Chapter 10
Micronutrients

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Abstract The status of 11 trace elements and 13 vitamins, collectively named micronutrients, is challenged in several critical care conditions. Inflammation and oxidative stress cause redistribution of micronutrients to organs involved in synthesis and immunity resulting in significant drops of plasma concentrations even in absence of real deficits. Nevertheless these changes alter the organism's capacity to respond to circulating stressors, and participate in worsening organ function in patients dependent on intensive care. Only one vitamin deficiency may be critical during the first 48 hours: Thiamine. Other alterations will result in later consequences in conditions characterized by the combination of a strong inflammation and of losses of biological fluids. The properties, risks and potential for intervention of the essential micronutrients are discussed, mainly regarding their immune, antioxidant and wound healing properties. The place in metabolism of carnitine and choline, actually missing in parenteral nutrition, is addressed.

Micronutrient is the collective name for trace elements and vitamins: both categories of substances are required for substrate metabolism, antioxidant and immune defences. They have no proper energetic value. Micronutrients are present in minute amounts and small changes will result in important changes in their distribution in the body [1]. Tables 10.1 and 10.2 summarise some aspects of their physiology and usual requirements: this knowledge only partially addresses the issues encountered during acute and chronic critical illness.

Oxidative stress and inflammatory response belong to the standardised body's answer to infection of any origin and severity or of any acute injury. Production of

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Table 10.1 Essential trace element in adults

Trace elements	Body stores	Location in the body	DRI	Parenteral nutrition recommendations
Cu – copper	100 mg	Liver, enzymes	0.9 mg	0.3–0.5 mg (5–8 umol) 1.3 mg (20 umol) in major burns and GI losses
Se – selenium	6–20 mg	Liver, kidney > muscle, bone, blood	55 mcg	30–70 mcg (0.4–0.84 umol)
Zn – zinc	1.4–2.3 g	Bone > genitalia, skin, liver, kidney, muscle, pancreas	11 mg	2.5–5 mg (38–76 umol) plus 2.5–4 mg (38–62 umol) in catabolic states but not >30 mg in ICU
Fe – iron	3 g (female) – 4 g (male)	Liver, spleen > Hb, myoglobin, cytochromes	8 mg	0 to 1.0–1.2 mg (18–20 umol)
Mn – manganese	12–16 mg	Mitochondria (liver, bone, kidney, pancreas, small intestine)	2.3 mg	0–55 mcg (1 mmol max)
Mo – molybdenum	9–16 mg	Mitochondria (same as Mn)	45 mcg	100–200 mcg (1.0–2.1 umol)
Cr – chromium	4–6 mg	Spleen, heart, kidney	35 mcg	10–15 mcg (0.2–0.3 umol) 20 mg (0.4 umol) in ICU
F – fluoride	<1 mg	Bone, teeth	4 mg	0.95 mg (50 umol)
I – iodide	20–50 mg	60 % thyroid > muscle, ovaries, blood	15 mcg	70 mcg (0.6 umol)
Co – cobalt	<1 mg	Blood	None	None
V – vanadium	20–25 mg	Throughout, stored in fat tissue	None	None

Adapted from [62, 63]
DRI dietary reference intake

reactive oxygen species (ROS) is a normal phenomenon that is amplified as soon as inflammation is activated. But the ROS production may overwhelm the endogenous antioxidant defences and reinforce inflammation. Pro-inflammatory mediators (such as TNF-a, IL-1, IL-6, bradykinins, leukotrienes, prostaglandins) are released in amounts proportional to the severity of the condition [2]. They may contribute to the development of multisystem organ dysfunction and even failure, when uncontrolled by the anti-inflammatory defence mechanisms and mediators (e.g., IL-4, IL-10, etc). After the initial hyper-inflammatory state, cytokine levels generally return to normal, a passage of hypo-inflammatory status being possible [3].

Micronutrients are very sensitive to circulating cytokines and other biomarkers of inflammation, which divert them from the circulating compartment to specific tissues and organs, reducing the blood concentrations. Insufficiency of the endogenous defences may result from deficiency or suboptimal status prior to disease or to this redistribution. This is particularly the case with the micronutrients involved in antioxidant defences such as selenium, zinc, ascorbic acid and α-tocopherol. Indeed Se and Zn concentrations below reference ranges during criti-

Table 10.2 Essential vitamins

Vitamins [13]	Units	EN recommended min-max	PN recommended dose	Absorption site	Main location
A – retinol	ug	700–3600	1000	Duodenum, upper jejunum	Various target organs
D – cholecalciferol	ug	10–50	5	Small intestine	Lymph, kidneys, adrenals, bones, intestines
E – alpha-tocopherol	mg	10–60	10	Small intestine	Lymph, all tissues
K – phylloquinone	ug	70–400	150	Small intestine, colon	Lymph
B1 – thiamine	mg	1.2–10	3	Small intestine	Heart, brain, kidney, liver, skeletal muscle
B2 – riboflavin	mg	1.6–10	3.6	Small intestine	All tissues, little storage
B3 – niacin (PP)	mg	18–60	40	Throughout gastrointestinal tract	All tissues, particularly liver
B5 – pantothenic acid	mg		4–7	Throughout gastrointestinal tract	All tissues
B6 – pyridoxine	*mg*	1.6–10	4	Throughout gastrointestinal tract	Brain liver kidneys
B8 – biotin (H)	mg	15–150	60	Throughout gastrointestinal tract	Liver, brain
B9 – folic acid	µg	200–1000	400	Small intestine	Liver tissues
B12 – cobalamin	*mg*	1.4–14	50	Ileum	Liver, heart, kidney, spleen, brain
C – ascorbic acid	mg	45–440	100	Intestine	Plasma, body cells

Adapted from [62, 63]

cal illness are associated with increased oxidative stress and elevated inflammatory biomarkers, particularly in patients with sepsis [4]. Several trace elements and vitamins will exhibit blood concentrations below reference ranges even in the absence of a true deficiency state: Fe, Se, Zn and vitamin concentrations are heavily altered. Suboptimal Se and Zn status in turn worsens oxidative stress [5]. This was recently confirmed in 114 critically ill patients: elevated CRP and low Se, Zn and albumin values were a constant finding [4], as it was in 800 non-critically ill patients referred for nutritional assessment.

In the intensive care unit (ICU), micronutrient prescription is generally confined to parenteral nutrition (PN). The below text will describe conditions in which this concept is insufficient to address the patient's requirements.

10.1 Which Micronutrients Matter in Critically Ill Patients?

In patients staying less than 4 days in the ICU and in absence of pre-existing deficiency, there is little time for micronutrient problems to develop or become source of concern, with one major exception: acute thiamine deficiency in the context of the refeeding syndrome which develops in a few hours upon re-administration of carbohydrates in patients who have not been fed for a few days [6] (see below Sect. 10.10.5).

But several acute conditions requiring ICU treatment are characterised by major micronutrient alterations, which have been identified as contributors to the worsening of their condition: they are generally characterised by the combination of a strong inflammation and of losses of biological fluids such as major burns and multiple trauma, patients on continuous renal replacement therapy, acute pancreatitis, and any patients with drains and high-output intestinal fistulae.

More and more patients survive the initial acute phase of disease: they are particularly fragile and exposed to cumulated progressive complications including alterations of micronutrient status. Patients enter a state called chronic critical illness: it is a recent phenomenon which has changed the ICU world and increases in incidence [2].

10.1.1 Trace Elements

The essential trace elements were defined in the 1960s [1] as inorganic substances, mainly metals and metalloids, constituting <0.01 % of body mass, that are present in constant concentrations <50 μg/g tissue or fluid. Their absence causes reproducible biochemical, structural and functional deficiencies, while these alterations can be prevented/corrected by the intake of the single element. Among the 11 essential trace elements listed in Table 10.1, copper, iron, selenium and zinc are of special interest during critical illness and will be discussed hereafter.

10.1.1.1 Copper

This element was rarely considered a problem in the ICU, being confined to neurological pathologies such as insufficient (Menkes disease) or excess copper (Wilson's disease) [7]. Recent changes in the ICU population have emphasised the importance of this element. But Cu deficiency remains a differential diagnosis which is rarely mentioned. Its potent redox activity makes copper a key modulator of cell signal transduction pathways. Copper deficiency can result in impaired energy production, abnormal glucose and cholesterol metabolism, increased oxidative damage, delayed wound healing (altered due to insufficient elastin and collagen synthesis), structure and function of circulating blood and immune cells, abnormal neuropeptide synthesis and processing, aberrant cardiac electrophysiology, impaired myocardial contractility and persistent effects on the neurobehavioral and the immune system [8].

Severe copper deficiencies appear several months after bariatric surgery, particularly in patients having undergone malabsorptive procedures: this is a growing

patient population resulting from the obesity epidemic. As copper is absorbed in the stomach and duodenum, deficiencies develop progressively [9]. In presence of cardiac and infectious complications, copper and ceruloplasmin concentrations should be determined, and copper prescribed by the intravenous route to be efficient as the gut is unable to absorb it.

Continuous renal replacement therapy is frequently required in chronic critical illness. The effluent losses contain several micronutrients, including copper [10]: the losses generally exceed one daily dose for standard PN. In patients undergoing prolonged renal replacement, blood copper should be monitored along with selenium to prevent development of extreme hypocupremia [11].

Major burns in patients have long been known to develop severe copper deficiencies caused by large losses from their burn wound exudates [12]. Death by cardiac arrest has been associated with extreme copper deficiency [13]. Early repletion of this element contributes to the restoration of immunity and of wound healing after major burns [14].

10.1.1.2 Iron

This element plays a central role in oxygen transport, being the core of haemoglobin, but also in electron transfer, nitrogen fixation or DNA synthesis and all essential reactions for living organisms. Iron deficiency is the main cause of anaemia worldwide, as well as a cause of fatigue and decreased effort capacity [15]. Anaemia is very frequent in the ICU, affecting nearly 70 % of patients. But systematic data on iron status in critically ill patients are few as the status is difficult to determine, the main indicators being affected by the omnipresent inflammatory response. A Belgian prospective study including 95 patients showed that the iron status measured by a combination of blood count, iron, ferritin, transferrin and transferrin receptor concentrations and transferrin saturation was rapidly altered in the majority of patients and remained so for many days [16]. True iron deficiency should be suspected as it is frequent in the general population [17], and therefore many patients start with iron deficiency or even anaemia. Critical illness worsens the status; hemorrhagic conditions and blood sampling contribute to depletion. It should also be considered when ferritin is in the lower range of normal, as this protein increases with inflammation. The clinical availability of the best marker of iron status in critical illness, hepcidin [15], is still to come.

10.1.1.3 Selenium

Selenium is essential for maintenance of overall health, especially for the thyroid, immunity and homeostasis. It is also important for reproduction [18]. It has a very important role in virology. Among the micronutrients with an antioxidant function, selenium is the one which has attracted most attention, followed by zinc. Indeed it constitutes the core of the glutathione peroxidase family of enzymes, which constitute the most important antioxidant defence system in the organism [19].

Critical illness and particularly those involving septic pathologies are characterised by inflammation and oxidative stress. Selenium concentrations are generally low, and the decrease of blood concentrations compared to reference ranges reflects the severity of disease [20].

A recent study combining in vitro and in vivo investigations confirmed that plasma concentrations of interleukin-6, other biomarkers of inflammation and markers of oxidative damage to proteins and lipids were elevated, particularly in patients with sepsis, and were inversely related to plasma selenium and zinc concentrations [5].

10.1.1.4 Zinc

Zinc is the structural and regulatory element in more than 300 enzymes, essential in all metabolic pathways, for genomic stability, DNA function and reparation, cell proliferation and apoptosis. It is also essential for the function of numerous hormones such as growth hormone, gustine, thyroid hormones, thymuline and insulin. It plays key roles in antioxidant and immune defences. The multiple functions of zinc require a dedicated review [21, 22].

In critical care research has focused on the antioxidant and immune functions mainly in sepsis, as well as on tissue repair.

10.1.1.5 Vanadium

This element is a new comer on the list, although no clear clinical deficiency state has yet been identified. The essential role of vanadium as an inorganic enzyme cofactor in maintaining haemostasis has long been known [23], although the mechanisms of action of vanadium salts remain poorly understood. Vanadium complexes are cofactors for several enzymes and also exhibit insulin-mimetic properties, making vanadium of interest to diabetes specialists [24]. The best accepted model of vanadium compounds' mechanism of action is to consider that they behave as phosphate analogues: vanadium would activate the protein tyrosine phosphorylation (PTP) of solubilised insulin receptor and autophosphorylation of this receptor in a mechanism analogous to insulin. Vanadium compounds increase glucose uptake and transport from the intracellular compartment to the cell surface through the insulin-dependent glucose transporter GLUT4 in the mechanism regulated by phosphoinositide 3-kinase and protein kinase B [25].

The average diet provides 10–160 μg of vanadium per day, mainly from mushrooms, seafood, black pepper, parsley, fennel seeds, grains and spinach. After entering the bloodstream, vanadium compounds are converted into vanadyl cations, which form complexes with transferrin and ferritin and, less frequently, with albumin, haemoglobin or low molecular components of plasma (citrate, lactate and phosphate) [23]. There are still no recommendations regarding this TE in artificial nutrition, as the toxicity limits are not yet well defined: hence actual multimicronutrient preparations do not contain any vanadium.

10.1.2 Vitamins

They are by contrast with trace elements, organic substances that are required in minute amounts, which cannot be synthesised by the body in sufficient quantities to match the requirements to prevent deficiencies. While all those listed in Table 10.2 are essential, some seem to be of special interest during critical illness and are discussed below.

10.1.2.1 Vitamin B

Among the vitamin B family, thiamine is on the frontline in critically ill patients. This vitamin exists under various forms, the most important being thiamine pyrophosphate (TPP), which is the coenzyme for mitochondrial oxidative decarboxylation. It is hence essential for the metabolism of carbohydrates and branched amino acids. Thiamine influences reactions that protect against oxidative tissue damage by maintaining reduced NADP+, and thiamine deficiency decreases GPx activity [26].

Different studies have shown a high incidence of thiamine deficiency, varying between 28 and 71 % on admission to the emergency department or ICU [27]. It is particularly frequent in populations at risk of alcohol abuse. Further, depletion after admission has also been shown to occur within a few days [6]. Thiamine insufficiency should be kept in mind in different clinical scenarios such as severe sepsis, major burns, unexplained heart failure or lactic acidosis and neurological disorder in patients with a history of alcoholism, starvation, chronic malnutrition, long-term parenteral feeding, hyperemesis gravidarum or bariatric surgery [6]: it should also be suspected in patients who have been in hospital for a few days and submitted to investigations, which frequently result in acute starving sufficient to prompt a refeeding syndrome.

But the association of thiamine status with outcome is complex. While depletion of thiamine during the refeeding syndrome is rapidly lethal and may precipitate lactic acidosis and Wernicke–Korsakoff encephalopathy, a Brazilian study including 108 patients in septic shock showed that thiamine deficiency on admission despite being present in 71 % of patients was not associated with oxidative stress or mortality [28].

10.1.2.2 Vitamin C

Ascorbic acid is a water-soluble antioxidant vitamin circulating in plasma. It is taken up by the intestine via the sodium-dependent vitamin C transporter. Vitamin C scavenges reactive oxygen species such as superoxide and peroxynitrite in plasma and cells (preventing damage to proteins, lipids and DNA): it prevents occludin dephosphorylation and loosening of the tight junctions [29]. Ascorbate improves microcirculatory flow impairment by inhibiting tumour necrosis factor-induced intracellular adhesion molecule expression, which triggers leukocyte stickiness and slugging [30]. Severe vitamin C deficiency, or scurvy, is a clinical syndrome with lethargy, perifollicular petechiae, erythema, gingivitis, bleeding, impaired wound healing and depressed immunity, conditions rarely observed in ICU. But very low plasma

concentrations have repeatedly been measured during critical illness and considered to reflect acute deficiency [31]. The low plasma concentrations are associated with inflammation, severity of organ failure and mortality [32]. It is of high potential interest in critically ill patients with a strong inflammatory response.

10.1.2.3 Vitamin D

This vitamin has recently become a major centre of interest. It was long confined to bone disease and to the maintenance adequate calcium levels for bone mineralisation and optimal skeletal muscle function [33]. It has been shown in the last decade to have pleiotropic effects, including on the immune system. In critically ill patients, the multiple effects of vitamin D including its role in immune function are of great interest, as deficiency defined by low to very low blood concentrations seems to be rather common [34]. On the basis of optimal bone health, vitamin D deficiency is defined as a serum 25(OH)D below 20 ng/ml (50 nmol/l), vitamin D insufficiency as a 25(OH)D of 20–30 ng/ml (50–75 nmol/l) and a normal vitamin D status as 25(OH)D above 30 ng/ml (75 nmol/l) [35]. These values have been directly applied to critically ill patients despite the fact that many factors differing from the general population may alter the blood concentrations such as fluid resuscitation and inflammatory state.

Two recent papers suggest that vitamin D deficiency is associated with adverse health outcomes including increased risk of cardiovascular disease, morbidity and mortality both in the general population and in critical illness [35, 36]. In a Brazilian study including 135 patients, the vitamin D level was an independent predictor of mortality [36]. Today it is not clear though whether vitamin D deficiency is a surrogate marker for increased morbidity or a therapeutic target.

10.1.2.4 Carnitine

It was isolated initially from a meat extract some 100 years ago. It was long not considered to be essential in mammals, having been discovered as an insect growth factor. It was later shown about 50 years ago to have important roles in metabolism as facilitator of β-oxidation and of transport of carboxylic acids (acyl group) across membranes, including that of coenzyme A [37]. It thereby performs a critical role in cellular energy metabolism. Carnitine is not required for transport of medium chain fatty acids, while facilitating their β-oxidation in skeletal muscles. It works as a key regulator of lipid metabolism in long chain fatty acid esterification and transport through the mitochondrial membrane [38]. It becomes conditionally essential in some clinical situations encountered in critical care.

Recent research has highlighted the importance of mitochondrial dysfunction in the metabolic and neuroendocrine changes observed in patients presenting with chronic critical illness [11]. Deficiency may develop as there is nearly no carnitine content in commercially available feeds nor in supplements. This small moiety may

be lost in large amount through the effluents of patients on continuous renal replacement therapy causing acute and chronic deficiency states manifested as a generalised mitochondrial dysfunction and multiorgan failure including the liver, with clinical consequences such as muscle weakness, rhabdomyolysis, cardiomyopathy, arrhythmia or sudden death [11]. Upon diagnosis of deficiency based on blood samples, repletion may be carried out by the enteral or intravenous routes in the doses of 1–2 g/day. Normal requirements are 2–5 mg/kg/day. Carnitine is absorbed in the small intestine by a few transporters which vary according to the dose being supplemented.

Parenteral nutrition solutions do yet not contain carnitine. Nevertheless based on actual knowledge, at least in neonatology, carnitine should be routinely added to parenteral nutrition formulations [39].

10.1.2.5 Choline

Choline is not a vitamin as it is synthesised endogenously from methionine or absorbed from the portal circulation [40], but it is recognised as essential since the 1990s. It is ubiquitous in the diet. Nevertheless deficiency has been described in a series of animals, who develop cirrhosis. In humans it has been investigated in association with intestinal failure-associated liver disease and chronic cholestasis in the entity called parenteral nutrition-associated liver disease (PNALD). Its deficiency activates cellular apoptosis and is involved in lipid transport and transmembrane signalling [40].

In patients on parenteral nutrition, plasma-free choline has been found to be below normal in the majority of patients, with a significant inverse relationship between this concentration and ALT and AST levels. In 2012 the ASPEN published recommendations for changes in the composition of parenteral nutrition solutions: the working group conclude that choline should also be routinely added to adult and paediatric PN formulations. However, such commercially available parenteral product is still to be developed [39].

10.2 Which Micronutrients Should Be Considered Eligible for Intervention?

A major issue to consider when organising a micronutrient prescription is the fact that they do not intervene in metabolism independently from others, as single standalone entities. They should be administered in combination. In case of PN, which as available from industry by definition contains macronutrients but no micronutrients, the additional daily administration of trace elements and vitamins is required as stated in the ESPEN guidelines [41]. The products available in Europe are designed for home total PN, or for stable patients only, and most of these products are adequate but do not address the specific requirements and high metabolic needs of critically ill patients.

Some micronutrients have an easily identifiable therapeutic objective and indication, such as the plasma GPX3 activity in case of selenium deficiency, but a well defined therapeutic objective is generally unavailable in clinical settings. In patients presenting acute biological fluid losses, whatever their cause, replacement of the losses is warranted: it should nevertheless be kept in mind that one micronutrient loss rarely occurs alone. Trace elements are more affected than vitamins according to published literature. Several studies have confirmed the clinical benefice of the multi-micronutrient concept in pathologies characterised by biological fluid losses such as major trauma [42, 43] and major burns [14, 44]: significant reductions of infectious complications, of length of stay and of mortality have been observed.

10.2.1 Selenium

Several randomised trials have tested moderate to very high-dose selenium supplements aiming at attenuation of oxidative stress and inflammatory response. As many of the trials include small cohorts, meta-analysis has been conducted including various numbers of randomised controlled trials. Doses of selenium have been variable between 300 mcg and 4000 mcg/day, and selenium has frequently been used in combination with other antioxidant micronutrients. In patients with sepsis, selenium supplementation at doses higher than daily requirement may reduce mortality [45]. Trials delivering >500 mcg/day of selenium showed a trend towards a lower mortality whereas trials using doses lower than 500 mcg had no effect on mortality [46].

10.2.2 Zinc

High-output intestinal fistulae are a unique condition in which zinc is lost preferentially to any other micronutrient: 20–30 mg of zinc by the intravenous route may be required per day to compensate the losses [47].

Major burns is another condition requiring such high doses of zinc by the intravenous route, for 2–4 weeks, but the needs are not focused on zinc only but on a combination of trace elements, particularly copper and selenium, in association with thiamine and ascorbic acid.

10.2.3 Copper

As stated above, isolated copper deficiency is rare, but found in pathologies at risk. It is a component of multitrace element solutions, but in quantities insufficient to compensate for an acute deficiency. Copper sulphate is the usually available form, prepared by the hospital pharmacies. Our Lausanne university pharmacy prepares

copper gluconate. Doses required for treatment of severe deficiency states vary between 2 and 6 mg/day administered as continuous intravenous infusion. Daily monitoring of liver tests AST and ALT is mandatory. In our own experience, no side effects are observed up to 8 mg/day in major burns [11].

10.2.4 Iron

It was long believed that iron supplementation would increase the risk of infections [48], and was therefore withhold in ICU patients, but this threat has not been confirmed, while the complications of iron deficiency and anaemia are obvious. A randomised placebo-controlled study in 200 anaemic cardiac surgery patients tested the enteral administration of ferrous sulphate 325 mg three times daily versus placebo and showed that the intervention was of limited efficiency, except for a reduced number of transfusions ($p = 0.03$), but at least did not increase infectious complications [49]. Indeed in critically ill patients, the enteral route is uncertain. The most recent intravenous iron formulations, available since the 1990s, seem to replenish iron stores safely and effectively [17]: in case of deficiency with low ferritine levels, only intravenous administraiton is efficient.

10.2.5 Thiamine: Vitamin B

The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines for parenteral nutrition in intensive care, published in 2009 [41], recommend empirical thiamine supplementation (100–300 mg/day) during the first 3 days in the ICU for all patients at risk of thiamine deficiency. Thiamine supplementation should be prescribed liberally in ICU patients [6], without any blood determination being required prior to empirical administration: such a sampling should though be done in case of searching for a specific diagnosis such as cardiac beriberi.

10.2.6 Vitamin C

The doses required to achieve normalisation of blood concentrations during critical illness are much higher than the daily 100 mg recommended for healthy subjects. Up to 3 g daily for 2–6 days are needed to restore normal plasma concentrations in ICU patients [31].

Clinical trials in sepsis, trauma and major burns testing high-dose vitamin C have shown clinical benefits. Phase I studies in sepsis seem to confirm safety of very high doses (200 mg/kg/24 h) delivered for a short period of time [50] and

potentially a clinical benefit reflected by faster and significant reductions of the sequential organ failure assessment (SOFA) scores in patients receiving high-dose treatment in a double-blind placebo-controlled setting. In major burns megadose vitamin supplements (66 mg/kg/h) delivered intravenously during the first 24 h reduce fluid requirements during resuscitation, resulting in lesser weight gain and improved blood oxygenation [51]. It is still too early to introduce this strategy in clinical practice: further large-scale studies are required to confirm the safety of such high doses.

10.2.7 Vitamin D

A large randomised Austrian trial including 475 critically ill patients with vitamin D deficiency [52] showed that the administration of high-dose vitamin D3 (540,000 IU) compared with placebo did not reduce hospital length of stay, hospital mortality or 6-month mortality. Nevertheless in the severe vitamin D deficiency subgroup, lower hospital mortality was observed: this finding should be considered hypothesis generating until further studies confirm these findings. Recently a study (VITD) including 25 ICU patients with vitamin D deficiency an oral ultra-high dose (540,000 IU corresponding to 13.5 mg) corrected the deficient blood concentrations within 2 days without any side effect (no hypercalcaemia or hypercalciuria) [53].

In major burns, vitamin D deficiency develops over time [54]. Focus has been in paediatric patients. The mechanism causing this deficiency is mainly limited exposure to sun after burn injury and decreased skin synthesis [55], which contribute to osteoporosis observed after burns. It was recently shown in a Belgian cohort of 24 adult patients on standard vitamin D intakes (400–600 ui/day) that 22/24 were vitamin D deficient or insufficient very early after injury and remained below references [56]. In another cohort of 29 burn patients, an oral dose of 100,000 IU D3 succeeded in increasing circulating levels by a median of 33 % [57].

Vitamin D has been investigated in paediatrics as deficiency threatens child growth. A meta-analysis of paediatric trials shows that rapid normalisation of vitamin D levels is best achieved by using loading therapy that considers disease status, baseline 25(OH)D and age (or weight). Nevertheless this meta-analysis concludes that loading doses of 300 000 IU should be avoided until trials are conducted that better evaluate risk and benefit [58].

Based on actual data, low vitamin D levels at ICU admission may serve as an indicator for vitamin D replacement. Available parenteral multivitamin preparations contain about 200 IU of vitamin D2 or D3, in addition to other fat-soluble vitamins: no intravenous vitamin D mono-preparation is available [52]. Oral preparations exist with doses up to 800 UI: considering the variable intestinal absorption existing in critical care patients, this route is the only actually available.

10.3 How Should Micronutrients Be Prescribed and Delivered?

The mode of administration during PN is highly variable depending on each institution's practice in the absence of strong guidelines. While TE are stable, but risk to cause separation of the lipid emulsions, vitamins are not: many studies have shown that the various vitamins but particularly vitamins A, E and C are very rapidly degraded, being extremely sensitive to light. This latter reason is probably the best argument in favour of an administration separate from the PN solution delivered separately over 6–12 h in light-protected bags as for vitamins [59].

Another argument is associated with the limited retention in the case of rapid administration: a very complete balance study was conducted in 1977 [60] with the intravenous micronutrient solutions available in the 1970s (Addam®, precursor of Addamel and Lipovit® solutions). It showed that some micronutrients were retained such as Fe, while others appeared not to be. Other elements retained were Ag, Co, Cr, Cu, Sb, Sc and W, while Br and Rb were lost by the patients. Negative balances were also found for As, Au, Cd, Cs, Mo, Se and Zn. Serum concentrations of thirteen TE (Ag, Br, Co, Cs, Cu, Fe, Hg, Mo, Rb, Sc, Se, W and Zn) were found to decrease during the period of total PN. The doses available in these preparations were not much different from those on the market in the twentieth century. Therefore these results remain pertinent and call for monitoring of trace elements.

Many preparations available on the market were developed more than 30 years ago. In 2012 the American Society for Parenteral and Enteral Nutrition (ASPEN) called for a revision of their composition in a very well-documented position paper [39]. Single trace element solutions are not easily available on the market: iron solutions have been developed, as well as selenium preparations. The situation seems a little better with vitamins which have been upgraded in the recent decade. Nevertheless the actual commercial vitamin solutions are also due for revision [61]. In patients on long-term PN and chronic critically ill patients, monitoring of blood levels is therefore required for both TE and vitamins.

Whatever the dose considered, the micronutrients should not be delivered as bolus in clinical settings. Micronutrients should be infused over as long a period as possible [59]. However, the problem is the potential interactions in the bag. Trace elements are entirely stable, but some of the water-soluble vitamins are not. Especially ascorbic acid is extremely labile and interacts with copper, resulting in ascorbic acid destruction.

10.4 Conclusion

In critically ill patients with inflammatory conditions, recent research shows that micronutrient prescription is not confined to parenteral nutrition. The solutions available in clinical practice are probably insufficient to cover the basal requirements in the vast majority of critically ill patients: therefore in conditions at risk as

described in the above text including patients on long-term artificial nutrition, blood sampling remains the only tool available to detect deficiencies and should be considered in patients requiring critical care for more than a week as well as in those with important losses of biological fluids.

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