these ions are normally safely sequestered with proteins such as transferrin, lactoferrin, ceruloplasmin, and albumin (3,24,26,30,33,46). Because of these proteins, very little free iron exists, especially in plasma, and the generation of ROS from transition metals is not thought to occur in healthy persons (3).

Mechanical trauma, as well as several diseases and toxins, causes tissue injury and cell death. Ruptured cells release their internal contents, including transition metals, into the blood, where they may be available to catalyze the Fenton reaction. This mechanism may account for many reports of damage from ROS. Ischemic or traumatic injury may be even more damaging in the brain. The central nervous system is rich in iron but poor in antioxidants and has low concentrations of transferrin (28). Free heme and heme proteins released during hemorrhaging can also react with H_2O_2 (28,33,46). Metal-dependent reactions can be inhibited by chelating agents, such as deferoxamine, although this agent has notable toxic side effects, primarily hypotension, which limits its use in trauma patients (59).

WHY IS ISCHEMIA-REPERFUSION INJURY A FORM OF OXIDATIVE DAMAGE?

Ischemia, such as occurs during circulatory shock or myocardial infarction, followed by reperfusion greatly amplifies the generation of ROS (Figure 2). This oxidative stress results in the lysis of endothelial cells, leading to microvascular thrombosis and loss of organ function, which may lead to multisystem organ failure (30,60). The activation of neutrophils amplifies the oxidative damage from reperfusion, probably through secondary toxic metabolites (30,61). ROS produced during ischemia-reperfusion also seem to initiate the adherence of leukocytes to the vascular endothelium, leading to increased microvascular permeability (61,62). Allopurinol, which competitively inhibits xanthine oxidase, and superoxide dismutase have been used with some success in the treatment of reperfusion injury (3,30,60,61). Ischemia also leads to an increase in electron leakage from the respiratory chain and $\cdot\text{O}_2^-$ production because of a lack of adenosine diphosphate for oxidative phosphorylation. This electron leakage continues to

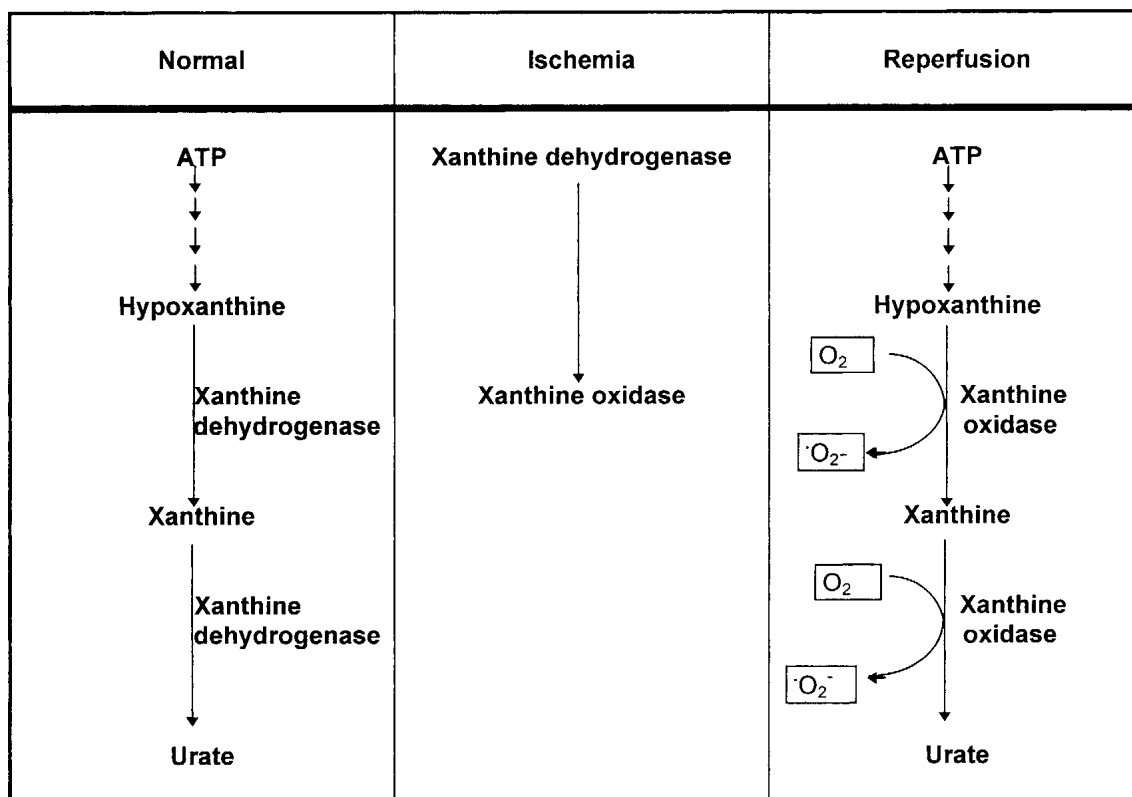


FIG 2. Generation of superoxide during ischemia-reperfusion. The purines, hypoxanthine and xanthine, which are produced from the breakdown of adenosine triphosphate (ATP) are normally catabolized to uric acid by the enzyme xanthine dehydrogenase. Ischemia causes the conversion of xanthine dehydrogenase to xanthine oxidase by either a reversible oxidation or irreversible limited proteolysis. Xanthine oxidase produces the superoxide radical from oxygen, but this reaction is blocked until oxygen is available. Reintroduction of oxygen during ischemia allows xanthine oxidase to start catabolizing the purines, generating superoxide. Source: references 30,60,61.

increase during reperfusion until adenosine diphosphate pools are replenished (48,61). Reperfusion injury, with loss of endothelial cell viability, also occurs during organ transplantation, along with severe antioxidant depletion and evidence of lipid peroxidation (63). The interaction of activated neutrophils with endothelial cells also leads to the conversion of xanthine dehydrogenase to xanthine oxidase within the endothelial cell. The resulting $\cdot\text{O}_2^-$ production may eventually lead to endothelial cell damage and/or death. Interestingly, the same inflammatory mediators that activate neutrophils may also initiate the activation of xanthine oxidase in endothelial cells (64).

WHAT ARE OTHER SOURCES OF ROS IN CRITICAL ILLNESS?

Tissue destruction can lead to disruption of the electron transport chain, causing an increased production of $\cdot\text{O}_2^-$ (3). An increase in metabolic rate may also lead to an increase in ROS. Urinary concentrations of modified DNA bases have been found to be positively associated with the amount of lean body mass in healthy human beings (65) and directly correlated with metabolic rate among different mammalian species, including human beings (43). These data suggest that the hyper-

metabolism associated with some critical illnesses may increase oxidative stress.

Excess ROS produced by oxidative stress lead to a decrease in ATP generation by inhibiting glyceraldehyde-3-phosphate dehydrogenase, one of the major enzymes of glycolysis, and decreasing the activity of ATP synthetase during oxidative phosphorylation in the mitochondria. Decreased ATP synthesis could lead to decreased cellular metabolism or even cell death (45). Inflammation and trauma enhance the metabolism of prostaglandins and leukotrienes from arachidonic acid by the enzymes cyclooxygenase and lipoxygenase, producing peroxy compounds and $\cdot\text{OH}$ (27,28,30,31,46). The enzymes lactoperoxidase, chloroperoxidase, and lipoxygenase all produce singlet oxygen (66). Catecholamines released during trauma and critical illness produce ROS by autooxidation (48). The iron-containing cytochrome P450 systems in the liver also produce ROS in vivo during the metabolism of many drugs (67).

WHAT IS THE CLINICAL EVIDENCE FOR OXIDATIVE STRESS IN CRITICAL ILLNESS?

A standardized method for determining the amount of oxidative stress has not been established, and, therefore, has not

been used in clinical diagnosis. Because ROS have extremely short half-lives, they are difficult to measure directly. Instead, we can measure several products of the damage produced by oxidative stress, such as TBARS (68). Another method of determining oxidative stress is to measure the disappearance of antioxidants, such as α -tocopherol, from the blood. Because the majority of plasma tocopherols are found in plasma lipids, which have been shown to decrease in the critically ill, any measure of plasma tocopherols in the critically ill population should be indexed to total cholesterol (69).

The acute-phase response has been linked to the presence of oxidative stress, even in nonhospitalized patients. Boosalis et al (70) studied the relationship between the acute-phase response and antioxidant concentrations in 85 nuns aged 77 to 99 years. Ten of the women (11%) demonstrated an acute-phase response, defined by an elevated serum concentration of C-reactive protein¹ (≥ 143 nmol/L). The presence of an acute-phase response was significantly and negatively correlated with plasma lycopene ($P < .05$), beta carotene ($P < .05$), alpha carotene ($P < .05$), and total carotenoid ($P < .01$) concentrations. Concentrations of α -tocopherol, cryptoxanthin, zeaxanthin, and lutein were not significantly correlated with the presence of an acute-phase response. None of the subjects were recovering from trauma or surgery, yet even mild forms of inflammatory disease, such as acute-phase response, appear to negatively affect antioxidant status (70).

The presence of oxidative stress has been studied in patients with sepsis, multisystem organ failure, and shock. Goode et al (2) studied antioxidant status and lipid peroxidation in 16 patients (7 women, 9 men) aged 16 to 79 years with sepsis and multisystem organ failure. Plasma concentrations of α -tocopherol (indexed to plasma lipids) were significantly lower than in healthy control subjects ($P < .01$). Beta carotene and lycopene concentrations were decreased below the reference range ($0.19 \mu\text{mol/L}^2$ and $0.27 \mu\text{mol/L}^3$, respectively). The decreased carotenoid concentrations are not surprising because these patients were receiving parenteral nutrition, which contains no carotenoids. Plasma concentrations of TBARS were elevated in the 7 patients who had 2 or more dysfunctional organs. The 5 patients with 3 or more dysfunctional organs had significantly increased TBARS compared with the patients with 2 or less dysfunctional organs ($P < .05$). TBARS showed a negative correlation with α -tocopherol ($r = -0.48$, $P < .005$) (2). Borrelli et al (71) measured daily plasma concentrations of ascorbic acid and α -tocopherol as a predictor of multisystem organ failure in 16 intensive-care patients aged 19 to 70 years who were determined to be at risk for developing multisystem organ failure. Ten patients developed multisystem organ failure and 5 of these patients died. None of the 6 patients who did not develop multisystem organ failure died. Plasma ascorbic acid concentrations were significantly lower in the patients with multisystem organ failure than in those without it ($P < .05$) for every day studied, but α -tocopherol levels were not significantly different (71). Poll et al (72) studied levels of lipid peroxidation (measured by carbonyl concentration) in erythrocytes from 12 subjects in circulatory shock. They found

significantly increased lipid peroxidation in the cells of subjects in shock compared with 12 healthy control subjects. In addition, they found different aldehyde patterns, mainly the presence of the highly toxic 4-hydroxynonenal, in the cells of patients in shock that did not appear in the cells of control subjects. The cells of patients in shock also had an increase in serum transaminase levels, strongly suggesting irreversible cell damage.

Several studies have reported an association between oxidative stress and ARDS. Leff et al (5) investigated serum antioxidant enzyme concentrations as predictors of ARDS in 26 patients (age and gender not reported) with sepsis. They found that 9 to 12 hours before the development of ARDS, serum concentrations of superoxide dismutase and catalase were significantly higher in patients with sepsis who later developed ARDS than in patients with sepsis who did not develop ARDS ($P < .05$). The concentration of superoxide dismutase remained high in patients with ARDS for 48 hours and then decreased to the concentration of patients without ARDS. Catalase concentrations progressively increased for 48 hours in patients with ARDS but decreased in patients without ARDS. Richard et al (4) studied plasma α -tocopherol and TBARS in 12 patients with ARDS (8 men, 4 women) who were aged 36 to 82 years. Blood samples were taken at the time of diagnosis of ARDS and at 6, 9, 12, and 24 hours. At the onset of ARDS, α -tocopherol concentrations (indexed to plasma lipid levels) were significantly decreased in the patients with ARDS compared with healthy control subjects ($P < .001$). Plasma concentrations of TBARS were significantly increased in ARDS patients ($P < .05$) and inversely ($r = -.78$, $P < .01$) related to plasma α -tocopherol concentrations. A high (>0.5) fraction of inspired oxygen did not change the plasma α -tocopherol concentrations in 4 patients in a coma who were being mechanically ventilated and who had no history of lung disease (4). Bunnell et al (73) found a significantly decreased total glutathione concentration in the alveolar epithelial lining fluid of 11 patients (aged 22 to 69 years) with ARDS compared with 7 normal subjects ($P < .0001$) as well as with 3 patients with cardiogenic pulmonary edema ($P < .001$). In addition, they found a greater percentage of total glutathione in the oxidized form in patients with ARDS (30.6%) compared with normal subjects (6.4%, $P < .003$) (73).

Antioxidant vitamin status has also been studied in surgical patients. Agarwal et al (74) studied the serum concentrations of ascorbic acid and the tocopherols in 57 surgical patients (age and gender not reported). Samples were taken before surgery and on days 1, 3, and 7 after surgery and were compared with samples from 5 fasting healthy patients and 5 fed healthy patients sampled at days 0, 1, and 3 of hospitalization. Initial vitamin concentrations were similar in all 3 groups. All vitamin concentrations decreased significantly in the surgical patients on day 1 after the operation, with a maximal decrease by day 3 after the operation (41% in ascorbic acid, 27% in α -tocopherol, 31% in γ -tocopherol). Vitamin concentrations had returned to normal by day 7 after the operation. The fasting control group also showed a decreased concentration of all vitamins at day 3 after the operation (25% in ascorbic acid, 13% in α -tocopherol, 18% in γ -tocopherol), although this decrease was significantly smaller and occurred later than in the surgical group. The subgroup of 26 surgical patients with postoperative infections had significantly lower preoperative concentrations of γ -tocopherol ($P < .02$). Lower preoperative concentrations of α -tocopherol and γ -tocopherol were significantly related to death ($P < .02$) in the 6 patients who died.

Oxidative stress has been studied in a wide spectrum of patients. Machiedo et al (75) studied 28 patients with sepsis

¹To convert nmol/L C-reactive protein to mg/dL, multiply nmol/L by 0.105. To convert mg/dL C-reactive protein to nmol/L, multiply mg/dL by 9.5. C-reactive protein of 50 nmol/L = 5.25 mg/dL.

²To convert μmol beta carotene to $\mu\text{g/dL}$, multiply $\mu\text{mol/L}$ by 53.68. To convert $\mu\text{g/dL}$ beta carotene to $\mu\text{mol/L}$, multiply $\mu\text{g/dL}$ by 0.01863. Beta carotene of 2.00 $\mu\text{mol/L}$ = 107 $\mu\text{g/dL}$.

³To convert $\mu\text{mol/L}$ lycopene to $\mu\text{g/dL}$, multiply $\mu\text{mol/L}$ by 53.68. To convert $\mu\text{g/dL}$ lycopene to $\mu\text{mol/L}$, multiply $\mu\text{g/dL}$ by 0.01863. Lycopene of 0.4 $\mu\text{mol/L}$ = 21.5 $\mu\text{g/dL}$.

aged 30 to 59 years, 15 patients without sepsis aged 22 to 64 years, and 5 healthy nonpatients. They found significantly increased plasma concentrations of TBARS in patients with sepsis compared with patients without sepsis and healthy nonpatients ($P < .05$). They also found a significant inverse correlation between plasma TBARS and the deformability of red blood cells ($r = -.51, P < .001$). A decreased deformability, or ability to bend, results in an abnormal microcirculatory flow, which may contribute to multisystem organ failure. Baouali et al (76) compared the plasma TBARS of 19 patients aged 43 to 90 years with circulatory shock and 10 patients aged 17 to 89 years being weaned from mechanical ventilation with 9 noncritical, nonventilated hospitalized patients aged 54 to 77 years and 9 healthy control subjects aged 24 to 28 years. TBARS were significantly greater in both the patients with circulatory shock (61% increase) and the patients on ventilators (40% increase) compared with hospitalized and healthy control subjects.

Dietetics practitioners
considering supplementing
antioxidant vitamins
in critically ill patients
should proceed with
caution and consider
the amounts of
antioxidant nutrients a
patient is already receiving
through an oral diet or
enteral/parenteral nutrition

However, they found no significant differences between the TBARS of subjects with or without ARDS. Takeda et al (77) compared plasma TBARS of 24 critically ill patients aged 4 to 81 years with those of a control group of 40 preoperative patients aged 8 to 78 years. All the critically ill patients were receiving mechanical ventilation and lipid-free parenteral nutrition containing 15 IU α -tocopherol per day, whereas the control group received a general diet. The TBARS were significantly higher in patients with sepsis ($P < .01$) and patients who had had cardiac surgery ($P < .01$). The TBARS were higher but not significantly higher in patients with pneumonia or central nervous system disorders. Disseminated intravascular coagulation (DIC) developed in 8 of the critically ill patients. TBARS concentrations during DIC were significantly greater than the values before the onset of DIC ($P < .05$) and the 3 patients with DIC who recovered subsequently had decreased TBARS. Al-

though plasma α -tocopherol concentrations were also studied, the levels reported were not adjusted for plasma lipids. Galley et al (78) studied the activity of xanthine oxidase and concentration of TBARS in 14 patients with sepsis aged 42 to 81 years, 10 critically ill patients without sepsis aged 34 to 76 years, and 20 healthy nonpatients. Xanthine oxidase activity was significantly increased in the patients with sepsis compared with the patients without sepsis ($P < .01$) and nonpatients ($P < .05$). TBARS were also significantly increased in the patients with sepsis compared with patients without sepsis ($P < .001$) and nonpatients ($P < .001$). Patients without sepsis also had significantly greater TBARS than nonpatients, although no significant difference in xanthine oxidase activity was found between patients without sepsis and nonpatients. Xanthine oxidase activity was the highest in the 6 patients with sepsis who survived ($P < .05$). Serum lactate concentrations were increased in all patients with sepsis and were highest in the 8 patients who died ($P < .02$). Low xanthine oxidase activity and higher lactate concentrations in the patients with sepsis who died implies a more severe ischemia with incomplete reperfusion. Xanthine oxidase activity did not relate to the presence of organ dysfunction.

The aforementioned studies provide support for the role of oxidative stress in critical illness. In general, serum antioxidant vitamin concentrations seem to decrease and measures of oxidative stress seem to increase in critically ill populations. Oxidative stress has been associated with sepsis, shock, mechanical ventilation, organ dysfunction, ARDS, DIC, surgery, and the presence of an acute-phase response. In addition, higher levels of oxidative stress seem to occur in patients with more substantial injuries.

WHAT ARE THE IMPLICATIONS OF MEDICAL NUTRITION THERAPY?

The aforementioned studies seem to indicate a decrease in serum concentrations of several antioxidant vitamins in the critically ill population. However, decreasing serum levels do not necessarily indicate that the vitamin is being used against oxidative stress. In addition, any serum measurement is subject to hemodilution, especially in critically ill patients who have been aggressively resuscitated with fluid. The effects of individual antioxidant nutrients are difficult to determine, leading to the idea of a functional overlap within a network of antioxidants defending against oxidative stress. Thus, the administration of 1 antioxidant nutrient may not lead to clinical improvement and use of a combination of antioxidant nutrients may be more beneficial (29,79).

Surprisingly, very little clinical evidence exists for supplementing antioxidants in the critically ill population. Most studies have simply measured serum levels after supplementation. We found no studies that explore the supplementation of antioxidants and other markers of oxidative stress, such as TBARS, or clinically relevant outcome variables. Seeger et al (80) found that supplementation of 3,000 mg α -tocopherol per day in patients with acute respiratory failure showed either no increase or a delayed increase in serum α -tocopherol concentrations. In contrast, supplementation of 1,000 mg/day α -tocopherol in healthy control subjects showed a rapid increase in serum α -tocopherol concentrations. In addition, these researchers did not observe an increased appearance of the main metabolite of α -tocopherol after free radical attack, leading to the hypothesis that lower serum concentrations were a result of reduced absorption of α -tocopherol in critically ill patients.

Antioxidant nutrients may have adverse effects as well. Every antioxidant is a redox agent, protecting from ROS in some circumstances and promoting ROS in others (81,82).

Examples of pro-oxidant effects include the production of H₂O₂ by the auto-oxidation of ascorbic acid and the reduction of ferric iron to the more reactive ferrous form by ascorbic acid (83). Goode et al (84) found a significantly different response to ascorbic acid supplementation between patients with sepsis and healthy control subjects. Plasma ascorbic acid, the ascorbyl radical, and free iron were measured before and after infusion of 1 g ascorbic acid. Free iron was significantly increased in the group with sepsis compared with healthy subjects ($P < .002$). Although the postinfusion concentrations of the ascorbyl radical were significantly increased in both the healthy patients and the patients with sepsis, the ascorbyl radical concentrations were significantly higher in the healthy patients than in the patients with sepsis ($P < .0001$), leading these researchers to suggest that the different response to ascorbic acid infusion may have been caused by redox cycling of iron. Furthermore, beta carotene supplementation has been associated with an increased risk (8% to 18%) of lung cancer in smokers and drinkers in 2 large clinical trials (85,86), leading to speculation that under these conditions, beta carotene may have been a pro-oxidant, amplifying damage instead of inhibiting it.

Dietetics practitioners considering supplementing antioxidant vitamins in critically ill patients should proceed with caution and consider the amounts of antioxidant nutrients a patient is already receiving through an oral diet or enteral/parenteral nutrition. For example, parenteral nutrition contains no carotenoids, but lipid emulsions contain a pharmacologic dose of the tocopherols (71 mg/L; 10% Intralipid, Nestle, Deerfield, Ill). The antioxidant levels in enteral formulas vary greatly. Because clinical trials have yet to demonstrate efficacy, clinicians should treat additional antioxidant supplementation in critically ill patients as a promising yet unproven approach and set up protocols that will evaluate the outcomes of antioxidant therapy, whether positive or negative.

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