Introduction

Trace elements and vitamins are essential components of nutrition (unless specified, vitamins and trace elements will hereafter be designated globally as micronutrients). Trace elements are metals and metalloids present in the body at fairly constant concentrations. Trace elements act as a structure of enzymes or as cofactors, and frequently they exert electron transfer functions. Their absence causes reproducible structural or biochemical deficits, and they are associated with specific biochemical alterations. These alterations can be prevented or corrected by the intake of the deficient element alone. Vitamins are organic substances required in minute amounts, and they are not synthesized by the body (or not in sufficient quantities). Vitamins are cofactors in the different metabolic steps of enzymes, carbohydrate, protein, and lipid metabolism.

Micronutrients are involved in the prevention of nutritional deficiencies, immune humoral and cellular defense, regulation of gene expression during the acute phase response, antioxidant defense, and prevention of chronic diseases. Most micronutrients have been discovered due to acute nutritional deficiencies causing specific diseases, such as ascorbic acid and scurvy, zinc and delayed wound healing and dwarfism, selenium and skeletal myopathy, and iron and anemia.

Micronutrient deficiency in the general population is infrequent, but inadequate intake is widespread as shown by a series of epidemiological studies carried out over the last 2 decades [1–3]. Due to changes in nutrient
composition and in eating habits, a large proportion of the population does not ingest the recommended intakes for micronutrients such as iron, selenium, zinc, and vitamins B and C. Inadequate intakes are considered to contribute to the development of cardiovascular diseases, cancer and ageing in the general population [4, 5]. There is growing evidence that micronutrient deficiencies occur in the critically ill patient, particularly in sepsis, major burns, and conditions with ischemia-reperfusion. A previously compromised status will rapidly be unbalanced by acute disease, and the related increased demands on the body.

Key micronutrients in critically ill patients will be those that are directly or indirectly involved in metabolic support, as well as in antioxidant and immune defense. In the following their roles will be detailed.

**Systemic Responses of the Critically Ill**

Critically ill patients differ from noncritically ill in many respects. Outcome is influenced by the life-threatening conditions they suffer: such patients are dependent on artificial, technical and metabolic support, which the noncritically ill rarely are. The metabolic consequences of their diseases are extensive. They are generally hypermetabolic and subsequently have increased nutritional requirements [6]. In addition the wound healing process of surgical patients increases the general and specific nutrient requirements. Many patients have abnormal vitamin and trace element losses due to their disease or injury. For example, septic patients have high vitamin A urinary excretion [7]; trauma patients lose zinc and selenium through their drains, and burn patients lose major amounts of copper, selenium, and zinc with their cutaneous exudates [8, 9].

Most critically ill patients exhibit intense inflammatory and acute phase responses which cause major changes to endocrine and immune systems, and to metabolic regulations with resistance to nutrition. The acute phase response is associated with increased production of cytokines and other mediators, with subsequent reorientation of hepatic protein synthesis, redistribution of micronutrients to different organs and tissues, and their displacement from the circulating compartment. Activation of the nuclear transcription factor κB (NFκB) is a key step in the development of the full-blown inflammatory picture [10]. The acute phase response is also associated with a major increase in free radical production. The production of ROS and nitric oxide (NO) species is particularly enhanced in conditions, such as acute respiratory failure, sepsis, acute renal or hepatic failure, pancreatitis, major trauma and burns, and organ transplantation (table 1). An acute inflammatory response constitutes a serious risk factor for the development of organ dysfunction and failure in critically ill patients.
### Key Micronutrients in the ICU

<table>
<thead>
<tr>
<th>Condition</th>
<th>↑ ROS production</th>
<th>Vitamin and trace elements at risk or depleted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute illness</td>
<td>Lipoperoxides, plasma</td>
<td>Vitamin B1 [19]</td>
</tr>
<tr>
<td></td>
<td>redox status [a]</td>
<td>Ascorbic acid [b]</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>TBARS [c]</td>
<td>Selenium [d]</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>TBARS [e]</td>
<td>Selenium, ascorbic acid, and β-carotene [f]</td>
</tr>
<tr>
<td>Acute liver failure/cirrhosis</td>
<td>Lipoperoxides [g]</td>
<td>Zinc [h, i]</td>
</tr>
<tr>
<td>ARDS</td>
<td>Lipoperoxides [j, k]</td>
<td>Vitamin E [k]</td>
</tr>
<tr>
<td>Brain injury</td>
<td>Lipoperoxides [l–n]</td>
<td>Copper, Zinc [o, 27]</td>
</tr>
<tr>
<td>Burns</td>
<td>TBARS [22, 24, p, q]</td>
<td>Selenium [8, r]</td>
</tr>
<tr>
<td>Myocardial ischemia</td>
<td>Lipoperoxides [v]</td>
<td>Vitamin E, Selenium [w]</td>
</tr>
<tr>
<td>Organ transplantation</td>
<td>NO mediated vascular</td>
<td>Copper [y], Selenium [2], Zinc [aa]</td>
</tr>
<tr>
<td>(heart, kidney, liver, lung)</td>
<td>responses [x]</td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Lipoperoxides [bbc]</td>
<td>Selenium [cc],</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Ethane, TBARS [42]</td>
<td>Vitamin A [dd], Selenium [21, ee], Glutathione [42]</td>
</tr>
<tr>
<td>Stroke (ischemic)</td>
<td>Lipoperoxides [ff]</td>
<td>Selenium [gg]</td>
</tr>
<tr>
<td>Trauma</td>
<td>[hh]</td>
<td>Selenium, Zinc [ii, 25]</td>
</tr>
</tbody>
</table>

*alphabetical references only appear in the present table, numeric references are quoted in the text*
Antioxidation and Immunity: Role of Micronutrients

Free radicals are atoms or molecules containing one or more unpaired electrons: they are unstable and strive to restore parity. They are also called ROS and their production occurs under normal aerobic metabolism. NO species are a normal byproduct of endothelial metabolism. ROS are mainly produced by leukocytes and by the respiratory mitochondrial chain. ROS are required for cell signalling, and for bacterial defense. In the normal subject the endogenous antioxidant defenses balance the ROS production. Antioxidants are substances, which inhibit or delay oxidation of a substrate while present in minute amounts [11]. Endogenous antioxidant defenses are both enzymatic (e.g. superoxide dismutase, glutathione peroxidases (GSHPx), catalase) and nonenzymatic (e.g. uric acid, glutathione, bilirubin, thiols, albumin, and nutritional factors, including vitamins and trace elements). The enzymes act in cascades and depend on trace elements for structure and activity. Nutritional antioxidants act through different mechanisms: (1) they directly neutralize free radicals; (2) they reduce the peroxide concentrations and repair oxidized membranes; (3) they quench iron to decrease ROS production, and (4) via lipid metabolism, short-chain free fatty acids and cholesteryl esters neutralize ROS [12]. Most antioxidants interact and contribute to their respective regeneration.

In clinical settings 'oxidative stress' has been defined either by direct evidence of increased ROS and NO production, respectively, of increased byproducts of lipid peroxidation (e.g. increased thiobarbituric acid reactive substances (TBARS)), or by determination of low antioxidant defense (losses or low circulating levels). Table 1 shows conditions in which such changes have been observed in the critically ill. In addition it shows which micronutrients have been shown to be deficient and at risk of depletion in the various conditions.

Immunity is frequently compromised in the critically ill patient. Immune defense is closely linked to antioxidant defense: membrane fluidity and integrity (vitamin E), genomic changes (selenium), and cell replication (zinc) are essential for immunity but depend on appropriate antioxidant control. The leukocyte membranes are constituted by saturated and unsaturated fatty acids that may be oxidized, and consequently destroyed by the ROS. The subsequent loss of fluidity of the membrane is associated with an alteration in lymphocyte function [13]. Selenium has a key function in antioxidant defense such as the electron carrier properties in GSHPx, which is essential for the immune defense. Selenium supplements have been shown to modulate NFκB expression under various circumstances, including HIV infection [14]. In animal and human trials selenium supplements have been shown to reduce the incidence of hepatitis B [15]. This is explained by the action of the viral genome. Selenium inhibits the activity of the reverse RNA transcriptase required for viral replication [16], an effect which is probably mediated by
GSHPx. The increased virulence of the Coxsackie B3 virus in selenium-deficient mice is another example of the impact of the antioxidant status on the stability of the viral genome [17], as the viral phenotype can be modified by the selenium status [18].

The B vitamin group contributes indirectly to antioxidant defense through the intermediary metabolism. Thiamine (vitamin B₁) is the coenzyme of carbohydrate decarboxylation reactions. Thiamine deficiency is very frequent in critically ill patients [19]. Riboflavin (vitamin B₂) is constitutive of flavine adenine dinucleotide and is an electron carrier in the oxidation and reduction reactions of the flavine coenzymes in the mitochondrial respiratory chain. Vitamin PP (B₃ = niacin) is converted in the tissues to nicotinamide adenine dinucleotide (NAD⁺; involved in hydrogen transport) and NAD phosphate (NADP⁺; fatty acid synthesis and pentose cycle). NAD⁺ and NADP⁺ play important roles in the antioxidant spiral, providing electrons for the reduction of oxidized glutathione.

In healthy subjects with adequate nutritional status, endogenous antioxidants including vitamins and trace elements are able to neutralize normal ROS production. But about 1% of the ROS production escapes antioxidant control and contributes to ageing phenomena. In the critically ill, the unstable equilibrium is lost in most pathologies (table 1). Under such stress conditions, an imbalance results from enhanced free radical production combined with depletion of the endogenous antioxidants through losses, redistribution, and inadequate intake. This contributes to worsening of acute illnesses and to the development of organ failure due to the side effects of the persistence of an intense systemic inflammatory response syndrome (SIRS).

Supplementation Trials in the Critically Ill

Before considering trace element and vitamin supplementation, a distinction should be made between the previous diets and the provision of immunomodulating diets. The latter diets have been used extensively during the last decade. Various diets on the market contain ‘immunomodulating substrates’ (e.g. glutamine, arginine, n-3 fatty acids, nucleotides) and variable amounts of antioxidant micronutrients, bringing uncertainty as to what has caused the changes. But while immunomodulating diets have been associated with increased mortality in critically ill patients [20], this has never been shown to occur with micronutrient supplements alone. Therefore the latter may be considered as safe.

Research on antioxidant supplementation in the critically ill has focused mainly on five micronutrients: vitamins C and E, copper, selenium and zinc. Table 2 summarizes the available trials. Surprisingly, retinol has so far not been investigated in the critically ill. In 42 critically ill patients with SIRS due
Table 2. Studies on micronutrient supplementation in critically ill patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient category</th>
<th>Type of study</th>
<th>Patient number</th>
<th>Micronutrients</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angstwurm et al. [21], 1999</td>
<td>Sepsis</td>
<td>PRCT</td>
<td>42</td>
<td>Selenium</td>
<td>Renal failure Mortality</td>
</tr>
<tr>
<td>Berger et al. [22], 1995</td>
<td>Major burns</td>
<td>Prospective consecutive series</td>
<td>10</td>
<td>Copper, selenium, zinc</td>
<td>Length of stay</td>
</tr>
<tr>
<td>Berger et al. [23], 1998</td>
<td>Major burns</td>
<td>PRCT</td>
<td>20</td>
<td>Copper, selenium, zinc</td>
<td>Infections</td>
</tr>
<tr>
<td>Berger et al. [40], 2002</td>
<td>Major burns</td>
<td>PRCT</td>
<td>20</td>
<td>Copper, selenium, zinc</td>
<td>Tissue levels</td>
</tr>
<tr>
<td>Tanaka et al. [24], 2000</td>
<td>Major burns</td>
<td>Randomized by month of admission</td>
<td>37</td>
<td>Ascorbic acid</td>
<td>Resuscitation fluid volume and retention</td>
</tr>
<tr>
<td>Berger et al. [26], 2001</td>
<td>Trauma</td>
<td>PRCT</td>
<td>32</td>
<td>Selenium, α-tocopherol</td>
<td>Thyroid function Organ failure</td>
</tr>
<tr>
<td>Porter et al. [25], 1999</td>
<td>Major trauma</td>
<td>PRCT</td>
<td>18</td>
<td>NAC, ascorbic acid, α-tocopherol, selenium</td>
<td>Infections</td>
</tr>
<tr>
<td>Preiser et al. [41], 2000</td>
<td>Critically ill</td>
<td>PRCT</td>
<td>37</td>
<td>Vitamin A, ascorbic acid, α-tocopherol</td>
<td>Ex vivo LDL tolerance to oxidative stress</td>
</tr>
<tr>
<td>Young et al. [27], 1996</td>
<td>Traumatic brain injury</td>
<td>PRCT</td>
<td>68</td>
<td>Zinc</td>
<td>Neurological outcome</td>
</tr>
<tr>
<td>Ortolani et al. [42], 2000</td>
<td>Septic shock</td>
<td>PRCT</td>
<td>30</td>
<td>N-acetyl cysteine, glutathione</td>
<td>Ethane breath, TBARS plasma</td>
</tr>
</tbody>
</table>

PRCT = Prospective randomized controlled trial; NAC = N-acetyl cysteine; LDL = low-density lipoprotein; TBARS = thiobarbituric acid reacting substance.
to an infectious disease, selenium supplementation for 9 days was associated with a significant reduction in acute renal failure (3/21 patients versus 9/21, \( p = 0.035 \)), and a nonsignificant reduction in mortality [21]. In major burns, copper, selenium and zinc supplements amounting to 6–8 times the RDA intakes were associated with reduced lipid peroxidation and a reduction in infectious complications [22, 23]. In the same trial the interleukin-6 levels were lower in the supplemented patients after 24 h of trace element supplementation including 350 \( \mu \)g/day selenium [23]. Mega doses of ascorbic acid, provided during the first 24 h of resuscitation in patients with major burns, reduced fluid requirements by about 30% [24] by reducing alterations in capillary permeability. Providing N-acetylcysteine, selenium and vitamins C and E or placebo to 18 trauma patients was associated with a decrease in infectious complications (8 versus 18) and fewer organ dysfunctions (0 versus 9) [25]. A trial using selenium in combination with vitamin E, or placebo in 32 patients with major trauma was associated with a normalization of thyroid function (triiodothyronine and thyroxin concentrations in particular) [26], with significant changes in antioxidant status in the supplemented patients [26a]. In severe brain injury, zinc supplements (20 mg for 2 weeks) were associated with improved neurological recovery [27]. The reinforcement of the antioxidant defenses is argued to be the mechanism leading to the clinical benefits observed in these trials.

**Supplementation Strategies**

The aims of supplementation can be summarized as follows: (1) to provide basic nutritional support, the increased nutritional requirements related to hypermetabolism and wound healing; (2) to prevent or correct deficiencies [9], and (3) to modulate the acute phase and immune responses by reinforcement of the endogenous antioxidant defenses. While classical, this sequence 1–3 ought to be reversed in the critically ill, starting with antioxidant reinforcement.

**Micronutrients: Basic Nutritional and Antioxidant Requirements**

There are changing paradigms regarding the methods to establish micronutrient requirements in the general population. Making universal recommendations among the different ecological, anthropological, and geographical settings appears futile as lower than normal body stores may be adaptive [28]. Establishing requirements is even more difficult in the critically ill. There are still gaps in our knowledge regarding the bases of
nutrient requirements. Moreover trace elements are inorganic, with a potential for accumulation: the fear of toxicity has delayed the recognition of increased requirements. The American Food and Drug Administration has recently recognized that vitamin requirements are increased during acute illness, particularly in critically illness [29], but this upgrading process has still not been completed for trace elements (table 3).

Available tools for the assessment of requirements include balance studies and depletion-repletion trials. These approaches have pitfalls, and losses are always underestimated. Nutrient requirements are defined as the amount required to replace endogenous losses or to maintain appropriate concentrations in the circulating compartment. Generally the latter does not reflect the status and the tissue and organ levels. The circulating levels only reflect the flow between the various organs. Moreover, estimating requirements from losses fails to consider homeostatic adjustments in nutrient metabolism. The functional approach, which is closer to metabolism and includes assessment of enzymatic activities depending on micronutrients (e.g. selenium and GSHPx, or zinc and alkaline phosphatase), requires the definition of other appropriate endpoints (only those for Se and Zn are defined), yet is not available in the critically ill [30].

Which doses should then be supplied? In general population intervention trials using nutritional doses close to the RDAs have achieved a reduction

<table>
<thead>
<tr>
<th>Micronutrient</th>
<th>RDI for i.v. use [43, 44]</th>
<th>Oral RDA [45] %</th>
<th>i.v. FDA 2000 [29] mg</th>
<th>Doses used in critically ill trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper</td>
<td>0.5–1.5 mg</td>
<td>45</td>
<td>–</td>
<td>Burns: 2.0–5.0 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Liver disease: 5.0 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Liver disease: 5.0 mg</td>
</tr>
<tr>
<td>Selenium</td>
<td>30–60 µg</td>
<td>70</td>
<td>–</td>
<td>Burns: 350 µg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SIRS sepsis: 300–900 µg</td>
</tr>
<tr>
<td>Zinc</td>
<td>2.5–4 mg</td>
<td>25</td>
<td>–</td>
<td>Burns: 35 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Liver cirrhosis: 10–20 mg</td>
</tr>
<tr>
<td>α-Tocopherol</td>
<td>10 mg</td>
<td>100</td>
<td>10</td>
<td>100 mg to 3 g</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>100 mg</td>
<td>160</td>
<td>200</td>
<td>1–110 g</td>
</tr>
<tr>
<td>Niacin</td>
<td>40 mg</td>
<td>250</td>
<td>40</td>
<td>–</td>
</tr>
<tr>
<td>Thiamine</td>
<td>3 mg</td>
<td>300</td>
<td>6</td>
<td>100–200 mg</td>
</tr>
</tbody>
</table>

The recommended i.v. doses of trace elements are proportionally lower than i.v. vitamin doses compared with the oral RDA, which shows the concern about trace element toxicity.

Key Micronutrients in the ICU

Table 3. Recommended daily intakes (RDIs) for intravenous (i.v.) administration according to the American Medical Association in comparison with nutritional micronutrient recommendations for the general population (RDA) [39] and in sick patients (FDA) [29], and examples of doses used in clinical trials in critically ill patients

The recommended i.v. doses of trace elements are proportionally lower than i.v. vitamin doses compared with the oral RDA, which shows the concern about trace element toxicity.
in infectious morbidity [31, 32]. But the RDAs are by definition not designed for the critically ill. There is actually no consensus as to which quantities should be proposed and whether the doses are the same in all critically ill patient categories. There is growing evidence that the micronutrients required for nutritional and antioxidant purposes should be considered separately.

**Timing**

Clinical trials in burns suggest that early intervention determines the antioxidant impact [21–24]. The most important decreases in circulating levels of micronutrients and the most important losses are observed early on during the first 2 weeks of the acute disease, during which the largest increases in ROS production occur. Therefore micronutrient supplements with antioxidant objectives should be supplied early in the course of disease, while nutritional requirements should be covered separately, and may be started later, when nutritional support is required.

**Single versus Combined Micronutrient Provision**

The advantage of providing a single nutrient is the possibility of investigating its effects and determining the dose required to achieve an action. Indeed multi-supplementation trials have the same disadvantage as immunonutrition trials: it would be interesting to know which of the single micronutrients is responsible for benefits or harm. The disadvantage of single nutrient trials is that as micronutrients function as a network, providing increased amounts of a single component may generate an imbalance. The rationale underlying the use of a combination of micronutrients instead of single elements is based on the observation of the biochemical properties of the endogenous antioxidant network [33]. Micronutrients depend on each other for regeneration in a continued spiral. In a few trials, selenium has been used alone, but there is a risk of increasing the internal imbalance by doing so, especially with large amounts.

**Route of Delivery**

The intravenous route is the only one that guaranties bioavailability in the circulating compartment, avoiding the absorption problems and the liver first-pass effect. The clinical trials that have used the enteral route in the critically ill are few (burns [34], trauma [25]). This is explained by the unpredictable
absorption in the critically ill [35], and the difficulty in guarantying full enteral delivery very early on during the course of acute illness. The large variability of enteral micronutrient absorption in healthy subjects is increased in the critically ill, for instance hemodynamic failure, bowel ischemia, bowel edema due to a local inflammatory response and fluid resuscitation [36] may compromise absorption. Vitamin E absorption is reduced in critically ill compared to healthy volunteers [37]. In addition many micronutrients compete for enteral absorption, such as copper and zinc, selenium and copper, and many others. These interactions may compromise the therapeutic intervention as observed for copper and zinc during a supplementation trial carried out in burned children, where enteral supplementation failed to correct copper and zinc deficiency [34]. Moreover, providing micronutrients by the enteral route after bowel surgery does not increase the circulating levels [38]. Therefore, to achieve systemic antioxidant effects, the intravenous route remains the only predictable one.

**Monitoring of Intervention**

There are actually no clinical laboratory determinations available that can be used as targets during antioxidant supplementation. Therefore such micronutrient treatments remain empirical for the moment.

**Perspectives**

There is increasing evidence that micronutrients play a major role in the nutritional and metabolic management of the critically ill. Early in the course of disease, their antioxidant properties modulate the inflammatory response and immunity, and later on, they are essential components of nutritional support. Future clinical trials should be performed in large patient populations to determine their effects in the prevention of remote organ failure and infectious complications.

**Conclusions**

Some vitamins and trace elements are particularly important in the critically ill patient, mainly thiamine, α-tocopherol, ascorbic acid, copper, selenium, and zinc. The key micronutrients are those that are involved in antioxidant and immune function as well as in the carbohydrate metabolism. Based on actual knowledge, patients that may benefit from early large micronutrient supplementation include subjects presenting an intense inflammatory response, and those who have demonstrable large micronutrient losses like major burns, patients on renal replacement therapy or with
abnormal intestinal losses (diarrhea, fistulae, aspirations), as well as those who have deficient clearances of metabolic end products due to hepatic and renal failure. Further research is required to determine the clinical endpoints and laboratory tests for clinical settings.

References

Key Micronutrients in the ICU


29. FDA. Parenteral multivitamin products; Drugs for human use; Drug efficacy study implementation; Amendment. *Federal Register* 2000; Vol 65: No 77.


Discussion

Dr. Martindale: Thank you, that was a wonderful review. What do you do in your intensive care unit (ICU) for vitamin C with the provocative data like those of Tanaka et al. [1] out there?

Dr. Berger: We need more information and some of the next data are probably going to come from Stuttgart in Germany where Biesalsky’s team has started investigating what is going on in the endothelium. It is too early to use such amounts yet. But the intervention lasts 24 h, and only 24 h: no deleterious effects have been observed, such as kidney stones, oxalate formation or any of those, no prooxidative lesions. We are watching these developments with very high interest.

Dr. Martindale: To follow up on the same question, I heard him saying that this mechanism involves membrane stabilization, avoiding alterations in the intracellular volume; which then is the catabolic response?

Dr. Berger: Yes exactly, you maintain hydration through the decrease in nitrosylation of the membrane. That is the actual hypothesis. So as soon as you alter cell hydration, you have a catabolic response.

Dr. Cynober: When I look at your figure with the zinc losses in burns, I notice that the urinary losses compared to others were very low, and I remember old studies on trace elements which indicated that in burn injury, there was an important decrease in copper reabsorption by the kidney [2]. Therefore my question is, what is typical for trace elements after major trauma, is it the zinc figure with low elimination in urine or copper with very high renal elimination?

Dr. Berger: Actually these amounts were considered very important and correspond to what Cuthbertson et al. [3] found. You have an increased excretion of zinc at the end of the first week and we found exactly the same patterns of excretion. If I had shown you the copper figure, you would see that copper is actually excreted very little in urine, but excretion essentially occurs by the biliary route and the cutaneous route in burns. The copper balance in burn trials were difficult to carry out also because copper has a slow intestinal transit early after injury, so the balances were not completely correct for copper as late losses occurred in the feces. At the intestinal level there is competition for absorption. It was actually attempted to give it enterally to children in a trial carried out in Zürich in 1978 and 1979 [4]. This trial showed that there was a competition and that both copper and zinc could not be increased when given together by the enteral route. Either you give copper or you give zinc, but then you have a corresponding decrease in the other's absorption.
Dr. Bozzetti: Could you better specify which patients should receive this supplementation? From your presentation I see that you have extensively studied burn patients, then you have shown the results of other critically ill patients, but I have some difficulty defining which the critically ill patients are. I mean, you can define critically ill patients as the patients who are in a critically ill condition really, but also the patients who are admitted to the critical care unit, and you have some elective surgery, surgical patients, so which are the patients for whom such a supplementation is advised?

Dr. Berger: Thank you for this question, which is a very important one. What we actually define as a critically ill patient who would receive an antioxidant cocktail, as we call it, in our unit, includes emergency patients admitted for acute respiratory failure, severe sepsis or septic shock, organ transplant, major trauma, major burns, pancreatitis. But we would not consider giving it to a patient just coming to us after elective surgery: those patients would not come to our unit anyway. But a patient in failure or organ failure would be an indication to give it, but you have to have organ failure, not just requiring monitoring.

Dr. Labadarios: On what evidence have you arrived at or do you recommend these doses? If you look at thiamine, it is almost the amounts that we used to treat Wernicke’s encephalopathy. Now I know we give a lot of glucose wrongly, but one would like to know the background to our recommendation. The second part of the question: the administration of vitamin C in daily doses exceeding 500 mg has been reported to have prooxidant properties [5, 6]. And the third part of the question: there are things that one needs to understand. Your second slide was actually showing tremendous losses in thermally injured patients which one understands. But I understood from your presentation that within 1 or 2 days in other types of injury you actually lose a lot of these micronutrients. Where do they go?

Dr. Berger: I am starting with the last question. Actually we have also made balance trials in critically ill trauma patients: they have also negative trace element balances. We have just completed a trial in patients with any condition requiring continuous renal replacement therapy. They are in negative selenium and copper balance. We have learned from these balance studies that whenever you have drains, whenever you have a therapy which will draw biological fluids from the patient, you have micronutrient losses, and frequently at that time you are just not providing these patients with any supplement: they are in a phase in which they just require more. We know that the deficiency itself comes on the top of a frequently suboptimal status before the acute hit. So in addition you threaten the status. As far as I know, nobody knows how large the stores are but we do know that there is increased stress to the patient who is critically ill. Now why these doses? Those doses are not my invention, they are those I found in the literature. I haven’t shown all the references, but lets take the example of thiamine. An article from the Netherlands shows clearly that acutely critically ill patients have very low thiamine activity [7]. The depression is correlated with outcome: this team recommended 100–200 mg/day for at least 3 days, to just compensate the depression and cope with our glucose infusions we just infuse some glucose to all our patients, and we don't know where they are standing with the thiamine status. Another nice article published from an Emergency Department in London [8], in alcoholic and nonalcoholic patients, shows that about 30% of them were deficient in vitamin B. So our emergency patients are just deficient and the critically ill too, for reasons which vary, depending on the condition. α-Tocopherol has been used in many trials and has been given up to 3 g/day [9], and this has been shown to have no deleterious effect when given by the enteral route. I haven’t indicated the route here but the route is perhaps of importance. These are doses which have been recommended for the burn and trauma patients and exist
since the 1940s [10], and they have not been reassessed since nor have they been
contradicted since. For selenium, different trials [11, 12] have shown selenium
deficiency: ours was based on a balance study. We also conducted a balance study in
major trauma, showing trace element deficiencies [13].

Dr. Bozzetti: There is the question of prooxidant damage that we may be doing to
these people and that is really the question behind the two regarding tocopherol and
ascorbic acid. I heard what you said and I accept what you said and I would probably
do the same as you, the question though is when we say it is free of side effects. Very
often we don’t know what side effects we are looking for, so I don’t know how we can
actually arrive at the conclusion that they are safe.

Dr. Berger: The 1,000 mg vitamin C/day? You are totally right, it is very important
to consider the potential side effects of something, and that was what I alluded to
when I said don’t give one single agent because you may end up in trouble and we don’t
know. This one has been built for burns and is also based on a trial by Schorah et al.
[14] which showed that within 48h after acute injury you are below 25% of the lowest
reference value in these patients, so it is a repletion. The things here should not be
considered for continued supplementation. What we have decided in our unit for the
moment is to give such things for 5 days and there are no deleterious effects shown
for such short supplementation periods. I agree with you, we don’t have anything we
can follow-up on.

Dr. McClain: These are intravenous doses?

Dr. Berger: Yes, except for tocopherol given enterally.

Dr. McClain: One of the things you get with some of these metals, like zinc, in low
doses is deficiency: There is nice work in a biochemical journal showing that if you give
very high levels you can actually induce zinc deficiency.

Dr. Berger: Yes these things do exist. Let’s come back to the doses. I was not precise
enough, but these doses are provided on the top of multivitamin and multitrace
element daily supplements because you should just give the full cocktail. So the doses
indicated in my presentation are the quantities you top up on: something in the
concept we have developed in Lausanne. The trials with zinc, and you can go back to
Chandra [15], showing that if you give more than 50 mg/day for prolonged periods of
time you have a decreased immune response. So clearly we do risk deleterious side
effects, as there is a true dose-response curve. The 20- to 30-mg zinc/day dose has
never to my knowledge been associated with deleterious effects when given for
periods of less than 2 months.

Dr. McClain: In the Chandra study the dose is given orally. Basically 3 mg of zinc
would keep a person in stable balance on home total parenteral nutrition, so 15 mg of
zinc orally is the same as 3 mg intravenously. I actually did a study giving 12 mg/day
i.v. and then switching over to 30 mg/day orally. So I think you have to be careful about
how much you are giving.

Dr. Berger: You are perfectly right, I was quoting your trial exactly for the reason
that you gave it over a prolonged period of time, and in our unit these doses have
not been given for very long except in burn patients who receive 30 mg zinc for
3 weeks. Supplementation should not proceed for ages, that is for sure. Critically
ill patients should not be continued on such high stress doses, as the stress is initial.
We have done the trials in burn patients, and we now have experience with 3 weeks
of 35 mg i.v. We are watching the immune response and we have observed no
deleterious effects. Our patients had 40–90% body surface area burns, but that is the
only category where we would continue with such high doses for prolonged periods
because the patients have persistent losses from the skin surface if not surgically
covered by skin grafts.
Dr. Allison: Under pressure from the chairman you rather rushed through the last bit about the effect of salt and water on gastrointestinal function, which is an area of interest to us. I wonder if you could just sort of review that and elaborate on the influence of fluid resuscitation on edema, and the effect this had on absorption. Are you saying that this impairs trace element absorption for a significant period of time?

Dr. Berger: I don't have definite evidences. I am just observing that during resuscitation things occur which have an impact at least on sugar absorption, and we know there is edema related to fluid resuscitation, and this occurs in hemorrhagic trauma as in burns, and this trial just nicely showed the edema in these areas. So you know that during shock you have alterations in cell energetics and the absorption of trace elements and vitamins is not a passive one. So as soon as you have edema you are likely to have altered absorption, and this may explain that when you give such doses orally, enterally, early you cannot count on a perfect absorption. It does not mean that the gut does not use it, but perhaps it is just not available in the blood, and that is also something we saw in our patients with gastrointestinal surgery. We were not able to maintain glutathione peroxidase activity despite 300 μg selenium/day for 5 days, and this we do easily by the intravenous route in both trauma and burn patients who are much more severely stress patients, but they are getting 300 μg i.v. So I hypothesize that without being able to prove it.

Dr. Allison: We have heard very little about salt and water today, which are the major problems in these patients and that is very interesting.

Dr. Ribeiro: I have two questions. First, a practical question. If your patients receive parenteral nutrition do you mix everything within the solution or do you give it intermittently?

Dr. Berger: We are doing quite a lot of research on it and as parenteral nutrition is only 15% of our nutrition days we just give it separately, and we have a continuous separate micronutrient infusion. We don't give it as a bolus but this is running for a 12-hour period. We have stability problems, so we give two small 100-ml sodium chloride solutions, one containing the trace elements and the other containing the vitamins.

Dr. Ribeiro: Are you worried about the degradation of vitamins?

Dr. Berger: Of course, the vitamins are protected from light, whereas there is no problem with the trace elements, they are not degraded.

Dr. Ribeiro: You mentioned that elderly people present low levels of some micronutrients. Do they eat less or do they absorb less?

Dr. Berger: As far as I know there are no data showing lower absorption in these patients, and in our trial with major surgery we had 80-year-old patients, and they just behaved like the others. What we all know with nutrition is that elderly patients tend to eat less and that their intake is simply lower.

Dr. Rosenfeld: You don't mention chromium in your key cocktail. There is concern about hyperglycemia in critically ill patients. It is important for glucose control and cytochrome oxidase. Isn't it time to look more for chromium supplementation?

Dr. Berger: We included it there, but there are not enough data. These have not yet been published, so in this table I just used the data which we know about. But you are absolutely right and chromium should probably be included. There are unresolved toxicity concerns with this trace element. Probably just providing the multitrace element products which contain 20–40 μg/day i.v. should at least decrease the issue of the problem, but here we went for 400 μg/day enterally. So yes, we should probably include chromium but the data are still not strong enough.

Dr. Nitenberg: You know that there is a controversy and some debate in the literature about what is called the antioxidant paradox, and I think we discussed that
before. Do you agree with the fact that the only thing we have to do now is to correct the deficiencies of the patients and not to overload patients with the so-called antioxidant products? That was my first question, and I think it is very difficult to achieve this goal. My second question is about the other micronutrients you have not discussed, mainly about iron deficiency because there is also a debate in the literature about the risks and benefits of iron supplementation. Could you comment on these two points?

Dr. Berger: It is very important to address these issues. Regarding burns, what we have been doing is basing our supplementation doses on balances. We knew we were just actually repleting acute depletion, but we do not know what the balances are for quite a few conditions. I only have balance trials in burns, trauma and now renal replacement therapy. These balances are very difficult to carry out in burn patients and in the critically ill in general, so there won't be many of these. We know that our patients are probably below the requirements when they start [16]. We have evidence of low levels of many micronutrients which can reflect redistribution as I said as deficiency. I think that at the present stage we know that we can reinforce antioxidant defenses and this is rather easy to measure when you measure plasma glutathione peroxidase: if you can restore its activity, then you should probably not go beyond the delivered selenium dose. Really if we continue much above the normal requirements for a prolonged period, we should have something to measure, because we don't know what we are doing, especially we don't know what we are doing by providing one single micronutrient. I am very worried about the trials which are giving 1,000 μg of selenium for 2 or 3 weeks, or even more, because we have evidence from the general population that we may have an inhibition of thioredoxin reductase with these large doses [17]. So there is evidence against the theory that more is better. The doses I have been talking about are those which have not been shown to have deleterious effects, whether on endocrine aspects or whatever: the duration of supplementation is of importance too. We have, I think, to tackle this progressively and try to discover the optimal replacement doses. What I mean is that there are proposals for discussion. I don't think we have a definitive answer yet, and more is not necessarily better. Then regarding iron: yes there is worry in those patients with an acute phase response and those with infection. Iron is required for quite a few metabolic steps, for electron transfer and so on, but it is also the main initiator of the prooxidative reaction. Iron also has catalase antioxidant effects. It is prooxidant when free. Our sick patients have a large proportion of free iron, and the free iron is the worry. And we also know that quite a few bacteria including Pseudomonas very quickly develop channels to incorporate just the free iron that they need for proliferation. So the current consensus, and this has been investigated in children with malnutrition, is that during the acute malnutrition phase you should be very cautious with a large supplementation and you should not give doses which are intended for correction of anemia, but just the basic thing. If you look at the trace element-containing products which are on the market, they just have this minimal level of iron, and everybody is very much worried about increasing that without clearly knowing exactly what to do. So as soon as the acute phase is fading you can probably increase the supplementation dose without any problem.

Dr. Labadarios: The WHO recommendations that you just referred to regarding malnourished children, are a little bit stronger than that, because they actually say don't give iron for the first 14 days of the patient's management course, am I right?

Dr. Berger: Yes you are right.

Dr. Déchelotte: Coming back to glutathione, I am pretty convinced that selenium will help to get back some reduced glutathione by glutathione reductase or peroxidase

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action, but oxidized glutathione is really lost, it passes well from cell membranes so maybe selenium will not be able to get it back. So don't you think that there is a need together with selenium to have some glutathione precursors such as glutamine or cysteine?

**Dr. Berger:** There is a very nice trial by Ortolani et al. [18] in septic patients, providing N-acetylcysteine, N-acetylcysteine plus glutathione versus placebo showing that you can reinforce much better if you give a combination. Now that there is free glutathione, and these groups are important to the body, we should also head in that direction. So I fully agree with you, but this was just next to the pure topic on vitamins and trace elements, but I think we should add cysteine to it, clearly.

**Dr. De Bandt:** If you associate micronutrients with n-3 fatty acids do you think that you have to decrease your supply in order to prevent the paradoxical effects of micronutrients?

**Dr. Berger:** I think it has to be investigated, as there are no data yet.

**Dr. Calder:** I think if one is going to give n-3 fatty acids you need the appropriate lipid-soluble antioxidants present, but the exact level or ratio between them isn't known.

**References**

