

## Trace Elements in Critical Illness

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### Abstract

Nutritional support of the critically ill patient includes daily provision of macronutrients and micronutrients including vitamins and trace minerals. Publications on nutrition support often emphasize macronutrient administration including proteins, fats, and carbohydrates. Although micronutrient supplementation is common practice, guidelines for their provision during critical illness are completely empiric. Trace elements are essential not only as intermediaries in metabolism but also for their potential roles in wound healing, cellular immunity, and antioxidant activity. This review is aimed at highlighting the important role of trace elements in the metabolic support of patients and also as pharmaconutrients in intensive care units. Future research in ICU nutrition should emphasize on the pharmaconutrient aspect of trace elements so as to determine the appropriate route, dose and timing of the intervention.

**Keywords:** Trace elements; Critical illness; Pharmaconutrients

### Introduction

Nutritional supplementation has traditionally been considered as an important supportive care in critically ill patients. However recent research in critical care nutrition suggests that it can have a positive therapeutic impact on patient outcomes in the intensive care unit (ICU). Nutrition in terms

of adjunctive care is giving way to a new paradigm – pharmaco-nutrition, in which certain key nutrients are used to modulate the inflammatory cascades caused by critical illness and protect against oxidative stress [1]. Trace element supplementation based on their strong antioxidant potential and other beneficial effects has become an integral component of this evolving nutritional strategy.

Nutritional support of the critically ill patient includes supplementation of the daily requirements of macronutrients and micronutrients including vitamins and trace minerals. Trace minerals include macrominerals (calcium, magnesium, phosphorus, sulfur, etc.) and trace elements (defined as those existing in less than one part per million body weight, e.g., zinc, copper, manganese, selenium, iron, iodine, chromium, molybdenum, etc.). Macronutrient supplementation is usually emphasized but there is relatively sparse literature available focused on the immense importance of the key trace elements in specific situations. This review is aimed at highlighting the important role of trace elements in the metabolic support of patients and also as pharmaco-nutrients in intensive care units.

### Trace Elements as Nutritional Supplement: General Considerations

#### Assessment of trace element status in the critically ill patient

Trace element status in critical illness may be evaluated using biochemical, physiologic, and clinical parameters [2]. Despite certain limitations, biochemical laboratory assessment is most frequently used to assess micronutrient status. It includes static indices (concentration of trace elements in the blood, tissue, or plasma) as well as functional measures. Static indices include serum and leukocyte levels for zinc (Zn), serum and urine levels of copper (Cu) and cuproenzymes, serum assay for selenium (Se) and plasma iron, transferrin and ferritin levels to assess iron stores in the body. However, these measures are of limited significance to reflect accurate trace element status in critical illness. Measuring serum levels of trace elements is difficult and requires

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**Table 1.** Recommendation for Trace Elements in Critical Illness

Trace Element	RDA	Standard Dose		Additional Supplementation
		PN Formula	EN Formula	
Zinc	15 mg	2.5 - 5 mg	11 - 19 mg/L	10 - 30 mg/day
Selenium	50 - 100 mcg	20 - 60 mcg	20 - 70 mcg/L	100 - 400 mcg/day
Iron	0 - 15 mg	0	12 - 20 mg/L	-
Copper	900 mcg	300 - 500 mcg	-	-
Manganese	1.8 - 2.2 mg	60 - 100 mcg	-	-

careful collection techniques, using special trace element-free tubes [3]. Previous balance studies have demonstrated the unreliability of serum trace element levels [4]. Serum levels may indicate recently administered trace elements and reflect short term status but do not accurately indicate tissue levels. Functional measures of trace elements include leukocyte chemotaxis and alkaline phosphatase for Zn, plasma glutathione peroxidase [GPx] assay for Se, lysyl oxidase for Cu and zinc protoporphyrin/heme ratio but these are also not reliable or practical.

### Absorption and interactions

Zinc, iron and selenium are absorbed mainly in the duodenum and jejunum, while chromium and copper are absorbed in the ileum.

Several interactions exist between the different trace elements affecting absorption via the gut and need to be kept in mind. Zinc supplementation decreases copper absorption and vice versa. Iron administration with enteral nutrition decreases the absorption of Cu and Zn and can lead to zinc deficiency [5].

### Altered distribution and metabolism of trace elements during injury and acute phase response

Trace elements are distributed in the body among certain dynamic pools like circulating, storage, and tissue pools. During the acute phase response subsequent to injury or sepsis, several factors such as fluid shifts, altered regulation of acid-base balance and reduced dietary intake can all affect the presence of a given nutrient within these pools [2].

Decreased absorption via the gastrointestinal tract, increased urinary losses and altered concentration of transport or binding proteins occur during acute severe illness and lead to altered bioavailability and requirements of trace elements. Inflammation results in release of cytokines through regulation of transcriptional factors and therefore, causes a rapid redistribution of zinc, iron, copper, and selenium within the

body due to decreased levels of the serum-binding proteins albumin, macroglobulin, and transferrin, whereas ferritin and ceruloplasmin levels are increased [6-8].

### Factors affecting trace element requirements in the intensive care unit

The spectrum of critical illness and patients' comorbidities affect trace element requirements. Geriatric patients, especially those in long-term care facilities are often trace element deficient and need early supplementation [9]. Certain disease processes alter trace element status. Patients with malignancies are susceptible to micronutrient deficiencies. Patients on hemodialysis or peritoneal dialysis often are deficient in trace elements (Se, Zn) possibly due to loss in dialysate or adsorption by the filters [10, 11]. Gastrointestinal losses (e.g., post-surgical patients with fistulas, diarrhea) result in deficiency of multiple trace elements, especially Zn and Se. Chylous leaks and fistulas lead to loss of large volumes of protein-rich fluid each day and result in deficiencies of selenium and other trace elements [12]. Parenteral nutrition is indicated in these situations and needs to be supplemented with these trace elements.

The extent of the procedures also affects the trace element status in post-surgical critically ill patients. Gastrectomy or terminal ileum resection may lead to iron deficiency. Micronutrient deficiencies have been reported after bariatric surgery for weight reduction, e.g., Fe and Zn deficiency after Roux-en-Y gastric bypass and gastric banding procedures [13-15]. The recommended trace element requirement in ICU is given in Table 1.

## Individual Trace Elements

### Zinc

The functions of zinc as an essential trace element include formation of metalloenzymes, protein metabolism, RNA

conformation and membrane stabilization. The key metalloenzymes with zinc as a constituent are carbonic anhydrase, alkaline phosphatase, alcohol dehydrogenase and superoxide dismutase. It plays a crucial role in cellular growth and replication, rapid epithelialization, wound healing, cellular immunity, and protection against oxidative stress [16]. Disturbances in the metabolism of the trace elements such as zinc and copper occur during burn, trauma or sepsis which is manifested by increased urinary excretion of these minerals despite normal or low serum levels. It is further exaggerated significantly after major surgical procedures [17]. Zinc is largely protein bound and increased muscle catabolism after surgery or major traumatic injury contributes to zinc loss from the body and hence the need for its supplementation in these situations [18].

Zinc deficiency also occurs in the patients with pancreatitis, renal disease, alcoholism, high dose steroids, and excess gastrointestinal losses such as high output fistulas. It may be manifested as skin rash (characteristic acrodermatitis enteropathica), glucose intolerance, poor wound healing, hepatic dysfunction and diminished work capacity of respiratory muscles. An amount of 25 mg/day of elemental zinc is usually recommended to meet the needs and to replace the urinary and cutaneous losses in critically ill adults [19]. However, additional zinc supplementation may be indicated for some patients (particularly in those with burns involving large surface area) who demonstrate poor wound healing or those with a preexisting deficiency [20]. Normal serum zinc level ranges from 70 - 150 mcg/dl. Low serum alkaline phosphatase may be used as an indirect measure of zinc deficiency.

Zinc plays a crucial role in the development and regulation of the immune system and its deficiency may lead to depleted immunity and increased susceptibility to infections. Hence, pharmacologic zinc supplementation, in addition to standard dietary intake, has been used to enhance immune function [21]. In a randomized clinical trial involving critically ill patients, zinc, was provided during the first 8 days as part of a combined intravenous trace element supplement (containing about 26 mg/day of zinc) and was found to be associated with a decrease in pulmonary infections and length of ICU stay. No adverse effects were noted with parenteral zinc supplementation in this study [22].

Zinc as a component of superoxide dismutase protects against oxidative stress by interacting with catalase and glutathione peroxidase. Excessive prolonged zinc intake may, in contrast, impair immune function and outcome in immunocompromised individuals. In vitro and in vivo studies demonstrate impaired chemotaxis and function of leukocytes. Copper deficiency has been noted with enteral zinc therapy [23]. Excess zinc intakes lead to severe copper deficiency, anemia, neutropenia, and leukopenia. Other manifestations of zinc toxicity include gastrointestinal symptoms (epigastric pain, nausea, vomiting), iron deficiency, altered lipoprotein

metabolism, and decreased glucose clearance. Many of the adverse effects of high dose enteral zinc are alleviated with intravenous supplementation. However, parenteral zinc supplementation (30 mg/day) in humans has also been reported to lead to an exaggerated acute phase response and increased levels of interleukin-6 [24]. In general, supplementation of two times the RDA is considered adequate and safe. In patients with increased zinc loss (pancreatitis, excess gastrointestinal losses, renal disease, burns, HIV, malignancy), daily supplementation of 55 mg/day may better accommodate the requirements. Patients with higher zinc supplement need to be monitored for serum copper and iron deficiency. Short term parenteral zinc therapy may also be considered as an alternative in these situations.

Additional supplementation may also be required in critically ill children with major burns and enteral intake of 25 mg per day or parenteral dose of 50 mcg/kg/day has been recommended in children over three years of age.

## Copper

Copper is important for wound healing, hematopoiesis and as an anti-oxidant. It is a co-factor for metalloenzymes involved with connective tissue cross-linking and norepinephrine synthesis [25]. It is poorly absorbed from the gastrointestinal tract and has low daily requirements. It is deficient in patients with long term parenteral or enteral nutrition and burns. Copper deficiency may be manifested as pancytopenia, myelopathy or peripheral neuropathy. The RDA for copper in adults is 900 mcg and parenteral dose is 300 - 500 mcg per day. In critically ill patients with hepatic insufficiency, Cu should be decreased or omitted from parenteral nutrition. Patients receiving parenteral copper supplementation may be needed to monitor serum copper to ceruloplasmin ratio to avoid hepatotoxicity. Although urinary copper excretion is further increased with copper supplementation, ceruloplasmin synthesis can be increased with higher copper intake [26]. Standard enteral nutritional supplements, when provided consistently at goal rate, seem adequate to meet the daily copper requirements in adults and children. However, in critically ill burn patients, supplemental copper intakes approximating 5 mg/day in adults and 20 mcg/kg/day in children are necessary to compensate cutaneous losses.

## Selenium

Selenium is a key component of the endogenous defense system against oxidative stress in human beings. It exists in two forms – selenomethionine (Se-Met) and selenocysteine (Se-Cys, the biologically active form). It is a constituent of glutathione peroxidase (GSH-Px), which acts as a free radical scavenger enzyme and inactivates hydrogen peroxide and fatty acid hydroperoxides. In addition, it aids in thyroid hormone production and inhibits nuclear transcription fac-

tor expression. Serum selenium level and enzyme assay for GSH-Px are used as monitoring indices in the intensive care unit. Like other trace elements, plasma selenium levels are decreased during critical illness [27]. Selenium deficiency occurs in patients with bowel resection, gastro-intestinal fistulas, alcoholism, chylous leaks, HIV infection, and those undergoing venovenous hemodialysis. However, unlike trace elements such as zinc and copper, overall urinary excretion of selenium is not significantly elevated above normal limits during critical illness [28]. Increased selective uptake of selenium by injured tissues for defense against reactive oxygen species may explain the progressive decline in plasma and urinary levels.

The current RDA for selenium is 55 mcg/day, as needed to maximize the GSH-Px activity. There is ample evidence for beneficial effect of selenium supplementation during critical illness. Low plasma values are inversely correlated with severity scores in the ICU. Supplementing routine nutritional therapy with an additional amount of 60 mcg/day of selenium in patients after major trauma and a larger intake (190 mcg/day) as part of an intravenous trace element preparation in burn patients result in improved patient outcomes. In critically ill children, 2 mcg/kg/day of additional intravenous selenium supplementation has been recommended.

Selenium supplementation needs to be guided by indices of selenium deficiency [29]. Increased plasma and urinary selenium levels and maximization of GSH-Px activity are acceptable indicators of adequate replenishment. Supranormal intake may lead to easy fatigue, irritability, neuropathy and gastrointestinal symptoms. Maintaining sufficient levels of other anti-oxidants like vitamins E, C, and beta-carotene can minimize reliance on selenium for antioxidant defense. In renal failure patients, plasma Se levels should be monitored. Se deficiency should be considered in patients with unexplained cardiac failure as its deficiency may cause cardiomyopathy leading to congestive heart failure and arrhythmias [30].

### Manganese

Manganese serves as a component of superoxide dismutase and is also important for arginine and pyruvate metabolism. Mn deficiency may manifest as defective carbohydrate and lipid metabolism. An enteral intake of 1.8 - 2.3 mg per day is considered acceptable while parenteral dose is 60 - 100 mcg per day. Dose should be decreased in patients with hepatic insufficiency [31, 32].

### Iron

Iron plays a central role in oxygen transport as the key component of the heme molecule and also other oxygen-carrying proteins including heme enzymes, myoglobin, and cytochrome *a-a<sub>3</sub>*. As a constituent of the functional groups of

many enzymes operating in the Krebs cycle, it is essential for energy metabolism. Enzymes like glutathione peroxidase, catalase, and a number of dehydrogenases need iron as a key element and hence it plays a crucial role in the body's defence against oxidative stress. Anemia during critical illness is multifactorial. The common causes of anemia in the ICU include increased destruction or impaired production of red blood cells combined with blood loss because of frequent diagnostic testing and operative procedures. Iron deficiency is also induced by cytokines during the inflammatory response [33]. Iron stores in the body are also diminished due to impaired absorption, nutrient antagonisms, and concomitant copper and vitamin A deficiencies.

There is conflicting evidence regarding the relationship between iron supplementation and infection. It has been shown to reduce respiratory infection rates and diarrheal episodes in anemic children. Decreased transferrin saturation in patients with major burns may lead to impairment of the erythropoietin response although serum erythropoietin levels are normal. Supplementing iron under these conditions can increase severity of infection and increase levels of free iron, which may be harmful as a chelator of free radical formation. Monitoring iron indices, particularly for a decreasing trend in ferritin, may be used to assess the timing and appropriateness of iron therapy.

### Trace Elements as Pharmaco-Nutrients

Traditionally critical care nutrition has been viewed as a supportive care and not as an active therapeutic modality. However, the concept of pharmaco-nutrition is based on the impact of nutrients being greater than just the provision of nutrition alone and stressing their impact on specific patient outcomes. In accordance with the emerging concept of pharmaco-nutrition, the administration of key nutrients should be dissociated from the provision of supplemental nutrition so that their full dose can be delivered, and their therapeutic effects (immune modulation and antioxidant defense) can be assessed appropriately [34]. Trace elements like selenium and zinc are the key micronutrients along with glutamine and omega fatty acids which are being investigated in most recent trials on pharmaco-nutrition.

### Antioxidant Role of Trace Elements

Oxidative stress caused by reactive oxygen species (ROS) is critical to the underlying pathophysiology of critical illness, especially the development of organ failure. During severe sepsis, mitochondrial dysfunction and ischemia-reperfusion injury may lead to increased generation of ROS and reactive nitrogen-oxygen species (RNOS). In critically ill patients, there are reduced stores of antioxidants, which have been

associated with an increase in free radical generation, an augmentation of the systemic inflammatory response, subsequent cell injury, increased organ failure, and even higher mortality [35]. Depletion of antioxidants is directly proportional to the severity of trauma or sepsis. Antioxidants are part of a complex endogenous defence system designed to protect tissues from the damaging effects of oxidative stress caused by excessive amounts of ROS/RNOS. These include selenium, zinc, manganese, iron, vitamins E and C, and glutathione which act as free radical scavengers and co-factors of crucial enzymes such as superoxide dismutase, catalase and glutathione peroxidase. A systematic review examining trials of antioxidant supplementation in critically ill patients has recently been conducted [36]. Thirteen studies were identified, most studied the effects of selenium either alone or in combination with other trace elements (Zn) and vitamins (A, C and E). When the results of all the trials were aggregated, overall antioxidants were associated with a significant reduction in mortality related to improved organ function, but had no effect on infectious complications or ICU length of stay in critically ill patients. A recent large, multicenter randomized trial of high-dose selenium supplementation in 249 patients with severe systemic inflammatory response syndrome, sepsis, and septic shock demonstrated a large, but not significant, reduction in mortality. A greater treatment effect, however, was detected in patients with high normal levels of selenium compared with normal levels of selenium, indicating that selenium is having an effect beyond restoring a deficiency [37]. Selenium has been identified as the cornerstone of the endogenous defence against oxidative stress and serum selenium levels correlate inversely with the severity of sepsis. Selenoproteins play an essential role in improving cellular immune function, activation of thyroid hormones and regulation of DNA synthesis. This may explain the fact that of all the pharmaconutrients, selenium supplementation has been associated with the most favorable outcomes.

### Ideal Route, Timing and Dosage of Pharmaco-nutrient Administration

In the evolving concept of pharmaconutrition, nutrients are treated as therapeutic agents rather than as part of a nutritional supplementation alone. Hence, like all new therapeutic modalities, there is a need to determine the most efficacious route, timing, duration and dosage of nutrient administration. However, there are no randomized trials published to date comparing enteral and parenteral delivery of pharmaconutrients, the most efficacious route remains to be determined and is a topic necessitating further research. Available evidence suggests that oxidative stress leading to mitochondrial dysfunction may become irreversible 48 hours after the onset of severe sepsis [38]. A decline in the cellular immune response occurs quite early with the onset of hyperinflammation and

severe sepsis. Therefore, the antioxidant trace elements (Se, Zn) should be started early on admission to the ICU in order to have a positive treatment effect.

The optimum dose of pharmaco-nutrients is also not yet determined. Studies using a higher than median dose of selenium (500 - 1000 mcg/day) have been associated with a trend towards significant reduction in mortality, whereas studies using a lower dose of selenium had no effect on mortality. Extremely high doses, however, may be associated with adverse effects and hence further research and dose-finding studies on pharmaco-nutrients are required [39]. In this context, a phase I, single-center, dose-escalating study involving 28 critically ill patients was recently conducted which demonstrated that intravenous selenium 500 mcg/day added to the 300 mcg/day enteral supplement, resulted in a greater reduction in markers of oxidative stress and improved mitochondrial function with no apparent adverse effect on organ function [40]. The results of this dosing study suggest that selenium supplementation at high doses is safe and may be needed to positively affect patient outcomes in the ICU. Based on the concept of pharmaco-nutrition, a multicenter, double-blind randomized controlled trial named the REDOXS study (Reducing Deaths due to Oxidative Stress) has been initiated to assess the therapeutic effects of glutamine and antioxidants like selenium in mechanically ventilated critically ill patients [41]. The outcomes of this trial are expected to significantly guide the intensivists regarding the optimum route and dose of the trace elements as pharmaco-nutrients.

### Conclusion

Supplementation of trace elements in critically ill patients should be considered as a crucial component of ICU care. This will not only correct the deficiencies present during critical illness but also their anti-oxidant potential and immunomodulating properties may improve the patient outcomes in severe sepsis. Future research in ICU nutrition should emphasize on the pharmaco-nutrient aspect of trace elements so as to determine the appropriate route, dose and timing of the intervention.

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