Trace element and vitamin deficiency: quantum medicine or essential prescription?

Mette M. Berger and Nawfel Ben-Hamouda

Purpose of review
In critical care, micronutrients remain perceived as 'quantum' part, that is, a little pertinent component of therapy. Some micronutrients have attracted more attention because of their antioxidant properties. During the last decade, some large size trials have tested their therapeutic potential, generally as 'single high-dose micronutrient intervention', with variable success. This review aims at taking stock of most recent.

Recent findings
Micronutrient blood levels are generally low in ICU patients, which has prompted the concept of replenishing or compensating deficits, or even realizing a pharmacological action. Single micronutrient trials have been conducted in large cohorts with selenium ($\geq$1000 μg/day), with limited success but no harm. Other trials have tested high-dose vitamin D (>400 000 IU), with nonconvincing results despite selecting patients with very low blood levels. High-dose vitamin C has been tested in septic shock (+/- thiamine, hydrocortisone) with variable results. A problem encountered in all studies is definition of deficiency based on blood levels as majority of the patients suffer inflammation, which causes redistribution of the micronutrients away from the circulating compartment in the absence of real deficiency.

Summary
Micronutrients are essential in the ICU. Due to their antioxidant properties and to the high prevalence of low blood concentrations suggestive of deficiency, several large-size RCTs have been conducted with variable success. Further research must clarify the respective importance of deficiency and inflammation.

Keywords
antioxidant, brain injury, critically ill, heart failure, selenium, septic shock, thiamine, vitamin C

INTRODUCTION

A definition of 'Quantum healing' is to be a form of alternative medicine, a pseudoscientific mixture of ideas [1]. A number of different versions exist, which allude to various quantum ideas including generally 'energy' and vibrations. Does this concept apply to trace elements and vitamins in critically ill patients? In the 90s, while administering trace elements to major burns, the first author of this article was asked if she was practicing homeopathy! The balance studies that supported the repletion studies required trace element extraction from cloths and bandages surrounding the patients: was it an intent to replace the hospital laundry? Hilarity subsided a few years later, when randomized controlled trials (RCT) showed that a trace element intervention reduced infectious complications, improved skin graft take, reduced protein catabolism, and reduced length of stay in major burn patients (Table 1). Selenium administration was shown to modulate the thyroid axis after major trauma, and an antioxidant cocktail (Se, Zn, vit C, thiamine) to reduce the length of hospital stay. Major effluent losses during continuous renal replacement therapy (CRRT) were observed, in a magnitude sufficient to compromise the body stores, resulting in reversible enzymatic and immune alterations as shown by the RCTs.

Quantum medicine frequently refers to 'energy' [1]. Without irony, energy transfer is the real basis of trace element action. Some essential trace elements, including the Co, Cu, Fe, Mn, and Mo are transition metals with partially filled d-orbitals [2] and have a number of different oxidation states: Zn, a metal with 2+, behaves similarly. Due to their variable electron valences, they are essential for the

Service of Adult Intensive Care Medicine, Lausanne University Hospital (CHUV), University of Lausanne, Lausanne, Switzerland

Correspondence to Mette M. Berger, Service of Adult Intensive care, Lausanne University Hospital (CHUV), BH08.612, Rue du Bugnon 46, CH - 1011 Lausanne, Switzerland. Tel: +41 79 55 60 509; e-mail: Mette.Berger@chuv.ch

Curr Opin Crit Care 2020, 26:355–362
DOI:10.1097/MCC.0000000000000737

KEY POINTS

- Vitamins and trace elements have essential roles in antioxidant and immune defences, as well as in energy and substrate metabolism. Some are of particular importance during critical illness: thiamine, vitamin C, and selenium.
- Compromised micronutrient and nutritional status are frequent upon ICU admission and contribute to worsening outcome.
- Micronutrient blood levels are generally below normal reference ranges in critically ill patients who present a strong inflammatory response: the low levels are often misinterpreted as deficiency, while they only reflect tissue redistribution.
- Intervention trials using one single very high-dose micronutrient, such as selenium, vitamin C, or vitamin D have not yet proven their efficiency.

respiratory chain and the antioxidant defences, and vitamins are central to ATP production: again, energy.

But with growing awareness during the last two decades, micronutrient deficiency has become considered by some as an 'invisible foe' [3] in ICU. The below review aims at summarizing some important new contributions.

GLOBAL CRITICAL CARE

When the patients starts on an ICU journey, the initial micronutrient status may be insufficient not only because of preexisting nutritional deficiencies but also because of the disease that caused admission [4]. Oxidative stress associated with inflammation and sepsis causes progression of organ failure and secondary organ damage. Investigation of this problem generated massive interest as reflected by the multiple publications. Searching PubMed for [critical illness and (oxidative stress or antioxidant) in humans) combined with [micronutrient] returned 34 475 hits the last 10 years. Some micronutrients have prominent roles as being part of endogenous antioxidant defence: vitamin C (vit C), vitamin E, Niacin (vit B3), Cu, Mn, Se and Zn are the main players, whereas vitamin D (vit D) appears as a global player (Fig. 1). Most ICU trials have included vit C and selenium, whereas thiamine has appeared on several occasions, because of its essential role in glucose and energy metabolism [5].

Endocrine disorders present in critical illness are also related to micronutrients. Thyroid function is frequently altered in critical illness, presenting as 'low T3 syndrome', a disorder linked to low thyroxine activation, a reaction that is under the control of blood Se, which is nearly always below normal. Indeed, presence of iodine, iron and Se have repeatedly been shown to be crucial to thyroid health [6], whereas Se administration restores thyroxine activity in critically ill trauma patients (Table 1).

Heightened oxidative stress is present in several acute inflammatory diseases, in acute renal failure (ARF), and after major trauma or major burns. Antioxidant micronutrient combinations have shown beneficial effects in trauma. Among the trauma studies, a before and after trial testing the combination of vit C (3 g), vit E (3000IU) and Se (200 μg) in 1622 critically ill trauma patients, whereas no effect on atrial arrhythmias was observed, the expected adjusted survival of patients with the antioxidant intervention was significantly higher compared with controls ($n = 2414$) [7].

Selenium

Se is essential for the activity of the principal family of antioxidant enzymes: the glutathione peroxidases (GPX). An observational cohort study enrolling 2382 patients with worsening heart failure showed that a Se level less than 70 μg/l (i.e. likely deficiency) was present in 20.4% patients, which was independently associated with impaired exercise tolerance and a 50% higher mortality rate [8▪]. Animal data show that a Se-deficient diet results in low blood Se GPX activity, which causes myocardial dysfunction [9]. Indeed, Se deficiency decreases myocardial antioxidant capacity, which is further worsened in case of insufficient protein intake: the combination of insufficient Se and protein intake does generate oxidative stress and causes cell apoptosis via the mitochondria-mediated pathway [9]. This combination observed in animals applies to inpatients who are frequently malnourished with low micronutrient intakes.

A recent cohort study including 85 critically ill confirmed that plasma Se and Zn are low upon admission to the ICU, and that the alteration was proportion to the severity score SAPSIII [10]: in addition, and this is new, the authors showed that erythrocyte Se was low in a significant proportion of patients reflecting a longer insufficient intake. This contributes to make these patients more susceptible to oxidative stress. Several micronutrient deviations contribute to the mitochondrial dysfunction, and Se is particularly important but there is yet no defined dose or combination of micronutrients proposed as treatment strategy [11]. Impact of the initial status

Table 1. Trace element and vitamin balance and intervention studies showing the impact of trace elements on immunity, metabolism and clinical course

ICU condition	Study design, patients and intervention	Results	Reference
Balance studies			
Major burns	Observational balance study $n=10$, age 36 years, 32% BSA	Exudative losses of Cu, Se and Zn were shown representing 20–30, 10 and 10% of body content, respectively. Prolonged depression of serum levels of the three elements (particularly copper) and of GPX3	Berger *et al. Burns* 1992; 18 : 373–80 Berger *et al. Clin Nutr* 1992; 11 : 75–82
Major trauma	Observational balance study, $n=11$, age 40 years, ISS 29	Increased urinary losses of Cu, Se, Zn persisting until D20. Se and Zn levels were decreased until D7. Negative Se balances despite administration of complements	Berger *et al. J Trauma*, 1996; 40: 103—109
Renal failure CRRT	Observational 8 h crossover* balance study $n=11$, age 65 years, SAPS II = 62	Continuous losses of thiamine, Cu, Se, Zn in quantities amounting to one to two daily doses of multi-MNs per day were measured. Balances were negative for thiamine, Cu and Se, but not for Zn *Crossover was for the replacement solution (lactate versus bicarbonate)	Berger *et al. Am J Clin Nutr* 2004; 80 : 410–16
Randomised controlled studies			
Major burns	$n=10$, age 34 years, 41% BSA TTT-iv: Cu 4.5 mg, Se 190 μg, Zn 40 mg for 7 days+ multi-MN	Intervention improved Cu, Se and Zn status (increase in serum levels GPX3, and various protein indicators), improved neutrophil response shorter hospital stay (45 versus 57 days). Lower grafting requirements in intervention group	Berger *et al. Nutrition* 1994; 10 : 327–34
Major burns	$n=20$, age 41 years, 48% BSA TTT-iv: Cu 40.4 μmol, Se 2.9 μmol, Zn 406 μmol for 7 days + multi-MN	Reduction of nosocomial infections. Number of infections per patient was significantly ($P<0.05$) lower in TTT group (1.9 ± 0.9) than in placebo (3.1 ± 1.1) because of fewer pulmonary infections. Shorter hospital stay when data were normalized for burn size	Berger *et al. Am J Clin Nutr* 1998; 68 : 365–371.
Major burns	$n=21$, age 42 years, 45% BSA TTT-iv: Cu 59 μmol, Se 4.8 μmol, Zn 574 μmol/day for 14–21 days+ multi-MN	Intervention-modulated antioxidant status and clinical course, with higher circulating plasma and skin tissue contents of Se and Zn and improved antioxidant status. Clinical course was improved (fewer pulmonary infections, better wound healing). Tissue changes: increased skin tissue content of Se and Zn and a reduction in skin protein catabolism	Berger *et al.* Am J Clin Nutr 2007; 85 : 1293-300. Berger *et al. Am J Clin Nutr* 2007; 85 : 1301–1306
Major burns	Aggregation of two trials $n=42$, age 42 years, 46% BSA TTT-iv: Cu 2.5–3.1 mg, Se 315–380 μg, Zn 26.2–31.4 for 8–21 days versus placebo+ multi-MN	Enhancing trace element status and antioxidant defences was associated with an infections reduction in TTT patients from 3.5 ± 1.2 (placebo) to 2.0 ± 1.0 episodes per patient ($P<0.001$). Nosocomial pneumonia reduction drove the decrease: 16 (80%) in placebo versus 7 (33%) in TTT patients ($P<0.001$), and of ventilator-associated pneumonia from 13 to 6 episodes, respectively ($P=0.023$).	Berger *et al. Crit Care* 2006; 10: R153
Major trauma	$n=31$, age 42 years, ISS 30 TTT-IV: Se 500 μg, Zn 13 mg, α-tocopherol 150 mg for 5 days + multi-MN	Se supplements increased the circulating Se levels. Supplementation was associated with modest changes in thyroid hormones, with an earlier normalization of T4 and reverse T3 plasma levels	Berger *et al. Intensive Care Med* 2001; 27: 91–100
Major trauma cardiac	$n=200$, age 59 years, SAPS 38 TTT-iv: AOX cocktail Se 270 μg, Zn 30 mg, vit C 1.1 g, vit B1 100 mg) for 5 days + multi-MN	No effect on length of ICU stay and of hospital stay in cardiac patients (16.5 AOX versus 20 days in placebo) Length of hospital stay shorter in AOX trauma patients (-10 days: $P=0.045$). Plasma concentrations of Se, Zn and GPX3, low on admission, increased significantly to within normal values in AOX group. C-reactive protein decreased faster in the AOX group ($P=0.039$).	Berger *et al. Crit Care* 2008: 12: R101

AOX, antioxidant; BSA, burned body surface; CRRT, continuous renal replacement treatment; GPX3, plasma glutathione peroxidase; ISS, injury severity score; IV, intravenous; multi-MN, multitrace element and vitamin parenteral nutrition doses; SAPS II = 62 simplified acute physiology score; TTT, intervention.

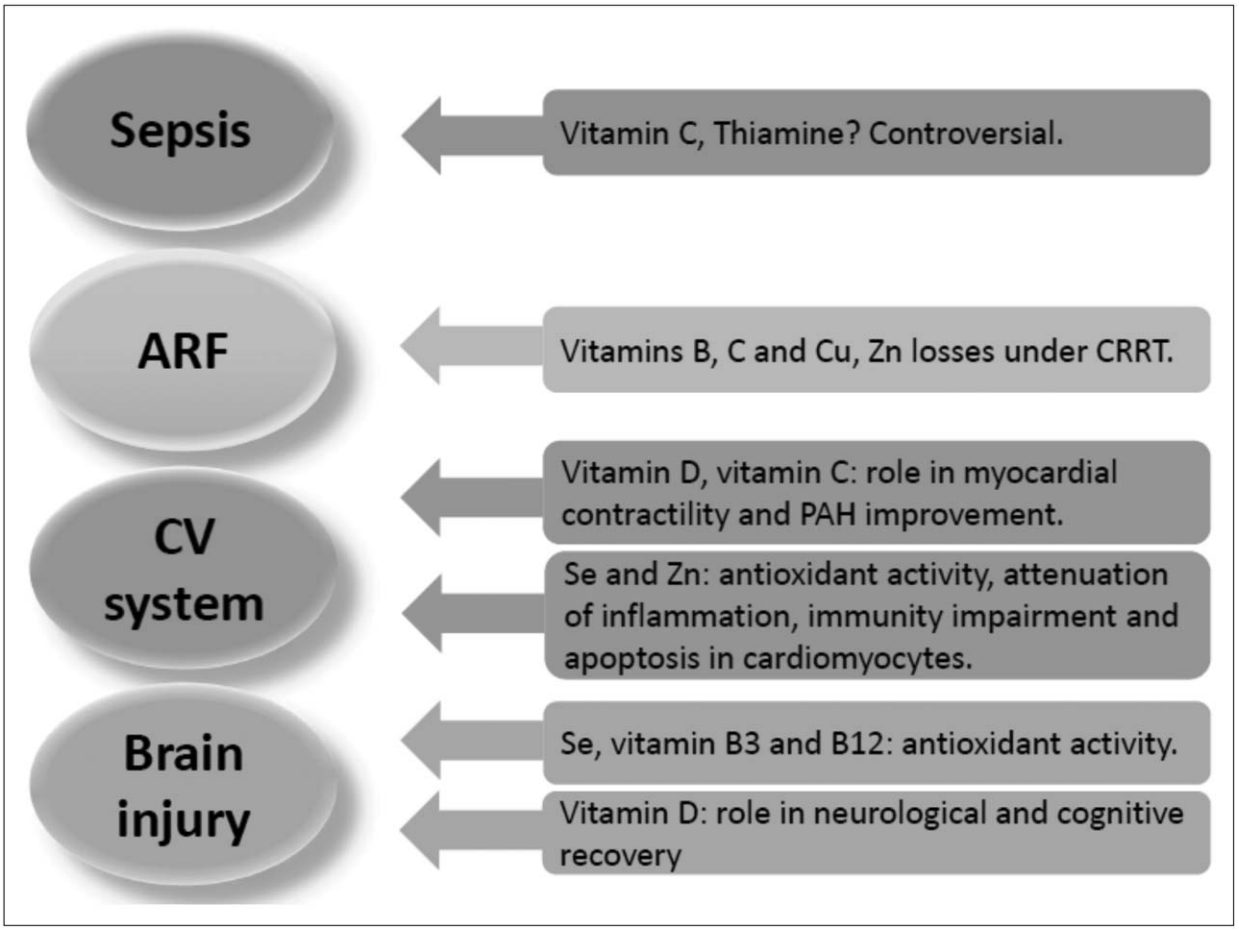

FIGURE 1. Principal critical care diseases for which micronutrients play an important role. ARF, acute renal failure; CRRT, continuous renal replacement therapy; CV, cardiovascular; PAH, pulmonary arterial hypertension.

on outcome was confirmed in 167 patients: low Cu, Se and Zn levels upon admission were associated with higher mortality, the latter being lower if Cu and Zn levels were close to normal [12].

Should we be delivering 'some Se' to all ICU patients? A recent meta-analysis suggests that Se administration might reduce the total mortality (but not length of mechanical ventilation or ICU stay): trial sequential analysis seems to indicate that no more randomized controlled trials were needed [13▪▪]. The question is how much Se, and for how long? Should Se be given alone, or in combination with vit C and thiamine? The most successful Se trials were delivering medium doses (300–800 μg/day), with some other micronutrients. Indeed, high-dose single Se is of limited interest [14], as confirmed by a few trials. Mechanically ventilated patients randomized to receive Se (3000 μg on admission and 1500 μg/day for 9 days) or placebo: despite increasing the serum Se and the antioxidant activity (GPX-3), Se did not affect the incidence of ventilator-associated pneumonia [15]. Isolated Se intervention is probably bound to fail as it does not support the entire antioxidant system.

Vitamin D

Low blood levels have been repeatedly shown to be present in ICU patients, and have been called 'deficiency'. With this definition, the prevalence of vit D deficiency in ICUs ranges between 40 and 70% [16]. The causes are multiple: preexisting to the admission and/or because of therapeutic interventions, such as fluid resuscitation, renal replacement therapy, surgery, extracorporeal membrane oxygenation, cardiopulmonary bypass and plasma exchange may significantly reduce not only vit D levels [16] but also inflammation [17,18▪▪].

Vit D deficiency is a potentially reversible contributor to morbidity and mortality among critically ill patients. Is (very) low vit D the hen or the egg, the consequence of disease, or does it have proper effects? Although the seasonal variation of blood levels has been demonstrated [19▪▪], there is clear

also a strong impact of inflammation on blood levels as shown by a large cohort of patients undergoing nutritional assessment: the higher the C-reactive protein (CRP), the lower the vit D (among other micronutrients) [17]. Several trials are attempting to answer the question with different designs. The VITdAL-ICU had shown promising results of high doses in the subgroup of patients with very low blood levels of vit D (≤12 ng/ml) with lower hospital mortality but not in the others [20]. The recently published VIOLET trial [21] casts some doubts about benefice: 1360 patients considered vit D-deficient based on a point-of-care blood screening underwent randomization: 1078 were considered severely vit D-deficient at baseline [25-hydroxyvitamin D <20 ng/ml (50 nmol/l)]. Randomization within 12 h of admission was to single enteral dose of 540 000 IU of vit D3 or matched placebo. This single intervention did not provide any advantage regarding 90-day mortality or other, nonfatal outcomes. Two ongoing RCTs in Europe and the United States might give the final answer as they aim to recruit greater than 5000 patients [16].

Thiamine

Also called vitamin B1, thiamine is an essential nutrient that serves as a cofactor for a number of enzymes, mostly within the mitochondria. The brain is highly vulnerable to thiamine deficiency because of its heavy reliance on mitochondrial ATP production [22▪], multiple neurological and psychiatric disorders, have been shown to be caused by thiamine deficiency [22▪]. Deficiency is frequent and constitutes a public health concern in several low-income and middle-income countries [23]. Cardiovascular patients on diuretics are at particularly high risk [24]. In ICU patients, an unexplained metabolic acidosis with elevated lactate should raise the suspicion of thiamine deficiency.

Refeeding syndrome

Refeeding syndrome (RFS) is a potentially fatal acute metabolic derangement that involves thiamine and phosphate. The real prevalence of RFS remains unknown [25]. Malnourished patients continue to account for 40% of hospital and ICU admissions. A recent subgroup analysis of a large nutritional intervention trial in medical patients (EFFORT) [25], showed that RFS increased risk for ICU admission (odds ratio 2.71, $P < 0.05$). The treatment includes electrolytes (P, K and Mg) and large doses of thiamine (300–600 mg/day). It also requires a proper nutritional management: caloric restriction for 48–72 h and gradual increase of caloric intake over days is part to the strategy as shown by two studies [26,27]: phosphate alone is insufficient [26].

Lack of hard data is the reason why the MEN (metabolism-endocrinology-nutrition) section of the ESICM initiated a 1-day prevalence survey (NCT04201899) and a systematic review of existing literature to gather objective data.

SEPSIS

Septic shock remains a prominent cause of death in critical care, and search for adjunctive therapy remains intensive. The combination of vit C and thiamine, with or without hydrocortisone is the most frequent combination in ongoing trials: the rationale for this combination in sepsis includes the prevention of the conversion of vit C into oxalate [28▪,29].

But the doses of vit C and thiamine to be used remain an unresolved issue [30]. The CITRIS-ALI trial (n = 167) administered high-dose vit C (16 g/day for 5 days in an 80 kg patient), but no thiamine, and hydrocortisone was used in majority of patients [31▪▪]: the authors observed a significant reduction of mortality. The most recently published trial (VITAMINS-RCT) used a triple combination in 216 septic shock patients [32]: vit C 6 g/day, thiamine 400 mg/day and hydrocortisone 200 mg/day. No significant results were observed [33]. The reason might be an insufficient vit C dose [30]. Indeed, the doses used by Fowler *et al.* [34] were not by chance but were based on a prior dose finding safety trial, which showed that this higher dose was required to increase circulating ascorbic acid concentration. Several upcoming trials should provide an answer [29].

ACUTE RENAL FAILURE

ARF is characterized by multiple metabolic alterations including an increased oxidative stress. When CRRT is required, multiple nutrients are lost including water-soluble vitamins (vit B family, vit C) and trace elements, resulting in acute depletion of body stores after a few days (Table 1). Severe complications may occur during prolonged CRRT (>2 weeks): Cu deficiency may become a cause of death by arrhythmia [35]. Recently, continuous losses of nutrients including Cu and Zn were confirmed [36]. Importantly, the CRRT modality matters: intermittent hemodialysis uses diffusion, continuous venovenous hemofiltration uses convection, whereas sustained low-efficiency diafiltration (SLEDf) uses a combination of these and has the largest impact [36].

To prevent ARF would be highly desirable. As cardiac surgery patients, particularly those operated

on pump, are at high risk of developing ARF, different strategies have been trialled with limited success until now, as shown by a RCT testing a combination of Se, vit C and N-acetylcysteine in patients undergoing off-pump Coronary Artery Bypass Graft (CABG) Surgery; no benefice was observed [37].

CARDIOVASCULAR SYSTEM

Vitamin D suppresses activation of the cardiac renin–angiotensin system and of the natriuretic peptides. It regulates calcium flux, and myocardial contractility. Deficiency is prevalent in heart failure especially in the elderly (≥60 years) [38]. Low vit D serum levels were associated with reduced functional capacity in patients with diastolic dysfunction or heart failure and were predictive for an increased rate of cardiovascular hospitalization [39]. Atamanuk *et al.* [40] compared vit D serum levels in 53 patients presenting a pulmonary arterial hypertension (PAH) versus patients presenting low ventricular function and healthy subjects: lower vit D levels were observed in the PAH versus the two other groups. These clinical data suggest an important role of vit D in the cardiovascular system, reinforcing experimental results reporting the identification of vit D receptors vascular smooth muscle cells, endothelial cells and in the myocardium [40].

The antioxidant properties of vit C have been tested in cardiac patients. In a double-blind RCT including 50 patients who had CABG surgery, high dose of vit C (5 g intravenously) before the induction and the same dose in the cardioplegic solution, improved ventricular function 72 h after surgery and shortened the ICU stay [41]. Previous articles underlined the consequence of vit C deficiency in patients with PAH. Gayen *et al.* [42] reported a case of a reversal severe PAH (mean pulmonary arterial pressure 41 mmHg) treated only by vit C repletion. For trace elements, recent studies indicate the relevance of selenium and zinc [8▪,43]. A multicentre international, prospective study, enrolling patients with worsening heart failure, showed that Se deficiency (serum level <70 μg/l) was associated with higher all-cause mortality, and with impaired exercise tolerance. The in-vitro part of the study concluded to impaired mitochondrial function and increased reactive oxygen species (ROS) levels in cardiomyocytes in selenium deprivation condition [8▪]. In addition, a recent systematic review tried to explain the relationship between zinc and heart failure [43]. Data collected suggest that Zn deficiency may be under-evaluated and under-recognized in heart failure. This systematic review suggests a cellular and biological mechanisms linking Zn deficiency to the development and progression of heart failure. In the heart, Zn deficiency leads to immunity impairment and to increased inflammation through cytokine modulation, Zn reduces the activity of TNF-α and caspase 3, thereby blocking apoptosis, finally, prevents oxidative stress by acting as a cofactor for nitric oxide synthase and as a cofactor of superoxide dismutase an powerful antioxidant mitochondrial enzyme [43].

BRAIN INJURY

Selenium administration in brain-injured patients may improve outcome in two distinct brain injuries conditions. Reactive oxygen species (ROS) play an important role in brain ischemia–reperfusion injury after cardiac arrest [44]. Selenium, via the GPX [4] might reduce this stress. In a cohort including 28 cardiac arrest patients (any cause), a better neurological outcome was observed at discharge in patients receiving Se (1000 μg bolus followed by 1000 μg intravenous perfusion) within the 24 h after return of spontaneous circulation (ROSC) compared with a matched control group [44]. Similarly, the administration of the combination Se and Niacin after ROSC reduced ROS, attenuated neuronal injury, and improved neurological outcome in a rat cardiac arrest model [45]. The benefit of Se in the traumatic brain injury (TBI); however, is still controversial. Khalili *et al.* [46▪], in a prospective study including 307 severe TBI, showed that prophylactic Se supplementation (1000 μg intravenously once/day for 5 days followed by 500 μg once/day for 5 days) was associated with an improvement in functional at discharge and 6 months after. This benefit is not observed in a double-blind RCT including 113 severe and moderate TBI [47]. In TBI patients vit D supplementation (cholecalciferol 100 000 IU intramuscularly followed by alfa-calcidol 0.5 mg/day if oral route available) in patients with deficiency, defined by serum level below than 30 ng/ml showed a long-term performance and cognitive improvement but only in mild-to-moderate ones. Vitamin B12 (vit B12) deficiencies have been reported in the literature to be related to neurologic complications, especially an acquired myelopathy with paraesthesia, ataxia and muscle weakness [4]. Indeed, vit B12 is involved in the synthesis of both phospholipids and myelin. Moreover, vit B12 showed superoxide scavenger properties contributing to neuronal cells' axonal growth [48]. In a recent experimental TBI model (mice), vit B12 administered after TBI improved neurological functional recovery. The result may be because of downregulation of the endoplasmic reticulum stress-related apoptosis-signaling pathway in the injured brain [48]. In brain-injured

patient especially in TBI and regarding to the heterogeneity of the injuries and their severity, micronutrients prescription strategy should be individually adapted.

CONCLUSION

Recent data confirm the importance of considering micronutrient status in the development of organ failure (Fig. 1), and of covering at least the basal needs in patients exposed to increased oxidative stress. The strategies that have proven most beneficial are those that aim at correcting an actual deficiency status, whereas very high doses of single micronutrient trials have been disappointing. It is important not to forget that providing micronutrients does not replace general feeding, which continues to remain insufficient in the hospital setting, and contributes to worsening of micronutrient status [4]. Inflammation has proven to be an important confounder when selecting patients based on blood concentrations [17,18▪▪], inflammation being generally not considered when deciding about deficiency.

Further knowledge is needed. Among the reasons for the few high-quality trials, we find the elevated costs of trace elements and vitamins analytics, and the limited availability of such determinations with results that are not timely available. As the micronutrient products are relatively inexpensive, industrial support for research is difficult to obtain, and revised funds only rarely support such trials.

Acknowledgements

None.

Financial support and sponsorship

This work was supported by the internal resources of the service of intensive care.

Conflicts of interest

M.M.B. has received speaker honoraria from Fresenius Kabi, Nestlé International and Baxter. N.B.H. has no conflict of interest.

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