The Beneficial Effects of Antioxidant Supplementation in Enteral Feeding in Critically Ill Patients: A Prospective, Randomized, Double-Blind, Placebo-Controlled Trial

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We investigated whether intervention with antioxidant vitamins C and E in enteral feeding influenced oxidative stress and clinical outcome in critically ill patients. Two-hundred-sixteen patients expected to require at least 10 days of enteral feeding completed the study. One-hundred-five patients received enteral feeding supplemented with antioxidants, and 111 control patients received an isocaloric formula. Plasma lipoperoxidation (by thiobarbituric acid reactive substances [TBARS] and prostaglandin $F_{2\alpha}$ isoprostane levels), low-density lipoprotein (LDL) oxidizability, and LDL tocopherol content were determined at baseline and at the end of the 10-day period. The clinical 28-day outcome was also assessed. Plasma TBARS and isoprostanes were 5.33 ± 1.26 nM/mL and 312 ± 68 pg/mL, respectively, before treatment and 2.42 ± 0.61 nM/mL and 198 ± 42 pg/mL after intervention ($P < 0.01$ for both comparisons). Antioxidants improved LDL resistance to oxidative stress by approximately 30% (the lag time before treatment was 87 ± 23 min and was 118 ± 20 min after treatment; $P < 0.04$). There was a significantly reduced 28-day mortality after antioxidant intervention (45.7% in the antioxidant group and 67.5% in the regular-feeding group; $P < 0.05$). Isoprostanes may provide a sensitive biochemical marker for dose selection in studies involving antioxidants.

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Oxidative stress is a disturbance in the balance between the formation of oxidizing species (reactive oxygen species and other radicals) and their effective removal by protective antioxidants (AOX). Overwhelming radicals generated in the bloodstream and tissues can induce oxidative damage to cell membranes, lipoproteins, proteins, and deoxyribonucleic acid. Major nonenzymatic defenses include vitamins E and C, β carotene, and free metal– and heme-binding proteins (1).

Critical illness can drastically increase the production of reactive oxygen species and other radicals. This compromises AOX capacity and leads to enhanced oxidative stress (1–4). Sources of oxidative stress in critical illness include activation of phagocytic cells; excessive peroxynitrite production by vascular endothelium; release of iron, copper, and metalloprotein; and damage caused by tissue and vascular ischemia/reperfusion. We previously reported that all these pathogenic events are exacerbated with increasing age (5,6). This clinical scenario suggests potential therapeutic strategies involving AOX repletion in such patients.

There is little clinical evidence for supplementing AOX in critically ill patients. Indeed, few studies have explored the supplementation of AOX and markers of oxidative stress (7). Accordingly, the goal of this study was to investigate whether dietary enteral supplementation with the AOX vitamins C (500 mg/d) and E (400 IU/d) would influence oxidative stress, AOX defenses, and the 28-day outcome of critically ill patients.

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In particular, we measured plasma isoprostanes, a reliable index for oxidative stress *in vivo* (8).

Methods

This study was a randomized, double-blind, placebo-controlled supplementation trial. Studies were conducted according to the rules established in Helsinki, and the study protocol was approved by the local ethical committee of intensive care units (ICU) in Naples, Novara, and Catania. Informed written consent was obtained from the patients (when possible) or their relatives. From February 1997 to May 2002, we selected 224 consecutive patients older than 18 yr who were expected to require at least 10 days of enteral feeding. Studies were conducted in coronary care units and medicosurgical ICUs. Trauma patients were enrolled within 48 h of sustaining their injury, whereas other patients were enrolled within 72 h of their admission to the critical care unit. Patients with isolated or severe head injury (Glasgow Coma Scale score of $\leq$6) or brain death and those needing anticoagulation therapy with warfarin were excluded from the trial.

According to the original study, a simplified acute physiological score was calculated within the first 24 h of ICU admission (9). The Injury Severity Score was measured in trauma patients (10). At all times throughout the study, the diagnosis of acute respiratory distress syndrome (ARDS) was made according to the American-European Consensus Conference (11). Septic shock was defined according to the criteria outlined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (12). Diagnosis of cardiogenic shock was made after documentation of myocardial dysfunction, excluding or correcting hypovolemia, hypoxia, and acidosis. Hemodynamic criteria included persistent hypotension (systolic blood pressure $<$90 mm Hg or requirement for catecholamines) and a cardiac index $<2.2\ \mathrm{L \cdot min^{-1} \cdot m^{-2}}$ in the presence of increased pulmonary capillary wedge pressure ($>$16 mm Hg) and clinical signs of cardiogenic shock (e.g., cold skin, mental confusion, and oliguria). Because the study was prolonged (5 yr), both groups were balanced over time regarding the techniques and protocols for ventilator management, hemodynamic support, and treatment of organ failures. Patients were randomized by using computer-generated random numbers. Blockwise randomization in a 1:1 ratio was used to obtain balanced sample sizes. The enteral solutions were prepared in the central pharmacy of the hospital and identified by a number code, and they were undetectable to the clinical team. The Harris-Benedict equation, multiplied by a correction factor of 1.3, 1.5, and 2 for low, moderate, and severe stress levels, respectively, was used for the estimation of daily caloric needs. Enteral feeding was delivered to achieve a minimum of 75% of the calculated basal energy expenditure within 48 h of initiation of enteral feeding.

All critically ill patients were receiving continuous feeding through a nasogastric probe (mean rate of 28 mL/h for the first day and 55 mL/h from the second day) with the standard isocaloric and isonitrogenous dietetic feeding preparation (containing 130 kcal/dL, protein 7.0 g/dL, free arginine 0.50 g/dL, carbohydrate 13.0 g/dL, lipid 4.5 g/dL, 10 IU of vitamin E, and 50 mg of ascorbic acid). Patients were excluded from the trial in case of enteral feeding suspension within 10 days from starting. Enteral feeding was suspended in case of gastric residues more than 300 mL and persistent diarrhea despite the use of drugs, resulting in caloric delivery less than 50% of that prescribed. Other criteria for enteral feeding suspension included surgery requirements, gastrointestinal hemorrhage, and pancreatitis.

Two-hundred-sixteen of these patients (age, 61.5 $\pm$ 7.0 yr) received 10 days of enteral feeding. Eight patients did not complete the study protocol as a result of enteral feeding suspension from several causes (five for surgery requirements, one for gastrointestinal hemorrhage, one for pancreatitis, and one for persistent diarrhea); these patients were excluded from the study (see below). Postrandomization, 105 patients received AOX supplementation with vitamins C (500 mg/d) and E (400 IU/d) in the enteral feeding preparation. Control patients (n = 111) received an equal amount of isotonic saline solution. AOX supplementation was maintained for 10 days. These AOX dosages were chosen on the basis of review of the literature together with the current clinical guidelines (13,14). The primary end-point of this study was the evaluation of variables of oxidative stress (see below). Secondary efficacy end-points included documented infection (by bacteriologic confirmation of positive blood culture or in bronchioalveolar lavage fluid); the development of multiorgan failure (MOF), defined according to the multiple organ dysfunction score of Marshall et al. (15); and clinical outcome measures, including the duration of mechanical ventilation, ventilator-free days, the 28-day outcome of critically ill patients, and hospital length of stay.

Plasma levels of lipid peroxidation were estimated by plasma malonyldialdehyde measured with the thiobarbituric acid reaction (TBARS) (16) and plasma prostaglandin $F_{2\alpha}$ isoprostanes measured by enzyme immunoassay (Cayman Chemical, Ann Arbor, MI), as previously described (17). Low-density lipoproteins (LDL) were isolated by short-term ultracentrifugations in a vertical rotor, as described previously (18). Plasma (micrograms per milliliter) and LDL-bound

Table 1. Baseline Characteristics of 216 Patients Who Completed the Study Divided into Two Groups

Variable	AOX protocol (n = 105)	Regular diet (n = 111)
Age (yr)	61.8 ± 7.4	61.2 ± 6.5
Sex	71 M/34 F	76 M/35 F
Comorbidity		
COPD, n (%)	6 (5.7%)	8 (7.2%)
CHD, n (%)	43 (40.9%)	48 (43.24%)
Cerebrovascular disease	14 (13.3%)	15 (13.5%)
Diabetes mellitus	10 (9.5%)	9 (8.1%)
Malignancy	18 (17.1%)	16 (14.4%)
Diagnosis		
Trauma[a]	44 (41.9%)	42 (37.28%)
Chronic renal failure	16 (15.2%)	12 (10.8%)
Cardiogenic shock	43 (40.9%)	40 (36%)
Septic shock	6 (5.7%)	5 (4.5%)
Hypovolemic shock	2 (1.9%)	4 (3.6%)
Illness severity		
SAPS (score)	18 ± 5	19 ± 6
ISS (score in trauma patients)	20 ± 10[b]	19 ± 8[b]

M = Male; F = female; AOX = antioxidant; COPD = chronic obstructive pulmonary disease; CHD = coronary heart disease; SAPS = Simplified Acute Physiology Score; ISS = Injury Severity Score.

[a] Trauma patients: n = 44 in the AOX protocol; n = 42 in the regular diet protocol.

[b] Enrolled within 48 h of sustaining their injury. Other patients were enrolled within 72 h of their admission to the critical care unit.

Table 2. Clinical Events Recorded in the Study Population

Variable	AOX protocol (n = 105)	Regular diet (n = 111)	P value
ARDS	18 (17.1%)	21 (18.9%)	NS
Multiple organ failure	22 (20.9%)	25 (22.5%)	NS
Patients requiring mechanical ventilation	79	84	
Duration of mechanical ventilation, (days) (mean ± sd)	6.2 ± 2.3	8.9 ± 1.8	0.05
Ventilator-free days (mean)	15.7	11.2	0.01
Hospital length of stay (days)	23.2	27.5	NS (0.092)

ARDS = acute respiratory distress syndrome; AOX = Antioxidant; NS = not significant.

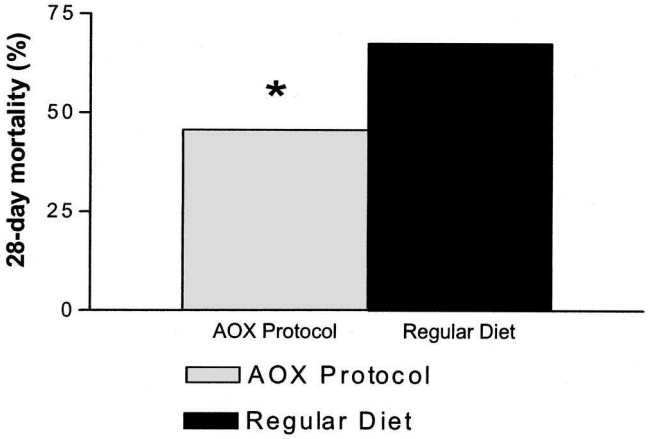

Figure 1. The 28-day mortality between groups of critically ill patients. *$P < 0.05$. AOX = antioxidant.

tocopherol levels (nanomoles of vitamin E per milligram of protein) were measured by high-performance liquid chromatography, as described in detail previously (16). *Ex vivo* LDL oxidizability was triggered by $CuSO_4$ (19). These variables of oxidative stress were determined from plasma samples drawn before randomization and at the end of the 10-day period.

All values presented in the text and figures are expressed as mean ± sd. Statistical analysis was performed with Student's t-test and one-way analysis of variance, as appropriate. A χ^2 test was performed for comparison of the clinical variables over time and between groups. Statistical significance was followed by Bonferroni's correction and accepted for $P < 0.05$. Interim analyses of treatment were performed in a blinded fashion to evaluate the significance of the treatment as compared with comorbidity. Statistical analyses were performed with StatView version 6.0.1 (SAS Institute Inc., Cary, NC).

Results

The baseline patient characteristics are shown in Table 1. Our selected patients were relatively old (average age of 61.5 yr) and had multiple comorbidities. The groups were similar in terms of sex, type of diagnosis or shock, and simplified acute physiological score. In trauma patients, Injury Severity Scores were similar in both groups. Table 2 describes the main clinical results obtained in 216 patients who, after randomization, completed the study. Although the number of patients who required mechanical ventilation was similar between groups (approximately 80%; P = not significant), both the duration of mechanical ventilation and the number of ventilator-free days were significantly reduced by AOX treatment (Table 2). Other variables, including ARDS, MOF, and hospital length of stay, were similar between groups (Table 2). Remarkably, there was a significant reduction in 28-day mortality after AOX intervention (48 dead patients [45.7%] in the AOX group and 75 dead patients [67.5%] in the regular-feeding group) (Fig. 1). In the intention-to-treat analysis, there was no difference between groups for any measured variable (Table 3). The incidence of

Table 3. Intention-to-Treat Analysis

Variable	Intention to treat		Evaluable	
	AOX protocol (n = 112)	Regular diet (n = 112)	AOX protocol (n = 105)	Regular diet (n = 111)
Age (yr)	61.9 ± 7.0	61.0 ± 7.3	62.1 ± 7.3	60.9 ± 6.7
SAPS	19 ± 4	19 ± 5 (NS)	18 ± 5	19 ± 6 (NS)
ISS	19 ± 11	19 ± 10 (NS)	20 ± 10	19 ± 8 (NS)
28-d mortality	49 (43.7%)	76 (67.8%) ($P < 0.05$)	48 (45.7%)	75 (67.5%) ($P < 0.05$)
ARDS	20 (17.8%)	22 (19.6%) (NS)	18 (17.1%)	21 (18.9%) (NS)
Multiple organ failure	24 (21.4%)	26 (23.3%) (NS)	22 (20.9%)	25 (22.5%) (NS)
Patients requiring mechanical ventilation	82	85	79	84
Hospital length of stay (days)	26.5	27.5 (NS)	23.2	27.5 (0.092) (NS)

SAPS = Simplified acute physiology scale; ISS = injury severity scale; ARDS = acute respiratory distress syndrome; AOX = antioxidant; NS = not significant.

documented infections (23% from pneumococcus, 12% from pneumonia, 30% from *Pseudomonas* species, 5% from *Escherichia coli*, and the remainder from viral infections) in the ICU was not different between the control and AOX-treated groups (P = not significant). Variables of oxidative stress are shown in Figure 2. In the AOX-treated group, plasma TBARS and isoprostanes were 5.33 ± 1.26 nM/mL and 312 ± 68 pg/mL before AOX treatment and 2.42 ± 0.61 nM/mL and 198 ± 42 pg/mL after intervention ($P < 0.01$ for both comparisons), respectively. Under our experimental conditions, all these variables were significantly improved by the administration of AOX. As expected, AOX also significantly increased the concentration of plasma and LDL-bound vitamin E (from 5.6 ± 0.5 μg/mL and 2.7 ± 0.6 nmol/mg of protein to 9.3 ± 0.8 μg/mL and 4.5 ± 0.8 nmol/mg of protein, respectively; $P < 0.01$ for both comparisons). More importantly, the intervention improved LDL resistance to oxidative stress by approximately 30% (the lag time before treatment was 87 ± 23 min and was 118 ± 20 min after treatment; $P < 0.04$). No such change was observed in the control group (Fig. 2). Interestingly, plasma levels of vitamin E were inversely correlated with the duration of mechanical ventilation in the AOX-treated patients ($r = 0.56$; $P < 0.05$).

Discussion

The most salient result of this study is that AOX supplementation reduces oxidative stress and 28-day mortality in critically ill patients. The pathogenic role of severe oxidative stress in critical care has been clearly demonstrated by experimental and clinical evidence. The presence of increased oxidative stress has been studied in patients with septic shock (2), MOF (20), and ARDS (3). In general, these studies demonstrated that in the critically ill population, serum AOX decreased while measures of oxidative stress increased (2–4). In addition, higher levels of oxidative stress were found to be associated with more extensive organ dysfunction and with increasing age.

In this study, malonyldialdehyde levels (TBARS) were increased in all patients, serving as a marker of massive oxidative stress at the onset of illness. Moreover, all patients had markedly reduced concentrations of plasma vitamin E and tocopherol carried on LDL. In accordance with our data, previous studies have shown an increased potential for oxidative stress in critically ill patients, in terms of increased lipid peroxides (2,3) and decreased tocopherol concentrations (2,20). Very small concentrations of vitamin C have been reported in critically ill patients (1,4), but we did not measure vitamin C levels in this study. Circulating lipid peroxides in critically ill patients have been shown to correlate with both tocopherol concentrations (3) and Acute Physiology and Chronic Health Evaluation score (2). However, another study was unable to show a relationship between the severity of organ dysfunction and tocopherol levels (20). Finally, altering the composition of the enteral preparation may influence hospital outcome (21). Thus, it is important to keep the nutritional status constant in critically ill patients.

Vitamin E is a nonenzymatic AOX present in biological membranes. It reacts as a chain-breaking AOX in the inhibition of the peroxidation of lipids and is the most important lipid-soluble AOX in humans. Vitamins E and C act synergistically, resulting in an α-tocopheroxyl radical that is then reduced back to α-tocopherol by vitamin C. In our study, relatively large doses of tocopherol and vitamin C supplementation caused a decrease in end products of lipid peroxidation and an increase in vitamin E levels, thus improving LDL resistance to oxidative stress (lag time). As expected, these changes were not observed in the untreated control group. The reduction of oxidative stress also positively influenced the patients'

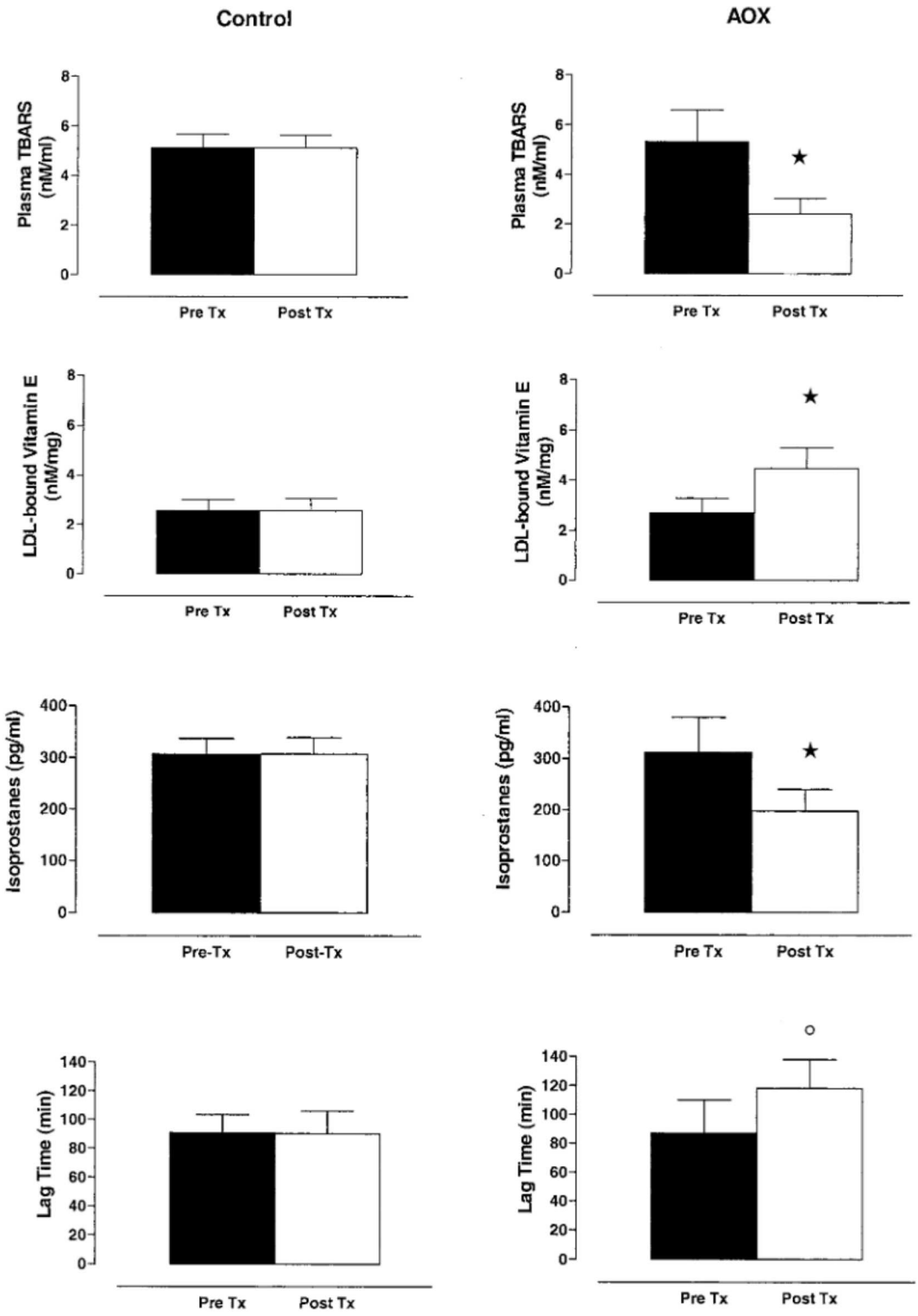

Figure 2. Plasma malonyldialdehyde, isoprostanes, low-density lipoprotein (LDL)-bound α-tocopherol, and LDL resistance to oxidative stress (lag time) before and after antioxidant (AOX) intervention (10 days) in the control group and the AOX group. $^{*}P < 0.01$; $^{\circ}P < 0.04$. Data are shown as mean ± sd. Tx = treatment; TBARS = thiobarbituric acid reactions.

clinical outcome. A previous study investigated the effect of IV AOX therapy (*N*-acetylcysteine and vitamins E and C) on AOX status, lipid peroxidation, and hemodynamics in patients with septic shock within 6 hours after the start of the therapy (22). This study also showed a reduction of vitamin C in septic shock

patients with normal total AOX capacity and increased lipid peroxide concentrations that were not significantly decreased by AOX administration. However, AOX intervention was associated with positive hemodynamic changes (increased heart rate and cardiac index and reduced systemic vascular resistance index). This lack of effect of AOX on lipid peroxidation might be related to the small doses administered and the brief clinical period of evaluation. In our study, the AOX were administered every day, and the blood determination was repeated at the end of the 10-day period. AOX could also correct immunodeficiency (23) and have an effect on several proinflammatory transcription factors in the cardiovascular system (24,25).

Similar results regarding lipid peroxidation were described in another recent study (26). In this study, the addition of AOX vitamins (vitamin A 133 μg/dL, vitamin C 13.4 μg/dL, and vitamin E 4.94 μg/dL in the enriched preparations administered continuously at 720 mL/d from Day 0 to Day 1 and at 1440 mL/d from Day 1 to Day 7) to the enteral feeding formula increased plasma vitamin concentrations and improved the resistance of LDL to oxidation. In contrast to our own study, no change was observed in total lipid peroxidation estimated by TBARS. This was probably due to the small amount of AOX vitamins obtained by the enteral route; also, there was no significant difference in clinical outcome.

This study demonstrates that AOX intervention reduces plasma isoprostanes, which are now considered the more reliable index for oxidative stress *in vivo* (13,14). Plasma isoprostanes are initially esterified to phospholipids and are then released in their free form. There are several favorable attributes that make measurement of isoprostanes attractive as a reliable indicator of oxidative stress *in vivo*: (a) isoprostanes are specific and stable products of lipid peroxidation; (b) isoprostane levels are present in detectable quantities in all normal biological fluids and tissues, allowing the definition of a normal range; (c) their formation increases dramatically *in vivo* after oxidative injury and is affected by AOX status; and (d) their levels are not affected by the lipid content of the diet. Our results are also consistent with those obtained in an experimental model of septic shock (27).

In summary, we show that AOX intervention with proper doses of vitamin E and C supplemental to enteral feeding prevents lipid peroxidation and oxidative stress *in vivo*. AOX intervention also significantly influenced the 28-day outcome in critically ill patients. In absolute terms, mortality was frequent, but this was expected because this condition is relatively common in elderly patients with frequent comorbidities (28,29). Among patients older than 65 years of age, Knaus et al. (28) reported hospital mortality rates of 60% with 1 organ system failure, 90% with 2 organ system failures, and 100% with 3 or more organ system failures.

Our findings are in agreement with those of a large clinical study (595 patients) showing that AOX supplementation reduces the incidence of organ failure and shortens the length of stay in a cohort of critically ill surgical patients (30). The lack of adverse effects, coupled with the minimal expense, supports the use of AOX in critically ill patients. Interestingly, there is growing interest in superoxide dismutase mimetics in critical care medicine (31). Obviously, other large clinical multicenter trials are recommended to better understand the effect of AOX therapy on the clinical outcome and mortality in critically ill patients. In this clinical setting, measurement of isoprostanes may provide a sensitive biochemical basis for dose selection in studies of natural and synthetic AOX.

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