

Nutritional Support in Intensive Care Unit (ICU) Patients

Topic 18

Module 18.5

Use of special substrates in ICU

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Learning Objectives

- To understand the rationale for the increased requirements of glutamine and antioxidants;
- To highlight the physiological importance of glutamine and antioxidant defense mechanisms.

Contents

1. Glutamine
2. Antioxidants
 - 2.1 Introduction
 - 2.2 Sources of reactive oxygen species
 - 2.3 Mechanisms of neutralization of ROS
 - 2.4 Presence of increased oxidative stress in critically ill patients
 - 2.5 Current recommendations
 - 2.6 Antioxidant vitamins
 - 2.7 Trace elements
3. Conclusions

Key Messages

- Addition of glutamine and antioxidants improves outcome in critically ill patients;
- Glutamine is involved in several pathways and systems involved and active during critical illness;
- The systematic increase in oxidative stress is associated with the rapid exhaustion of endogenous antioxidant defence mechanisms;
- Trace elements and antioxidant vitamins were found efficient in decreasing infectious morbidity and mortality in critically ill patients;

The particular alterations found in ICU patients are associated with increased demands for some otherwise unessential nutrients, or with specific mechanisms of tissue injuries. These findings led to the development of special solutions designed to fill the stores, or to blunt pathogenetic mechanisms. Among the numerous so-called "pharmacconutrients" investigated so far, the clinical efficacy was confirmed for some of them, including glutamine, antioxidants and modified lipids.

1. Glutamine

There is a considerable and continuous interest for glutamine as an adjunct in the treatment of critical care patients for several decades. Shortage of glutamine, mirrored by a low plasma concentration of glutamine in ICU patients on the day of admission is associated with an unfavourable outcome. Actually, a low plasma glutamine concentration (below 0.42 mmol/l) can serve as a predictive factor independent of the APACHE II scoring, and the mortality rate is double in the low plasma glutamine group as compared to the normal plasma glutamine group, despite only a marginal difference in the APACHE II score (1).

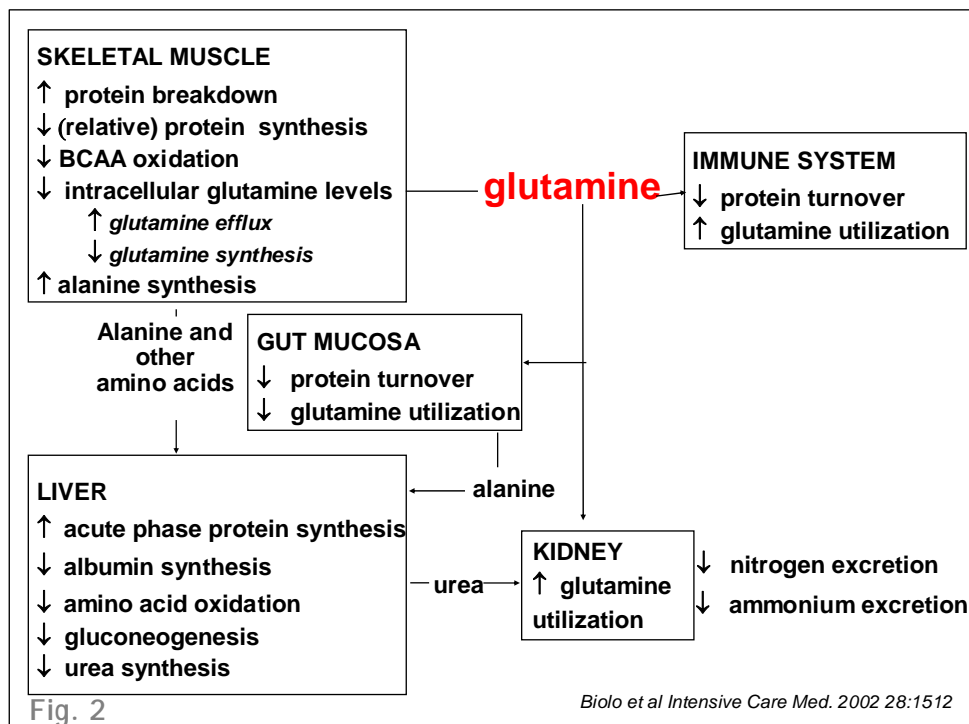
Nutrition in ICU

Glutamine-supplemented - PRO

- Glutamine is the most abundant amino-acid in the body
- Muscle represents the major body protein pool
- Semi-essential amino-acid during stress
- Primary fuel for all rapid proliferating cells (enterocytes, lymphocytes, etc.)
- Helps to maintain gut integrity
- Reduces muscle degradation

Fig. 1

The rapid depletion of the glutamine stores during critical illness has been reported (2, 3). Indeed, during the catabolic phase of critical illness states, a substantial part of the amino acid release from peripheral tissues is from branched-chain amino acids converted and released into the circulation as glutamine and alanine, in contrast with the normal gut and portal origin of amino acids in the physiological conditions.



Nutrition in ICU

Enteral glutamine

Houdyk*	Lancet 1998	Lower infectious morbidity
Jones*	Nutrition 1999	Lower hospital cost (30% per survivor)
Hall	ICM 2003	No effect
Garrell	CCM 2003	Lower infectious morbidity
Conejero	Nutrition 2002	Lower infectious morbidity
Zhou	JPEN 2002	Lower hospital cost

Fig. 3

Nutrition in ICU

Glutamine-supplemented PN

Griffiths	Nutrition 1997 (ICU)	Improved survival at 6 months
Goeters	Crit Care Med 2002 (ICU)	Improved survival at 6 months
Powell-Tuck	Gut 1999 (general population)	➤ los in surgical patients
Wischneyer	Crit Care Med 2001 (burned patients)	➤ gram-negative bacteriemia
Dechelotte	Clin Nutr 2002 (Abstract)	Improved outcome

Fig. 4

Nutrition in ICU

Glutamine-supplemented PN

- Prospective randomized study
- n = 84 patients
- Results:
 - survival at 6 months
24/62 (Gln) vs 14/42 (control); p 0.049
 - for Gln receivers, reduction of hospital cost (50%)

Fig. 5

Griffiths R et al, Nutrition 1997

Glutamine is actually the most abundant free amino acid in the human body and is found in higher quantities and concentrations than any other free amino acid.

Although it can be manufactured from α -ketoglutarate and glutamate via glutamate aminotransferase in all cells from and glutamine synthetase, the majority is built in skeletal muscle and transported to intestinal cells, kidney, and lymphocytes. Therefore, it is likely that, during critical illness, the status of glutamine moves from "conditionally essential" to essential. Importantly, the standard nutrition support solutions contain very few (polymeric casein-derived enteral formulas) or no glutamine (standard parenteral formulas).

Several studies of different sizes very consistently reported that supplemental glutamine is efficient when a daily dose higher than 0.20 g/kg is administered for at least 5 days (4 - 10).

Several possible mechanisms can be advocated to explain the beneficial effects of glutamine (11, 12), including metabolic, immunologic, anti-oxidant and gut protective effects listed in Fig 1. These effects can be exerted directly by glutamine, or via one of its byproducts (glutamic acid or nucleotides).

When intravenous glutamine is given to ICU patients there is a dose response situation. A dose of 20 g / 24 h normalizes plasma glutamine concentration in the majority of ICU patients. This indicates that plasma glutamine concentration may be a good surrogate parameter to titrate the dosage of glutamine necessary to put all ICU patients in a more favourable position in terms of glutamine supply.

It is recommended to give long-stayers in the ICU, which are only possible to feed by the parenteral route extra glutamine. This recommendation is not controversial, but perhaps one should rather try to prevent the state of glutamine depletion than wait to see it actually occur.

Therefore one might consider giving intravenous glutamine in parallel to the combination of enteral and parenteral nutrition but separately. This will guarantee the patient the prescribed dose of glutamine regardless of how enteral and parenteral nutrition is combined on the individual day.

POSSIBLE BENEFICIAL EFFECTS OF GLUTAMINE SUPPLEMENTATION

Preiser and Wernerman Crit Care Med 2003; 31:2555

- | | |
|---|--|
| <p>Metabolic</p> <ul style="list-style-type: none"> •Protein synthesis •Carbon and Nitrogen inter-organ transporter •Gluconeogenesis precursor •Ammoniogenesis (kidney) <p>Immunologic</p> <ul style="list-style-type: none"> •Replication of immune cells •T-cells function •IgA synthesis •HLA-DR on CD14 | <p>Gut protection</p> <ul style="list-style-type: none"> ■Enterocyte replication ■Maintenance of GALT ■Prevents hyperpermeability <p>Anti-oxidant</p> <ul style="list-style-type: none"> ■Glutathione synthesis ■Taurine precursor ■Haemoxygenase <p>Induction of specific pathways</p> <ul style="list-style-type: none"> ■HSP ■HO-1 |
|---|--|

Fig. 6

Glutamine dose

IV	: 0,13 - 0,57 g / kg / j
AMM	: 0,3 - 0,4 g / kg / j
soit	: 0,20 - 0,27 g Gln / kg / j

$$\text{Total AA : } 1,2 + 0,3 \text{ \textasciitilde{ } } 1,6 + 0,4 \text{ g / kg / j}$$

Fig. 7

Nutrition in ICU

Glutamine-supplemented PN

The committee noted that in patients receiving PN, there was a modest reduction in mortality associated with parenteral glutamine. The high cost and lack of availability of parenteral nutrition limit the application of this intervention.

Recommendations... when PN is prescribed to critically ill patients, parenteral supplementation with glutamine, where available, is recommended.

Fig. 8

Canadian Guidelines, JPEN 2003

INCREASED OXIDATIVE STRESS IN ICU PATIENTS

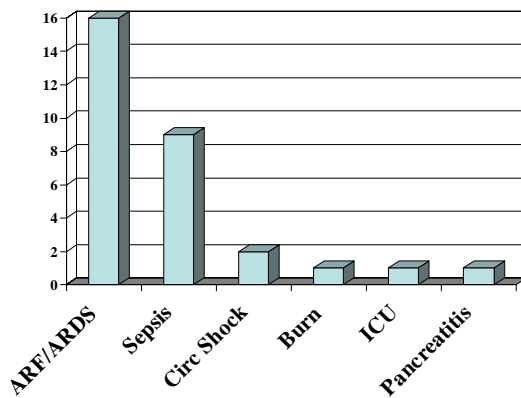


Fig. 9

ANTIOXIDANT LEVELS IN SICU PATIENTS

Quasim et al Clin Nutr 2003;22:459

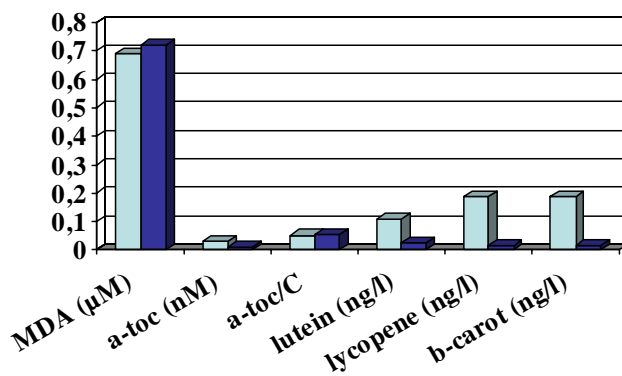


Fig. 10

Legend: Normal (light blue), ICU (dark blue)

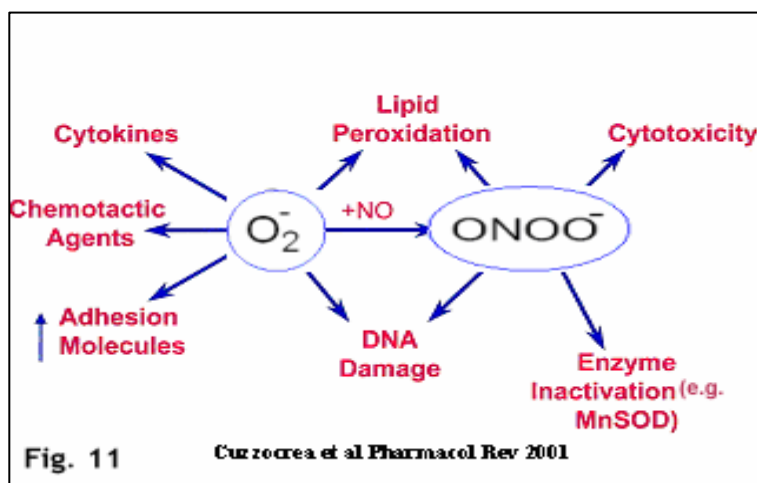


Fig. 11

Cuzzocrea et al Pharmacol Rev 2001

2. Antioxidants

2.1 Introduction

An increase in the oxidative stress is typically present in critically ill patients (Fig. 9), as a consequence of the overproduction of reactive oxygen species (ROS) and of the rapid depletion of the endogenous stores of anti-oxidants (14).

Importantly, oxidative stress has been incriminated in the pathogenesis of the systemic inflammatory response and the dysfunction of organs, via cellular energetic failure and via an interaction with several pathways following lipid peroxidation, and oxidative damage to proteins, DNA and RNA. (Fig. 10)

Therefore, the incorporation of exogenous antioxidants in the treatment of various models of experimental shock, inflammation and ischemia/reperfusion injury (15) and in different categories of critically ill patients have been considered from several years (16).

However, the efficacy of this strategy was confirmed in some studies, while others failed to demonstrate any benefit. Several reasons may be advocated to explain the failures:

- First, in physiological conditions, an increased oxidative stress is desirable for some cell functions (proliferation, gene expression, apoptosis). The role and importance of the ROS and RNS in the regulation of these functions is only partially understood during critical illness.

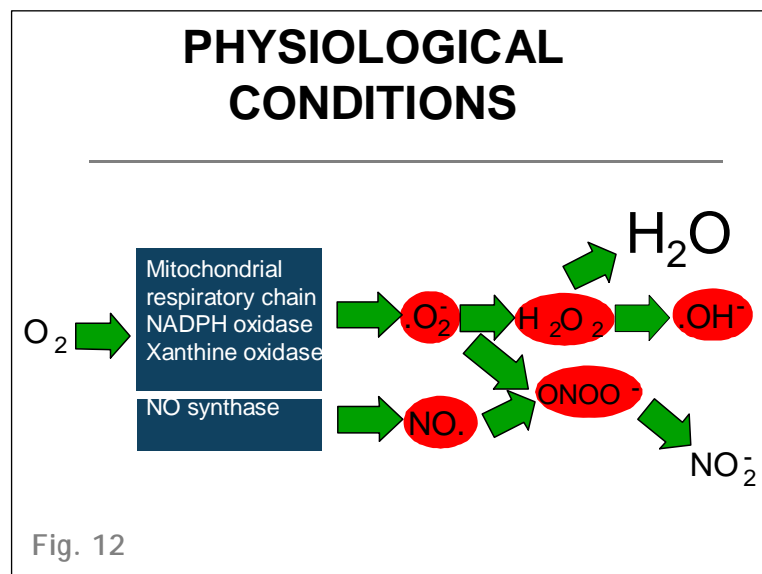
- Second, the amount of exogenous anti-oxidants required to restore the anti-oxidant capacity is not accurately known and could vary according to the clinical situation and could be influenced by several current therapeutic interventions, including the nutritional status. The bio-availability of some anti-oxidants administered enterally could also be impaired.
- Third, the issue of timing of antioxidant administration is probably a key factor, as the depletion of anti-oxidant would probably achieve a greater efficacy if given before a massive oxidative injury (major surgery, shock, severe sepsis). Therefore, the anti-oxidant approach can be considered as a preventive as well as a therapeutic modality.

2.2 Sources of reactive oxygen species

Stricto sensu, a free radical or reactive species is an unstable atom with an unpaired electron. ROS include superoxide ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2) and the hydroxyl radical ($OH\cdot$).

In critically ill patients, ROS can be produced from 4 different pathways:

- The mitochondrial respiratory chain produces $O_2^{\cdot-}$ as a byproduct of the reaction of molecular oxygen with semi-ubiquinone. In case of severe mitochondrial dysfunction, as observed during septic shock (17), this pathway could be up-regulated and massive amounts of $O_2^{\cdot-}$ could be released.
- The NADPH oxidase enzyme of neutrophils and macrophages is activated in case of cell stimulation and can produce massive amounts of $O_2^{\cdot-}$ as a microbiocidal mechanism. This pathway is probably predominant in the overproduction of ROS during severe sepsis.
- The xanthine oxidase enzyme is a ubiquitous enzyme activated during ischemia, which produced massive amounts of $O_2^{\cdot-}$ during the reperfusion phase. This pathway is probably activated during major cardiac and vascular surgery, and during solid organs transplantations.
- Some metallic ions (iron, copper) are released in case of cell lysis and can amplify the oxidative stress, as they are co-factors of the conversion of hydrogen peroxide into hydroxyl.



2.3 Mechanisms of neutralisation of ROS

If unopposed, the free electron of the ROS will bind to lipids, proteins, DNA, RNA, thereby triggering cell injury and tissue dysfunction. In physiological conditions, the free electron of ROS is scavenged by enzymatic or non-enzymatic anti-oxidant defence mechanisms.

The mechanisms of inactivation of ROS include successive steps: the dismutation of superoxide into hydrogen peroxide under the influence of SOD and the conversion of hydrogen peroxide into water under the influence of catalase and glutathione peroxidase. Importantly, trace elements (copper/manganese/zinc, iron and selenium) are respectively required for the activity of SOD, catalase and glutathione peroxidase.

The major non-enzymatic defence mechanisms include endogenous molecules (glutathione, urate, ubiquinones/ubiquinol, albumin and bilirubin) and vitamins (ascorbic acid, α -tocopherol, β -carotene).

CLASSIFICATION OF ANTIOXIDANTS	ANTIOXIDANT MECHANISMS
<ul style="list-style-type: none"> • Functional <ul style="list-style-type: none"> – Prevention of ROS formation (Primary) – Inactivation of ROS (Secondary) • Localisation (site of action) <ul style="list-style-type: none"> – Extracellular – Intracellular – Membrane-bound • Physico-chemical properties <ul style="list-style-type: none"> – Hydrophilic – Lipophilic 	<ul style="list-style-type: none"> • Free electron scavengers <ul style="list-style-type: none"> – Exogenous : Vitamins A, C and E – Endogenous : Glutathione • Enzymatic systems <ul style="list-style-type: none"> – Superoxide dismutase (MnSOD - CuZnSOD) – Catalase (Fe/Cu) – Glutathione peroxidase (Se)

Fig. 13

Importantly, the reduction of oxidised α -tocopherol, which is necessary for the perpetuation of its antioxidant effect requires the presence of glutathione or ascorbic acid. Therefore, an efficient antioxidant effect would be obtained by the simultaneous administration of vitamins C and E.

In addition to the generation of ROS, oxidative injury can be amplified or inhibited by reactive nitrogen species (RNS) (18, 19). RNS include nitric oxide (NO \cdot), peroxynitrite (ONOO \cdot),

nitrosonium (NO $^+$), nitrosyl (NO $^-$) and can induce per se nitrosative injuries, or combine to ROS to enhance or attenuate the oxidative injury. At present, the exact physiological role of RNS is only partially understood, and there are very few clinical data on the manipulation of nitrosative injury.

2.4 Presence of increased oxidative stress in critically ill patients

Due to the very short half-life of ROS, the proof of increased oxidative stress in patients implies the demonstration of a presence of byproducts of oxidative damage on lipids (thiobarbituric-acid reacting substances (TBARS measured by the malonyldialdehyde (MDA) assay, 4-hydroxynonenal, lipoperoxides), DNA or proteins) or a decrease in the stores of endogenous antioxidants (e.g. Total radical-trapping antioxidant parameter, TRAP) (for a detailed and comprehensive review see 20).

Numerous studies published until 2001 already demonstrated an increased oxidative stress, mainly in patients with acute respiratory failure, ARDS, sepsis or septic shock. More recent studies confirmed the presence of increased TBARS in patients with systemic inflammatory response syndrome and multiple organ failure (MOF) (21).

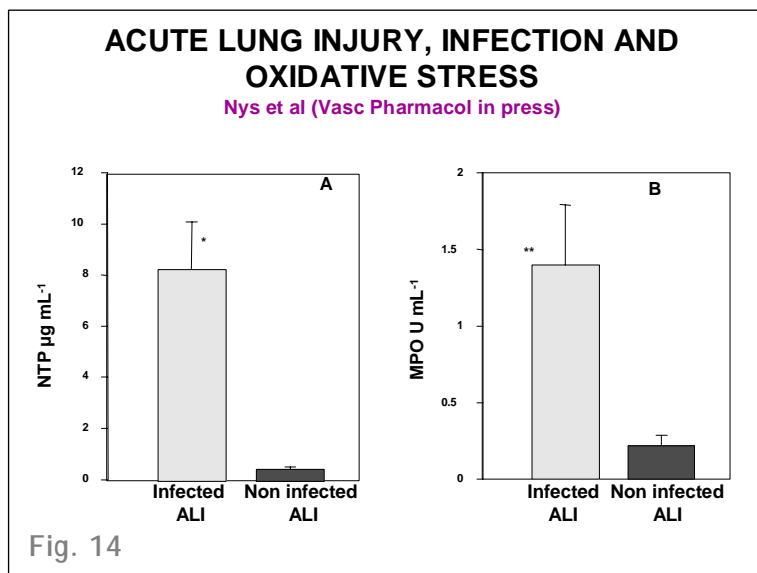


Fig. 14

The plasma level of TBARS was higher in patients with MOF than in those without MOF, and there was a correlation between the plasma level of TBARS and the Sequential Organ Failure Assessment score.

In another recent study performed in 50 critically ill patients (22), there was an increase in MDA and a decrease in the activity of SOD that were proportional to the disease severity.

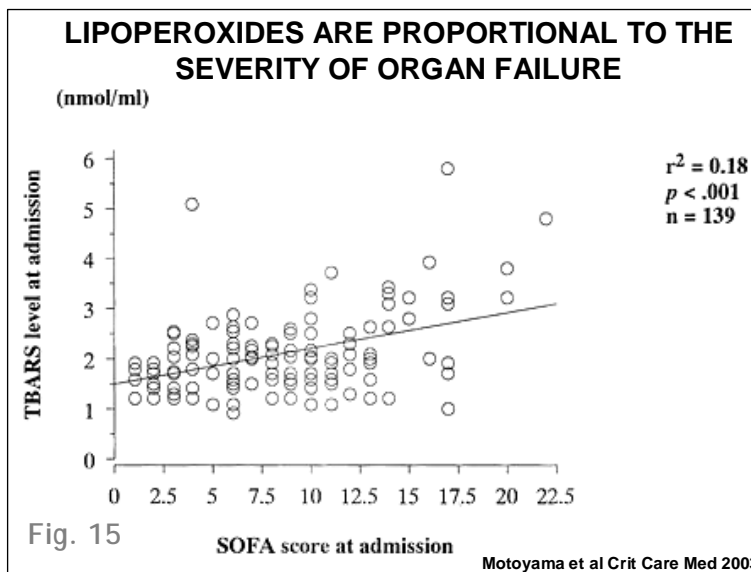
Consistently, Alonso de Vega et al (23) recently reported increased levels of MDA and 4-hydroxynonenal in 68 critically ill patients.

Similarly, the plasma lipoperoxides concentrations were higher before than after cardiac surgery (24), and were slightly higher in the presence than in the absence of postoperative MOF. TRAP was decreased in patients with SIRS and was progressively restored when patients' status improved or worsened (25). Interestingly, the increase in TRAP observed in survivors was essentially related to increases in the plasma levels of vitamins C, E and uric acid, whereas in non-survivors, the increase in TRAP was primarily related to an increase in plasma bilirubin.

2.5 Current recommendations

The currently used recommendations for the daily requirements in vitamins and trace elements are known as the Dietary Reference Intakes (DRI) (Table 1) and have been adapted for the enteral and parenteral support (26). However, higher doses could be necessary to meet the specific requirements of critically ill patients.

The most recent clinical studies reported the effects of antioxidants given prophylactically to patients "at risk" of oxidant-related complications, either as a component of nutritional support or as an individual medication. Other recent clinical trials assessed the effects of specific prophylaxis in patients before a scheduled procedure associated with intense oxidative stress.



CURRENT RECOMMENDATIONS FOR ANTI-OXIDANT VITAMINS

	Usual intake	RDA	Enteral	Parenteral	Experimental
B-carotene	1.5-3 mg		0.9 mg	1 mg	> 4 mg
Vitamin C	60-80 mg	60 mg	90 mg	100 mg	> 100 mg
Vitamin E	5-7 mg	8-10 mg	15 mg	10 mg	> 23 (100)

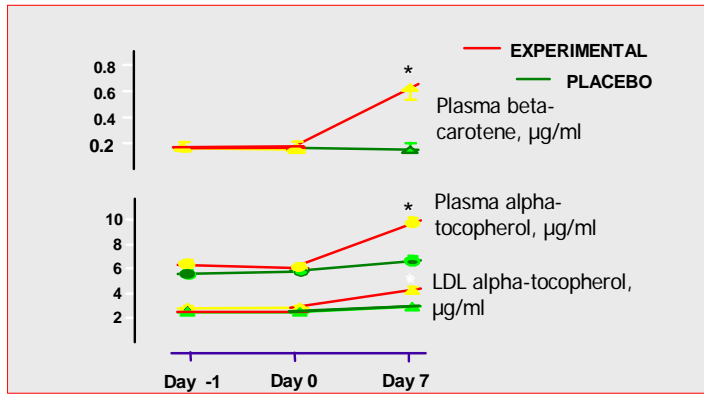
Fig. 16

Sources : ASPEN 2002, Carr, Frei AJCN 1999

Question : Are the anti-oxidants vitamins added to the enteral formulas absorbed, and efficient?

STUDY RESULTS

Fig. 17



2.6 Antioxidant vitamins

All nutritional support formulas contain antioxidant vitamins, already incorporated in the solution (enteral support) or added prior to infusion (parenteral support). We recently compared the effects of an enteral solution enriched with vitamin A (133 µg/dl including 66.7 µg/dl of β-carotene), vitamin C (13.3 mg/dl) and vitamin E (4.94 mg/dl) with an isonitrogenous, iso-caloric control solution in 37 critically ill patients with neurological impairment (27). This study demonstrated that α-tocopherol (total dose 350 mg over 7 days) and β-carotene (total dose 5000 µg over 7 days) were absorbed, as the plasma and lipoprotein-bound

fractions of these vitamins increased in the supplemented, but not in the control group. Importantly, these antioxidants were biologically active, as the resistance of low-density lipoproteins to experimental oxidative stress induced by copper sulphate increased. However, there was no difference in plasma TBARS level nor in the resistance of erythrocytes to oxidative stress. Similarly, Nelson et al (28) demonstrated in 98 patients with ARDS that α-tocopherol and β-carotene incorporated into a nutrition support formula were absorbed, but that the TRAP and the plasma lipid peroxide levels were unchanged, as compared with the control group. Importantly, clinical outcome variables including pulmonary function parameters (PaO₂/FiO₂ ratio, duration of mechanical ventilation) were found improved in patients receiving this solution (29).

Nathens et al (30) analysed the effects of prophylactic administration of vitamin C (1000 mg i.v.) and α-tocopherol (3,000 IU/day enterally) in 301 critically ill trauma patients. The plasma levels of both vitamins were increased. When compared to a matched group of 294 patients not receiving antioxidant supplementation, there was a significant reduction in the risk of developing multiple organ failure (relative risk 0.43, 95% confidence interval 0.19-0.96), and shorter durations of mechanical ventilation and length of stay in the intensive care unit. The incidences of pneumonia and ARDS tended to decrease in the group supplemented with antioxidants. In contrast, in a multi-center recent study on 220 critically ill patients (31) designed to compare the effects of a diet supplemented with antioxidant vitamins and arginine with an isonitrogenous isocaloric control formula on the incidence of nosocomial infections, there was a decrease in the rate of catheter-related infections, but not in the rate of other infections nor mortality.

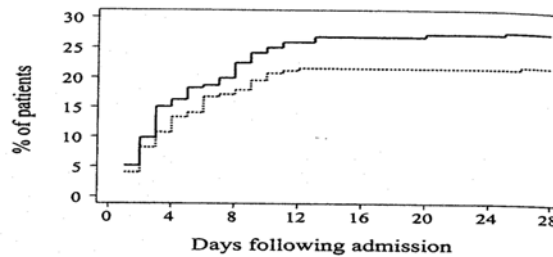
Nathens et al (30) analysed the effects of prophylactic administration of vitamin C (1000 mg i.v.) and α -tocopherol (3,000 IU/day enterally) in 301 critically ill trauma patients. The plasma levels of both vitamins were increased. When compared to a matched group of 294 patients not receiving antioxidant supplementation, there was a significant reduction in the risk of developing multiple organ failure (relative risk 0.43, 95% confidence interval 0.19-0.96), and shorter durations of mechanical ventilation and length of stay in the intensive care unit. The incidences of pneumonia and ARDS tended to decrease in the group supplemented with antioxidants. In contrast, in a multi-center recent study on 220 critically ill patients (31) designed to compare the effects of a diet supplemented with antioxidant vitamins and arginine with an isonitrogenous isocaloric control formula on the incidence of nosocomial infections, there was a decrease in the rate of catheter-related infections, but not in the rate of other infections nor mortality.

2.7 Trace elements

The effects of supplementations with large doses of selenium, zinc, copper and manganese, the four trace elements involved in the enzymatic antioxidant defence mechanisms were the focus of intense clinical research in the last decade (see 32 for review). However, during the last two years, there were few investigations specifically designed to document their effects on oxidative stress in critically ill patients.

EARLY ADMINISTRATION OF ANTI-OXIDANTS AFTER TRAUMA

Nathens et al Ann Surg 2002;236:814



Kaplan-Meier estimates of the risk of pulmonary morbidity (ARDS or pneumonia) among 301 patients receiving antioxidant supplementation and 294 patients receiving standard care. There is a suggestion that antioxidant supplementation might be associated with a lower likelihood of pulmonary morbidity ($P = .2$ by the log-rank test). Solid line: no antioxidant supplementation; dashed line: antioxidant supplementation.

Fig. 20

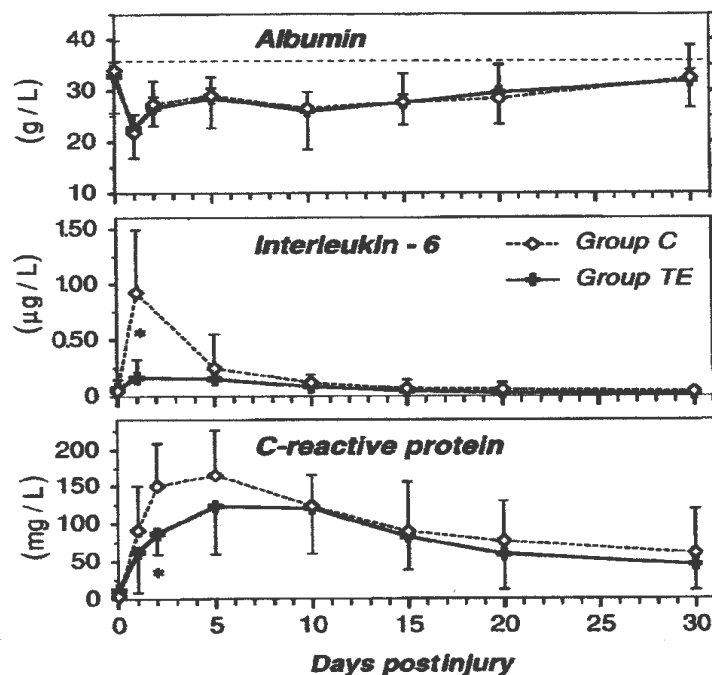


FIGURE 2. Evolution over time of albumin, interleukin 6, and C-reactive protein concentrations ($\bar{x} \pm SD$) in the trace element-supplemented (TE) and control (C) groups. Dotted line indicates the lower value of the reference albumin range. Number of samples per mean: $n = 10$ for all values of albumin and C-reactive protein until day 20 ($n = 6$ and 7 on day 30); for interleukin 6, $n = 10$ except on day 1, when $n = 5$ in group C and $n = 6$ in group TE, and on day 30, when $n = 6$ in group C and $n = 7$ in group TE. *For interleukin 6, $P < 0.001$; for C-reactive protein, $P < 0.03$.

EFFECTS OF TRACE ELEMENTS SUPPLEMENTATION

Berger et AJCN 1998

Fig. 21

ADDITION OF ANTIOXIDANTS RATIONALE

- ✓ Oxidative stress is increased in critically ill patients and contributes to organ damage / malignant inflammation.
- ✓ As the increase in oxidative stress is associated with depletion of the stores of anti-oxidants, the administration of anti-oxidants can be beneficial
- ✓ Adding anti-oxidant compounds to nutrition support is physiological.

Fig. 22

3. Conclusions

The importance of the implication of oxidative stress in the development of multiple organ failures is consistently demonstrated in critically ill patients. Therefore, the administration of antioxidants as a prophylaxis in patients at risk seems to represent an efficient approach, in view of the results of recent clinical trials. Optimal doses and combinations of antioxidants are still to be defined.

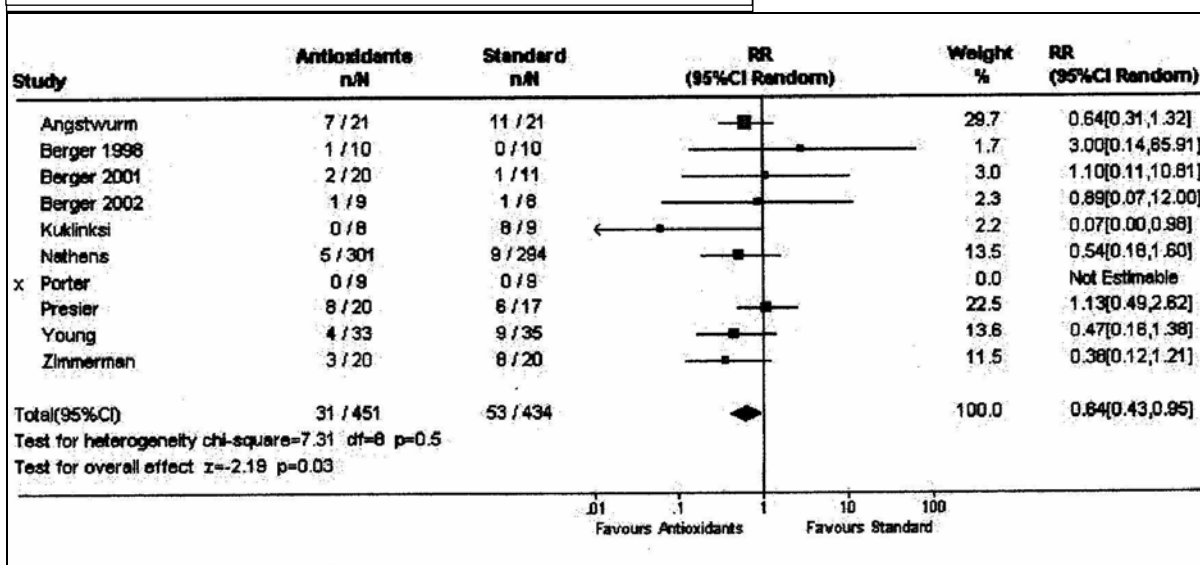


Fig. 23 META-ANALYSIS OF ANTIOXIDANT SUPPLEMENTATION
Heyland et al

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