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REVIEW

What do we know about micronutrients in critically ill patients? A narrative review

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Abstract

Micronutrient (MN) status alterations (both depletion and deficiency) are associated with several complications and worse outcomes in critically ill patients. On the other side of the spectrum, improving MN status has been shown to be a potential co-adjuvant therapy. This review aims to collect existing data to better guide research in the critical care setting. This narrative review was conducted by the European Society of Intensive Care Medicine Feeding, Rehabilitation, Endocrinology, and Metabolism MN group. The primary objective was to identify studies focusing on individual MNs in critically ill patients, selecting the MNs that appear to be most

For affiliations refer to page 50.

Abbreviations: AKI, acute kidney injury; ALI, acute lung injury; APACHE, acute physiology and chronic health evaluation; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CPTS, carnitine palmitoyl transferase system; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; Cu, copper; DFE, dietary folate equivalent; DRI, dietary reference intake; ECMO, extracorporeal membrane oxygenation; EN, enteral nutrition; EPO, erythropoietin; ESICM, European Society of Intensive Care Medicine; ESL, endothelium surface layer; ESPEN, European Society for Clinical Nutrition and Metabolism; F, female; FAD, flavin adenine dinucleotide; FMN, flavin mononucleotide; FREM, Feeding, Rehabilitation, Endocrinology, and Metabolism; GPX3, gluthatione peroxidase; HAT, hydrocortisone, vitamin C (ascorbic acid), and thiamin; Hb, hemoglobin; ICU, intensive care unit; IL, interleukin; IU, international unit; IV, intravenous; LDL, low-density lipoprotein; Na_2SeO_3, selenite; NAD, nicotinamide adenine dinucleotide; NAM, nicotinamide; PLP, pyridoxal 5′-phosphate; PN, parenteral nutrition; QPRT, quinolinate phosphoribosyl-transferase; RBP4, retinol-binding protein 4; RCT, randomized controlled trial; RE, retinol equivalents; ROS, reactive oxygen species Se-Met, selenomethionine; Se, selenium; SELENOP, selenoprotein-P; SIRS, systemic inflammatory response syndrome; SOD, superoxide dismutase; sTfR, soluble transferrin receptor; TBI, total body iron; TBSe, total body Se content; TOC, alpha-tocopherol; TSAT, transferrin saturation; TUIL, tolerable upper intake level; WHO, World Health Organization.

relevant and most frequently investigated in the last decade: A, B_1, B_2, B_3, B_6, folate, C, D, E, copper, iron, selenium, zinc, and carnitine. Given the limited number of interventional studies for most MNs, observational studies were included. For each selected MN, the review summarizes the main form and functions, special needs and risk factors, optimal treatment strategies, pharmacological dosing, and clinical implications all specific to critically ill patients. A rigorous rebalancing of research strategies and priorities is needed to improve clinical practice. An important finding is that high-dose monotherapy of MNs is not recommended. Basal daily needs must be provided, with higher doses in diseases with known higher needs, and identified deficiencies treated. Finally, the review provides a list of ongoing trials on MNs in critically ill patients and identifies a priority list of future research topics.

KEYWORDS
critical illness, inflammation, micronutrients, nutrition, oxidative stress

INTRODUCTION

Micronutrient (MN) status adequacy is essential for critically ill patients' recovery because of MNs' central role in optimizing anti-inflammatory, antioxidant, and immune defense mechanisms and metabolic pathways.[1] They do not act alone but interact in sequential metabolic steps and compete for positions on metabolic pathways. Requirements vary and dietary reference intakes (DRIs) have been elaborated for the general population.[2] Critically ill patients receive enteral nutrition containing DRI doses of MNs when the energy feeding target, usually approximately 1500 kcal/day, is reached but not during the feeding initiation or at low target values because of the fixed content of the solutions. In addition, these patients are at high risk for MN depletion or deficiency owing to premorbid nutrition status, underlying disease with increased metabolic consumption, reduced nutrition intake, and intensive care (ICU) therapies, such as the use of continuous renal replacement therapy (CRRT), extracorporeal membrane oxygenation (ECMO), and medication.[3] A deficiency of vitamins and trace elements can lead to suboptimal function of many vital enzymes, contributing to organ dysfunction and, ultimately, worse clinical outcomes.[1] Therefore, repletion of MNs aiming at restoring function is crucial when deficiency is present.

However, assessing MN body status in ICU patients is challenging. Plasma concentrations are not available in daily clinical practice, and, even more importantly, they only represent flow between organs, which reduces their capacity to represent the true body stores and intracellular function caused by the impact of inflammation. The release of cytokines nearly immediately decreases plasma concentrations of most MNs (except copper) and their binding proteins[4] because of redistribution to different compartments and other organs. This will cause an apparent, not an absolute, deficiency. The MNs most affected by this process are vitamins C and D, selenium, and zinc. Intracellular measurements (erythrocytes or leucocytes) or functional assays[4] appear to be less affected by inflammation but are generally not clinically available. In addition, it has not been demonstrated yet that supplementation based on these assays leads to a better clinical outcome than intervention based on plasma concentrations in critically ill patients. The term supplementation is used when the aim is to deliver higher than standard doses (ie, superior to DRI or parenteral nutrition [PN] recommendation) in an attempt to correct depletion or deficiency. This term does not include pharmaconutrition, which indicates treatment with a specific MN to improve host defenses, or any other biological endpoint associated with good clinical evolution that can improve the outcome of critically ill patients. To enable comparison of doses used in the different trials, Table 1 provides the standard DRI for the MN included in this review.[2] Generally, only one MN is prescribed, although it is not uncommon for critically ill patients to have multiple MN deficiencies that require treatment with more than one MN (e.g. iron and vitamin D deficiency).

Clinical symptoms are also not conclusive for the estimation of deficiency. Clinical signs of deficiency do not have time to develop in acute critical illness conditions. In prolonged critical illness, clinical symptoms of deficiency (such as muscle weakness, encephalopathy, stomatitis, delayed wound healing, low cardiac output, and recurrent infections) significantly overlap with the underlying condition's clinical features. Taken together, quick and accurate identification of deficiencies in critically ill patients is still impossible, although highly important. This has led to MN strategies varying between countries, hospitals, and physicians, mainly administering fixed doses of single or multiple MNs to all or subgroups of ICU patients.[5]

In 2022, the European Society for Clinical Nutrition and Metabolism (ESPEN) MN guidelines provided dose recommendations for all vitamins and trace elements in medical nutrition therapy.[2] This paper builds on these guidelines. We focus on MNs for critically ill adult patients; summarize the latest clinical studies of repletion, supplementation, and pharmacological dosing; discuss the clinical implications; and make suggestions for essential research topics to be investigated. For the definitions of the terms used throughout the manuscript regarding MN status and requirements we refer to the short version of the ESPEN MN guidelines.[2]

TABLE 1 Daily standard micronutrient requirements for the general population (DRI) for enteral nutrition and parenteral nutrition for the micronutrients discussed in this review.

	DRI per day, 31 to 70 years of age[a]	Enteral nutrition	Parenteral nutrition
Copper, mg	0.9	1–3	0.3–0.5
Iron, mg	8 (18 mg F 19–50 yrs)	18–30	1.1
Selenium, mcg	55	50–150	60–100
Zinc, mg	8–11	10–20	3–5
Vitamin A (retinol),[b] mcg	700–900	900–1500	800–1100
Vitamin C (ascorbic acid), mg	75–90	100	100–200
Vitamin B_1 (thiamin), mg	1.1–1.2	1.5	2.5
Vitamin B_2 (riboflavin), mg	1.1–1.3	1.2	3.6
Vitamin B_3 (niacin), mg	11–16	18	40
Vitamin B_6 (pyridoxine), mg	1.5–1.7	1.5	4
Vitamin B_9 (folic acid), mcg	400 DFE	330–400 DFE	400
Vitamin D_3 (cholecalciferol), mcg	15–20	25	200 IU/5
Vitamin E (alpha-tocopherol), mg	15	15	9–10

Abbreviations: DFE, dietary folate equivalent; DRI, dietary reference intake; F, female.

[a]DRI may differ for pregnant women.

[b]Retinol includes retinol and retinyl ester.

METHODS

Twenty-seven critical care professionals from the Feeding, Rehabilitation, Endocrinology, and Metabolism (FREM) MN group of the European Society of Intensive Care Medicine (ESICM) conducted this narrative review to examine the current evidence on MNs in critically ill patients. The primary objective was to provide the clinical implications for intensive care clinicians and set the stage for future research and intervention trials.

For this review, a comprehensive literature search of studies on humans was conducted up to 2024 (for search strategy, see Supporting Information) to identify studies focusing on individual MNs in critically ill patients. We selected those MNs that appear to be especially relevant for this population and have been most frequently investigated in the last decade. Given the limited number of interventional studies for many MNs, observational studies were included, if deemed appropriate, to generate the manuscript, evidence, currently ongoing trials tables (see Tables S1–S27), and clinical implications.

The review addresses key topics for each MN, including the summary of the main form and functions, plasma concentrations, supplemental and pharmacological dosing according to clinical studies, and clinical implications, all specific to critically ill patients.

Each MN was assigned to two to four members of the group who generated the initial text, evaluated relevant references, and formulated the clinical implications. The entire working group participated in the final version of the manuscript to ensure the accuracy and consensus of the findings.

Hereafter, the wording recommended in the ESPEN MN guidelines will be used to describe the type of prescription when the information is available. Complementation will be used to indicate the delivery of MNs to cover basal needs (eg, to complete enteral feeds or PN); repletion defines doses aiming to restore a normal status and where the deficit is known; supplementation is used for doses higher than standard doses (ie, superior to DRI or PN recommendation); and pharmacological dose indicates use of one single MN at doses often far greater than 10 times the DRI.

The diagnostic tools used to assess MN status, such as biomarkers and analytical methods, were recently extensively described in the ESPEN MN guidelines.[2] Additionally, a comprehensive review[4] elaborated on the pitfalls in interpreting blood tests for assessing MN status in critically ill patients with inflammation. Therefore, these authoritative sources are referred to, and this review will not further address these topics.

Lastly, the review provides a list of ongoing trials on MNs in critically ill patients and identifies a priority list of future research topics to guide future investigations in this field.

RESULTS

For each MN (vitamins A, B_1, B_2, B_3, and B_6; folate; vitamins C, D, and E; copper, iron, selenium, zinc, and carnitine), its main form and function, special needs, clinical studies, and clinical implications all specific to critically ill patients are presented.

Vitamin A (retinol)

Main form and function

Retinol, the body's storage form of vitamin A, is primarily bound to retinol-binding protein 4 (RBP4). RBP4 is essential for delivering vitamin A to the tissues.[6] Retinols are mainly stored in the hepatic stellate cells as retinyl esters and in organs with high demands, such as the retina, adipose tissue, and sexual glands. Consequently, physiological processes are sustained for long periods in case of decreased vitamin A intake.[7] The two active metabolites, retinal and retinoic acid, are formed from retinol and support embryonic development, night vision, innate and adaptive immunity, tissue repair, insulin sensitivity, and lipolysis regulation. As a result, vitamin A deficiency is associated with many clinical signs, including night blindness and respiratory, gastrointestinal, and renal dysfunctions.[8]

Plasma concentration in critically ill patients

Beyond the well-known vitamin A deficiency, which remains a problem in low-income countries as one of the four primary nutrition deficiencies worldwide,[9] a more insidious vitamin A deficiency may also occur in hospitalized patients. Some risk factors for vitamin A deficiency in critically ill patients are listed in Table 2.

In critically ill patients, a decrease in vitamin A plasma concentrations is reported to range between 24% and 65% in both medical and surgical patients[10–12] (see Table S1). Several hypothetical mechanisms may contribute to vitamin A deficiency in these groups, such as increased local capillary leakage of RBP, increased retinol urinary loss,[13] or decreased levels of RBP4 (the form of RBP measured in clinical laboratories).[14] In critically ill patients with coronavirus disease 2019 (COVID-19)–induced acute respiratory distress syndrome (ARDS), 14% presented with a clinically relevant reduced vitamin A plasma level (<0.2 mg/L).[12]

TABLE 2 Risk factors for developing micronutrient deficiencies in patients who are critically ill.

Micronutrtient deficiency	Risk factors
Vitamin A[2,3]	Sepsis; alcohol abuse; liver cirrhosis; bariatric surgery; anorexia nervosa; obesity
Thiamin (Vitamin B_1)[4–9]	Age >65 years; previous malnutrition; history of alcohol abuse; diabetes mellitus; prolonged hospitalization; renal replacement therapy; previous bariatric surgery; refeeding syndrome; diuretic therapy
Vitamins B_2 (riboflavin) and B_3 (niacin)[10–12]	Malnutrition; alcoholism; older adult; COPD; history of smoking; gastrointestinal disorders; chemotherapy drugs and tricyclic antidepressants
Vitamin B_6[13–15]	Malnutrition; HIV infection and treatment; alcoholic hepatitis; chemotherapy or radiotherapy; tuberculosis treatment with isoniazide; chronic kidney and liver diseases
Folate[16–19]	Hemodialysis; alcoholism; haemolysis; pregnancy; gastrointestinal malabsorption; sepsis; anticonvulsants, methotrexate, and sulfalazine
Vitamin C[18,20–23]	Malnutrition; older adult; alcoholism; after major surgery or cardiac arrest; hemodialysis; pregnancy; history of smoking; COVID-19; sepsis; multiple organ failure
Vitamin D[24–31]	Malnutrition or limited sun exposure; older adult; obesity; liver and kidney dysfunction; malabsorption syndromes; inflammation; glucocorticoids, anticonvulsants, antirejection medications
Vitamin E[32,33]	Malnutrition; chronic intestinal failure; parenteral nutrition; liver dysfunction; renal replacement therapy; sepsis; burns; anticonvulsants
Copper[34–37]	Malnutrition; gastrointestinal disorders: malabsorption syndrome; inadequate enteral or parenteral nutrition; post bariatric surgery; renal replacement therapy; major burns; extensive Lyell syndrome; inborn errors of copper metabolism; medications such as proton pump inhibitors, high-dose vitamin C; excessive zinc supplementation
Iron[38,39]	Acute or chronic blood loss; excessive blood sampling; gastrointestinal disorders: malabsorption; chronic illness; renal replacement therapy; medications such as proton pump inhibitors and H_2-receptor antagonists
Selenium[40–44]	Malnutrition; gastrointestinal disorders: malabsorption; inadequate enteral or parenteral nutrition; liver dysfunction; renal replacement therapy; medications such as antacids, proton pump inhibitors, and H_2-receptor antagonists; sepsis, COVID-19; major surgery; trauma, burn; chronic illness
Zinc[45–48]	Malnutrition; gastrointestinal disorders: malabsorption; inadequate enteral or parenteral nutrition; liver dysfunction; renal replacement therapy; medications such as proton pump inhibitors; sepsis, COVID-19, ARDS; chronic illness
Carnitine[49–52]	Genetic deficiency; gastrointestinal disorders: malabsorption; inadequate enteral or parenteral nutrition; malnutrition; renal replacement therapy; medications such as valproic acid; sepsis, COVID-19, ARDS; chronic illness (heart failure, kidney, and liver disease)

Abbreviations: ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019.

TABLE 3 Main biological functions of the copper-dependent enzymes by alphabetical order.

Enzymes	Biological function
Ceruloplasmin (multi copper ferroxidase)	Copper transport (carries >95% of plasma Cu), iron transfer from monocyte-macrophage to plasma
Copper-zinc superoxide dismutase	Catalyzes dismutation of superoxide (O_2^-) radical into either hydrogen peroxide (H_2O_2) or molecular oxygen (O_2)
Cytochrome c oxidase	Terminal enzyme of mitochondrial respiratory chain; reduction of oxygen to water
Dopamine beta-hydroxylase (also known as dopamine beta-monooxygenase)	Conversion of dopamine to norepinephrine
Hephaestin (ferroxidase)	Transporting dietary iron from enterocytes into circulatory system; oxidation of ferrous iron, released from enterocyte ferroportin, to ferric iron
Histaminase (also known as diamine oxidase)	Inhibits transepithelial permeation of exogenous histamine Inactivation of histamine
Lysyl oxidase	Crosslinking reaction and insolubilization of collagen and elastin
Tyrosinase	Melanin synthesis

TABLE 4 Manifestations of copper deficiency.

System	Details
Hematological	Anemia (normocytic, microcytic, or macrocytic), leukopenia, and, more rarely, thrombocytopenia; related to defective ferroxidase enzymes
Neurological	Myelopathy; prenatal: incomplete nervous system development; postnatal: myelopathy or myeloneuropathy and optic neuropathy; adults: myelopathy and sensorimotor polyneuropathy
Dermatologic	Depigmentation, defective keratinization related to altered tyrosinase activity; delayed wound healing and decubitus wounds secondary to an altered activity of lysyl oxidase
Cardiovascular	Bradycardia; increased atherosclerosis via an increased oxidation of LDL and other lipoproteins

Abbreviation: LDL, low-density lipoprotein.

Reduced baseline vitamin A levels significantly increased over time in patients with sepsis.[15] However, enteral complementation may not completely fulfill the recommended dietary intake of vitamin A in the first days of ICU admission when energy provision is gradually increased.[16] Consequently, parenteral administration may enable faster bioavailability and effective treatment of deficiency as shown in a study, whereby vitamin A levels were normalized within 3 days using an intravenous (IV) fat-soluble vitamin preparation.

Clinical studies testing high doses

Two studies investigated vitamin A administration in critically ill patients. In the first study, 63 patients with sepsis received vitamin A intramuscularly (100,000 IU/day, pharmacological dose) or placebo, but no significant benefit was reported on the duration of mechanical ventilation or mortality[18] (see Table S2). In a small ($n = 90$) randomized controlled trial (RCT) of patients undergoing coronary artery bypass, grafting vitamin A administration (5000 IU/day, supplementation) in patients with adequate zinc levels was associated with a decrease of malondialdehyde (a marker of oxidative stress) and a shorter ICU and hospital length of stay.[19]

Implementation in clinical practice

There is insufficient evidence to recommend additional vitamin A doses above the already established recommended daily dose (800–1100 mcg per day parenterally or 900–1500 mcg retinol equivalents per day when providing 1500 kcal).[2]

Thiamin (vitamin B_1)

Main form and function

Vitamin B_1, or thiamin, is an essential water-soluble vitamin pivotal in cellular metabolism. In the form of thiamin diphosphate ester or thiamin pyrophosphate, it is crucial for energy metabolism.[20] Insufficient intake, increased requirements, and enhanced elimination rapidly deplete existing thiamin deposits (approximately 30 mg), possibly predisposing critically ill patients to

thiamin-deficiency–related complications, such as cardiac and neurological dysfunction.[21]

Plasma concentration in critically ill patients

Depending on underlying risk factors (see Table 2), 10%–40% of critically ill patients are reported to have decreased thiamin plasma concentrations on ICU admission. In patients with sepsis, the reported prevalence of decreased thiamin plasma or whole blood concentrations varies considerably between 20% and 70%.[20,22–25] Considering that a thiamin assay is not routinely available and the impact of inflammation on plasma concentrations is unknown, the true prevalence of thiamin deficiency remains uncertain. Certain patients admitted to the ICU are predisposed to thiamin deficiency (Table 2).[26–31] Although patients may have thiamin deficiency at ICU admission, enteral nutrition using thiamin-containing commercial formula does increase plasma thiamin concentrations and can prevent the development of new deficiencies.[25]

Clinical studies testing high doses

Most clinical studies evaluating pharmacological doses of thiamin as standalone therapy have focused on septic shock (see Table S3). In these studies, thiamin administration (100–500 mg/day) improved lactate clearance.[32–34] Other reported beneficial effects included reduced serum creatinine, the need for RRT,[28] and a reduction in mortality observed in patients with proven thiamin deficiency.[32,34] Similarly, in a case-control study using a large and freely available dataset (MIMIC), early thiamin administration to critically ill patients with acute kidney injury (AKI) was associated with improved short-term survival.[35] In contrast, the analysis of a nationwide database including 18,780 patients with septic shock,[36] and another small RCT ($n = 72$),[37] did not support the hypothesis of a potentially beneficial effect of thiamin administration. Furthermore, no benefit from thiamin supplementation was reported in patients having cardiac surgery (300–1000 mg/day),[38] in critically ill patients after cardiac arrest (300 mg/day),[39] or in critically ill patients who developed hypophosphatemia while receiving enteral nutrition (400 mg/day).[31]

Recent RCTs administering high-dose (≥100 mg/day) thiamin as a component of hydrocortisone, vitamin C (ascorbic acid), and thiamin (HAT) therapy in patients with severe sepsis have reported contradictory results, with accumulating evidence that HAT therapy does not reduce mortality.[40–42]

Few studies have addressed refeeding syndrome. In a propensity score–matched analysis of 88 patients with COVID-19 considered at risk of refeeding, receiving 50–200 mg of B_1 for 7 days was associated with a reduction in mortality,[43] whereas in a multicenter RCT of 90 enterally fed patients who developed hypophosphatemia, 400 mg IV thiamin for 7 days did not affect blood lactate levels (primary end point) or clinical outcome.[31] However, the starting lactate levels were normal (1.7 mmol/L) in both patient groups, and therefore finding a significant effect was unlikely.

Implementation in clinical practice

The ESPEN MN guideline suggests that 100–300 mg/day of thiamin can be administered for at least 3–4 days from ICU admission. There is insufficient evidence to support prolonged pharmacological doses of thiamin in critically ill patients.

Vitamin B_2 (riboflavin) and B_3 (niacin)

Main form and function

Riboflavin and niacin are precursors of flavin mononucleotide (FMN), flavin adenine dinucleotide (FAD), and nicotinamide adenine dinucleotide (NAD), all central to body metabolism and energy production (Figure 1).[2] As components of the electron transport chain complexes I and II, they can theoretically mitigate the downregulated mitochondrial bioenergetic function during the acute and recovery phases of critical illness.[44,45] The riboflavin effect can be confounded by its role in the metabolism of other vitamins (B_3, B_6, B_{12}, and folate).[2] Riboflavin can treat methemoglobinemia, and niacin can be used for pellagra, hyperlipidemia, and secondary cardiac prevention in patients intolerant to statins, although evidence is limited.[46] Niacin administration can result in flushing, hypotension, and hepatotoxicity.[2] Despite being water-soluble, they have not been detected in the effluents from RRT.[47] Animal studies suggest niacin attenuates lung inflammation and improves sepsis outcomes.[48]

Plasma concentrations in critically ill patients

Severe hypotension and hypoglycemia despite normal adrenal function have been reported in association with undetectable niacin blood levels (see Table S5).[49] ICU-specific evidence is limited. One paper showed a close correlation between poor riboflavin status, estimated by the functional assay erythrocyte glutathione reductase activity coefficient, and ICU mortality.[50] Riboflavin status was suboptimal in 56% of the acutely ill older adults and even worse in those with chronic obstructive pulmonary disease and in smokers. The nutrition dose (1.3 mg) led to a transient increase in riboflavin status without clinical impact[51] (see Table S6).

Clinical studies testing high doses

Recent evidence points to a relation between impaired NAD+ biosynthesis and AKI after major vascular and cardiac surgeries.[52,53] In humans, NAD+ can be synthesized from tryptophan and nicotinamide (NAM), NAM riboside, NAM mononucleotide, and niacin (nicotinic acid) (Figure 1). Tryptophan or NAM supplementation can diminish renal injury in ischemia and nephrotoxin-induced AKI. Quinolinate phosphoribosyl-transferase (QPRT) is a rate-limiting enzyme in NAD+ synthesis from tryptophan highly expressed in the kidneys of mice

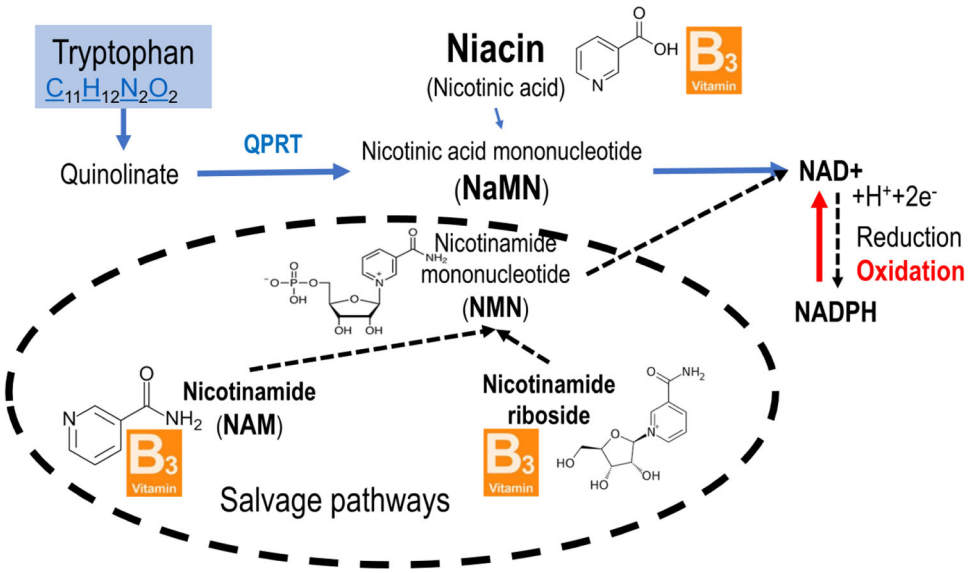

FIGURE 1 Pathways of NAD+ synthesis. There are three different pathways to ensure adequate levels of NAD+. The principal is under control QPRT, a rate-limiting enzyme in the NAD+ synthesis from tryptophan and is highly expressed in kidneys. It can become downregulated in a stressed kidney.[53] The two others are salvage pathways ensuring some redundance. NAD+, nicotinamide adenine dinucleotide; QPRT, quinolinate phosphoribosyltransferase. Adapted with permission from Koekkoek KWA, Berger MM. An update on essential micronutrients in critical illness. *Curr Opin Crit Care*. 2023;29(4):315-329.

and humans. Such pathways can become downregulated in the stressed, highly active kidney, requiring intense mitochondrial metabolism.[54] Following a pilot study testing NAM in cardiac surgery,[52] a small prospective cohort study including two groups of eight patients showed a high preoperative urinary quinolinate and quinolinate/tryptophan ratio (ie, an indirect indicator of reduced QPRT activity) to be associated with increasing creatinine.[53] Considering these promising cardiac and vascular surgery results, NAM (ie, B_3) is under investigation as a therapeutic option to restore NAD+.

Implementation in clinical practice

Riboflavin status is assessed by its urinary excretion and erythrocyte glutathione reductase. Niacin status is assessed by plasma levels and erythrocyte NAD, with the urinary excretion of metabolites. In shock states, blood sampling and determination might be considered. At this stage, there is no evidence to support administration outside of known deficiency.

Vitamin B_6

Main form and function

Vitamin B_6 refers to a group of six water-soluble vitamins (pyridoxine, pyridoxal, pyridoxamine, and their phosphorylated forms) crucial for amino acid biosynthesis and catabolism, erythrocyte formation, and cognitive development.[55] Pyridoxal 5'-phosphate (PLP) is the most active biologically.

Plasma concentrations in critically ill patients

During critical illness, vitamin B_6 deficiency can result from malnutrition, increased demands, and medications interfering with its metabolism.[56,57] Risk factors include HIV infection and treatment,[58,59] alcoholic hepatitis,[60] chemotherapy or radiotherapy, tuberculosis treatment with isoniazide, and chronic kidney and liver diseases.[61] Vitamin B_6 status (plasma and erythrocyte PLP) may boost the antioxidant activity in surgical ICU patients.[62] Two observational studies tested the association between vitamin B_6 status and clinical outcomes (see Table S7). No association was found between vitamin B_6 intake or status and ICU or hospital length of stay or ventilation duration. However, Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were significantly lower on ICU day 7 in patients with plasma PLP ≥ 20 nmol/L compared with <20 nmol/L measured on day 1.[57,63]

Clinical studies testing high doses

In ICU patients, vitamin B_6 can support protein metabolism and immune response and prevent or treat peripheral neuropathy and seizures.[64,65] In vitamin B_6–deficient patients, impaired cellular immunity has been reported, mainly because of a low T_4 lymphocyte count. Fourteen days of pyridoxine supplementation (50–100 mg/day) led to a significant increase in the total lymphocytic count as well as the T-helper and T-suppressor cells compared with the control group in an interventional ICU study ($n = 51$)[66,67] (see Table S8). It was also suggested to prevent and treat anemia, particularly sideroblastic anemia.[68] Recently, Wang et al showed no 28-day mortality benefit when supplementing IV vitamin B_6 (300 mg/day for 1 week) vs 0.9% saline to 128 patients with

sepsis and AKI. However, it reduced ICU stay, improved renal functions at day 7, diminished inflammatory markers (interleukin [IL] 6, IL-8, tumor necrosis factor alpha, and endothelin-1), and mitigated the oxidative stress (superoxide dismutase [SOD], glutathione, and malondialdehyde). Nevertheless, the small sample size and lower mortality than expected by the APACHE II score warrant further studies.[69] It is important to monitor vitamin B_6 levels, because prolonged high doses can lead to toxicity manifested predominantly as peripheral neuropathy.[70,71]

Implementation in clinical practice

The ESPEN guidelines suggest considering a repletion dose of 50–100 mg pyridoxine in patients with chronic poor intake in addition to the recommended daily dose of 1.5 mg per day in enteral nutrition and 4–6 mg per day in PN. High-dose pyridoxine may be needed in isoniazid overdose: 1 g of pyridoxine for each gram of isoniazid ingested with a maximum of 5 g. There is no evidence of beneficial effects of high-dose pyridoxine, and symptoms of toxicity may be observed with dosages >500 mg/day.

Folate

Main form and functions

Folate, a water-soluble vitamin also known as vitamin B_9, is the generic term for a family of compounds including folic acid and its derivatives (5-methyltetrahydrofolate, 5-formyltetrahydrofolate or folinic acid, 10-formyltetrahydrofolate and 5,10-methylenetetrahydrofolate).[72] Folate has essential cellular functions as a coenzyme in single-carbon transfers in the synthesis of DNA and RNA and amino acid metabolism.[73]

Plasma concentrations in critically ill patients

The World Health Organization (WHO) defines folate deficiency as a serum folate level <10 nmol/L (4.4 mcg/L) with plasma folate concentrations highly reflective of recent dietary intake. Red blood cell folate levels are regarded to be more reflective of long-term status of tissue reserves and are considered deficient at levels <340 nmol/L (<150 mcg/L). Therefore, their validity in patients with substantial inflammation is unknown. The most important factors predisposing to folate deficiency are hemodialysis, heavy alcohol consumption, hemolysis, pregnancy, gastrointestinal malabsorption, septic fever, and several drugs, such as anticonvulsants, methotrexate, and sulfalazine. Clinical deficiency can be serious, resulting in megaloblastic anemia, thrombocytopenia, leukopenia, sores and mouth ulcers, memory loss, depression, and diarrhea.

There is a paucity of data investigating folate deficiency in the general critically ill population, but studies suggest that between 2% and 65% of patients have serum folate levels below the reference range at admission[74–77] (see Table S9). Remarkably, in one study, plasma folate levels in critically ill patients were found to be higher than those of healthy controls on day 1 of ICU admission, although the SD was significant and >20% of patients presented with folate depletion on day 1, increasing to nearly 30% on day 3.[75] Throughout ICU admission, patients receiving RRT may be at risk of micronutrient depletion or deficiency, with plasma folate depletion being evident in 16%–30% of patients receiving RRT for different durations.[78,79]

Folate is vital for the conversion of homocysteine back to methionine. There is an inverse relationship between plasma folate and the prothrombotic homocysteine. However, no relationship has been found between plasma homocysteine levels and clinical outcomes from critical illness in patients with severe sepsis or acute lung injury (ALI)/ARDS.[80,81]

Clinical studiestesting high doses

Only two trials have investigated folate supplementation in critically ill patients[74,77] (see Table S10). In the first, 40 critically ill patients with documented folate deficiency were randomly given 0.5 mg IV folinic acid daily for 10 days or a 5 mg folinic acid IV injection once on day 1. Serum and red blood cell levels on day 11 were found to have increased significantly in both groups, but red blood cell folate was higher in the group receiving daily supplementation. Importantly, nearly 50% of patients still had serum levels below the reference range at the end of the intervention period. The authors recommend providing 0.5 mg of intravenous folinic acid daily in patients with documented folate deficiency.[74] The second study included 83 patients randomized at ICU admission to receive one of three prophylactic supplementation doses (5 mg/day IV folinic acid for 7 days, 50 mg folinic acid IV on day 1, or no folinic acid). Serum folate levels increased significantly in the two intervention groups, but to a greater extent in the group supplemented daily, and fewer patients had serum levels below the reference range at day 7 compared with the day 1 group, indicating that the best dosage may be 5 mg IV daily.[77]

Implementation in clinical practice

The WHO recommends a daily intake of 0.4–1 mg of folate; however, the precise folate requirements in critical illness are unknown. In patients at risk of malnutrition or having any predisposing factors (such as those receiving CRRT) to folate deficiency, folic acid status may be measured at first assessment and supplemented according to the results.

Vitamin C

Main form and function

Ascorbate is the main form of vitamin C in the human body. Vitamin C is crucial for recovery during critical illness because it optimizes the body's antioxidant and anti-inflammatory defense mechanisms, regulates norepinephrine and collagen synthesis, restores microcirculatory flow, prevents apoptosis, and reduces ischemia-reperfusion injury.[82]

Plasma concentrations in critically ill patients

Significantly depleted vitamin C plasma concentrations have been repeatedly reported in critically ill patients with heterogeneous conditions (68% vitamin C <23 μmol/L, 32% <11 μmol/L), but also in different subgroups: sepsis,[83] COVID-19,[76] after major surgery,[84] cardiac arrest,[85] and the lowest levels in patients with multiple organ failure.[86]

Clinical studies testing high doses

Despite the impressive evidence about vitamin C's key functions in the human body, limited evidence exists about the optimal application strategy to compensate for deficiencies and optimize the body's immune defense mechanisms. In critically ill patients, 2–3 g IV vitamin C is necessary to normalize vitamin C plasma concentrations.[87,88] Clinical studies investigated both repletion and pharmacological doses varying from 0.5 to 125 g per day and differed in treatment duration and route of administration.

In patients with sepsis and/or ARDS, positive effects were observed for standalone high-dose IV vitamin C in the CITRIS-ALI trial,[89] whereas no effect on mortality could be detected in RCTs using the HAT mixture (see Table S11). Neutralizing interactions as part of the HAT mixture could be a potential explanation.[90,91] However, the recent LOVIT landmark trial (n = 863) does not confirm this hypothesis. The composite primary end point of death or persistent organ dysfunction was significantly higher in patients who received vitamin C 50 mg/kg every 6 h for 4 days compared with placebo,[92] whereas interestingly no harmful effects could be demonstrated for vitamin C when comparing the effects of high-dose vitamin C on the single components of the outcome. A subsequent meta-analysis showed a benefit for short-term mortality in studies with a high risk of bias, whereas the point estimate was toward harm for the 90 day mortality outcome in trials with a low risk of bias. Furthermore, a more recent systematic review and meta-analysis demonstrated that despite the findings of the LOVIT study, IV vitamin C monotherapy may be associated with overall mortality benefits in critically ill patients with a high risk of dying.[93]

In patients with severe COVID-19, vitamin C might be particularly valuable because of its anti-inflammatory, antiviral, and immunomodulating properties.[94] However, in the very recently published harmonized RCTs of LOVIT-COVID and REMAP/CAP focusing on patients with COVID-19, the median number of organ support–free days was 7 (interquartile range, −1 to 17) days for the vitamin C group vs 10 (interquartile range, −1 to 17) days for the control group (adjusted proportional odds ratio [OR], 0.88 [95% CI, 0.73–1.06]) and the posterior probabilities were 8.6% (efficacy), 91.4% (harm), and 99.9% (futility).[95]

Probable explanations might again be the late initiation of the treatment and high use of corticosteroids, which before had been demonstrated to not be effective. In summary, despite some positive results coming from smaller high-dose vitamin C studies, such interventions cannot be recommended at this stage, because some signals of harm have been detected. Despite these negative results, research is still ongoing in more homogeneous patient populations characterized by inflammation, ischemia/reperfusion, or oxidative stress, such as patients after cardiac arrest,[96] cardiac surgery,[97,98] polytrauma and burn trauma,[99] ischemic stroke,[100] or undergoing major surgical procedures.[101]

Finally, it is worth mentioning that according to the European Food Safety Authority, insufficient data define a tolerable upper intake level for vitamin C.[102] Nevertheless, available data from clinical studies show that current levels of vitamin C intake cannot be considered a health risk for the general population.[103] Over the last few years, clinical studies administering high-dose vitamin C in ICU patients have not reported oxalate nephropathy.[104]

Implementation in clinical practice

The recent ESPEN guideline on MNs recommends administering 100–200 mg vitamin C per day in patients receiving artificial nutrition and potentially higher doses (200–500 mg per day) in patients with chronic oxidative stress or malabsorption. During critical illness with intense inflammation irrespective of origin, an IV repletion dose of 2–3 g/day, might be provided early after ICU admission.[2,87,88] A repletion dose might be delivered during CRRT,[2] which is associated with more significant micronutrient loss. In critically ill patients, pharmacological doses (>3 g per day) of vitamin C should not be administered.

Vitamin D

Main form and functions

Activated vitamin D (1,25 vitamin D) comes from two sources. Cholecalciferol (vitamin D_3) is synthesized in the skin under the action of ultraviolet B before being 25-hydroxylated in the liver, then 1 alpha-hydroxylated in the kidney and other tissue-like inflammatory cells. Another source is the vitamin D_2 or D_3 ingested via the oral route, which also is transformed in the liver and kidney.[105] Vitamin 1,25 D has a ubiquitous role in the immune cells; lung epithelial, muscle, and cardiac function; and calcium and bone metabolism.[106]

Plasma concentration in critically ill patients

Estimates indicate that 30%–50% of the general population have low vitamin D levels,[107] which is associated with higher mortality risk.[108] Critically ill patients commonly have low vitamin D levels, which are associated with elevated mortality and morbidity.[109–116] Vitamin D receptors and vitamin D metabolic enzymes are distributed widely, and vitamin D may be a modifiable target for improvement of critical care outcomes. Indeed, RCT data relating to the supplementation of high-dose vitamin D and outcomes of critical illness outcomes now exist.

Clinical studies testing high doses

The neutral VITdAL-ICU trial,[117] a single-center, randomized, double-blind, placebo-controlled trial of high-dose enteral vitamin D_3 in 475 critically ill medical and surgical patients with 25(OH)D ≤ 20 ng/ml showed in a secondary outcome a significant mortality decrease in patients with decreased vitamin D serum concentrations at randomization (25[OH]D ≤ 12; see Table S13). RECTIFY was a single-center, randomized, double-blind, placebo-controlled trial of early single high-dose enteral vitamin D_3 in 436 neuro ICU patients with 25(OH)D ≤20 ng/ml.[118] The RECTIFY trial was stopped at interim analysis for medical futility of the primary outcome length of hospital stay following enrollment of 274 patients. The VIOLET trial,[119] a 1360 patient multicenter, double-blind, placebo-controlled phase 3 trial of patients with high risk for ARDS and mortality randomized to single high-dose enteral vitamin D_3 supplementation showed no benefit. Most recent meta-analyses demonstrated inconclusive results.[120,121] The meta-analysis of Menger et al follows the best practice of meta-analyses as recommended by the Cochrane handbook. Although Menger et al found that vitamin D may be associated with reduced mortality, ICU length of stay, and duration of mechanical ventilation, the level of certainty is low and further studies are warranted to confirm these results.[121] Notably, it was further demonstrated that the parenteral administration of vitamin D was associated with a more significant effect on overall mortality than enteral administration, although these results are only hypothesis generating.[121]

Implementation in clinical practice

The evidence does not advocate the use of single high-dose vitamin D in all critically ill patients. Low plasma concentrations can be restored with daily doses. A loading dose might be helpful, and the route of administration may play an important role, especially under conditions with high need. Yet, the existing evidence for the use of high-dose vitamin D is not well established.

Vitamin E

Main form and function

Vitamin E and its main form, α-tocopherol (TOC), are best known for their antioxidant effect. Its universal presence in cell membranes protects against lipid peroxidation induced by oxidative stress. Absorption, transport, and plasma levels are lipid related, so the recommendation is to express it as a lipid ratio (eg, TOC/cholesterol).[2,4,122] Clinical deficiency manifestations are predominantly neurologic and most often observed in patients with chronic intestinal failure. Signs include muscle weakness and pain, coordination difficulties, numbness, vision problems, and reduced immunity.

Plasma concentrations in critically ill patients

Observational ICU studies frequently show reduced plasma levels exaggerated by high C-reactive protein (CRP) levels, but such findings become much less evident using the lipid ratios.[15,17,123–129] Vitamin E deficiency incidence ranged between 27% and 42% on admission to ICU, and another 6% developed it during ICU stay among a heterogeneous ICU population[11] (see Table S15). A cohort of patients with sepsis had a median serum value below the reference range (<20 µmol/L), indicating deficiency,[130] and in another cohort, patients with sepsis had a TOC level approximately one-third that of the healthy controls (3.2 ± 1.3 vs 9.9 ± 2.0 mcg/ml; $P < 0.001$).[131] Meanwhile, when corrected as a lipid ratio, patients with sepsis had significantly lower levels than the healthy controls despite still being within the reference range.[15] In trauma patients, vitamin E serum levels were in the low-normal range.[99] Of note, red blood cell concentrations were considered comparable in the healthy and critically ill.[132] CRRT does not significantly clear vitamin E, but the urinary and bile excretion becomes upregulated in case of increased total body stores, leading to unpredictable plasma levels.[133,134]

Clinical studies testing high doses

Few small trials studied TOC in critically ill patients as a sole intervention (see Table S16). In traumatic brain injury, 400 IU/day of vitamin E significantly lowered hospital mortality (16.9%) compared with placebo (29.7%) or low or high vitamin C (26.9% and 30.4%, respectively; $P = 0.04$). However, such findings are limited by the small sample size ($n = 100$ divided into four groups), more patients in a comatose state in the vitamin E compared with the placebo group, and reduced effect at 6 months (mortality 25% vs 29,7% in vitamin E and placebo groups, respectively).[135] Two small RCTs ($n = 20$ and 25) showed benefit in mechanically ventilated patients with ARDS regarding Sequential Organ Failure Assessment (SOFA) and APACHE II scores.[136] However, those results are limited by the small sample and higher baseline disease severity in the intervention group.

A recent Bayesian meta-analysis suggested with very low certainty that TOC ranks best among antioxidants for potential mortality reduction (absolute risk difference, 0.19; 95% CI, −0.54 to 0.16). It may also reduce infectious complications, although the certainty of evidence is very low.[137] A pharmacological dose of TOC has not been defined. Prolonged high daily doses (>1000 IU/day) may be associated with an increased risk of bleeding in patients receiving anticoagulant therapy.[138–140]

Implementation in clinical practice

The ESPEN guidelines suggest supplementation of vitamin E if plasma TOC levels are <12 µmol/L, starting with 100 mg/day. There is no evidence supporting high doses of vitamin E.

Copper

Main form and function

Copper (Cu) is an essential catalytic cofactor for various proteins exerting critical biological functions in growth and development. The main form in the body is Cu^{2+}. Because of the high redox potential of the Cu^{2+}/Cu^{+} system, it is used for oxidation reactions, such as the superoxide generation by SOD (Cu-Zn SOD) and catecholamines by tyrosinase. The main biological functions of the Cu-dependent enzymes are summarzed in Tables 3 and 4, and leading clinical deficiency manifestations are shown in Table 4.[141] Unlike all other trace elements, blood Cu increases in the presence of inflammation because Cu is mainly bound to ceruloplasmin, a positive acute-phase protein.[2]

Plasma concentrations in critically ill patients

Cu deficiencies might be more frequent than previously thought among critically ill patients and represent a cause for delayed recovery.[142] In an observational study including 100 patients transferred from the ICU to the ward, 21% had low levels of Cu despite appropriate complementation during the ICU stay.[143] Cu levels should be measured according to the ESPEN recommendations in patients at risk,[2] such as after bariatric surgery and in those with malabsorption, major burns, extensive Lyell syndrome,[144] and prolonged CRRT for >2 weeks because replacement solutions or dialysates typically do not contain Cu[145–147] (see Table S18) A shorter CRRT (median, 2 days) does not cause a significant depletion.[148]

In patients with COVID-19, elevated Cu levels have been observed, as expected in the presence of inflammation[149]: unfortunately, CRP and ceruloplasmin levels were not explored.[149] Another study highlighted that patients with COVID-19 with increased serum Cu concentrations during the ICU stay had significantly lower mortality.[150]

Cu accumulation in the liver has mainly been observed in chronic diseases such as intrahepatic cholestasis of childhood and in Wilson disease; it then manifests as liver cirrhosis and neurological signs. No deleterious effects have been observed with the Cu doses included in PN multitrace element products.[151]

Clinical studies testing high doses

Clinical studies in ICU patients with Cu monotherapy have not been performed. Because of its role in immune function, some have postulated that Cu supplements might be beneficial during COVID-19 infection, but delivering Cu without proven deficiency should not be undertaken.[152]

Implementation in clinical practice

Monitoring of Cu levels should be routine in patients at risk, and in PN (every 6–12 month) Cu repletion should be based on blood levels (Figure 2). Depletion may develop rapidly (within 2 weeks) as in the case of CRRT or major burns or slowly (months) after bariatric surgery or malabsorption, with deficiency demonstrated by blood levels <12 µmol/L. Ceruloplasmin should be determined to confirm the diagnosis, and low values confirm deficiency and orient the route and dose of treatment. With Cu values <8 µmol/L (and low ceruloplasmin), the repletion should be IV (6–8 mg/day for 7–10 days). With moderate deficiency, the oral route can be used with the same doses (as absorption is only approximately 30%–40% of ingested).

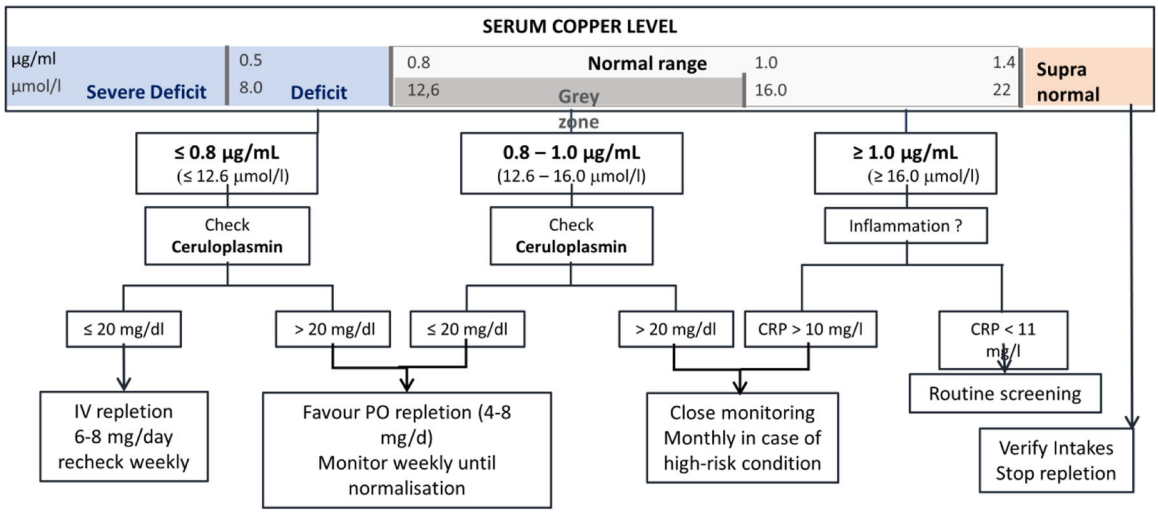

FIGURE 2 Treatment algorithm for copper deficiency or excess: Factors to consider are a depletion mechanism, the acute-phase response reflected by CRP, and ceruloplasmin. Low ceruloplasmin (<20 mg/L) orients the therapy: IV or oral repletion dose will be determined by the severity and presence or absence of clinical symptoms. Routine screening refers to home enteral nutrition or parenteral nutrition and bariatric surgery every 6–12 months. CRP, C-reactive protein; IV, intravenous. Reproduced with permission from Altarelli M, Ben-Hamouda N, Schneider A, Berger MM. Copper deficiency: causes, manifestations, and treatment. *Nutr Clin Pract*. 2019;34(4):504-513.

Iron

Main form and function

Iron is the most abundant micronutrient in humans (3–5 g in adults). Its role is linked to hemoproteins, redox equilibrium, inflammatory processes, and innate immune reactions against infections and cancer.

Plasma concentrations in critically ill patients

Critical illness alters iron metabolism, and its specific requirements during ICU stay are not well defined.

Ferroptosis

Acute disease can disrupt the redox systems, causing intracellular iron overload and lipid peroxide accumulation in ferroptosis, an iron-dependent, nonapoptotic cell death.[153,154] Ferroptosis has been linked to sepsis,[155] viral infections,[156] and ALI[157,158] and may contribute to multiorgan dysfunction in practically every ICU patient.

Anemia

Anemia may affect up to 90% of ICU patients, requiring blood transfusion in 15%–35%.[159] The two leading causes of iron-related anemia are

- Iron deficiency anemia: absolute iron deficiency owing to poor intake/adsorption or increased loss owing to phlebotomies[160] and hemorrhages, affecting 20%–40% of ICU patients.
- Anemia of inflammation[161]: Inflammation causes iron storage in the macrophages to reduce redox stress and hide iron from infectious pathogens, leading to iron-deficient erythropoiesis independently from erythropoietin levels.[162]

The most used biomarkers to determine iron status are iron plasma levels, ferritin, and transferrin, which enable the calculation of transferrin saturation. These are highly affected by inflammation and poorly differentiate between anemia because of inflammation or iron deficiency in acute phases of disease.[163,164] The newer biomarkers hepcidin and soluble transferrin receptor (sTfR) are expensive but increasingly available; they are less affected by inflammation, making these biomarkers promising in critically ill patients. Iron deficiency anemia is diagnosed by microcytic hypochromic anemia, increased sTfR, and reduced ferritin and hepcidin levels. Anemia of inflammation is diagnosed by normocytic normochromic anemia, normal sTfR, and increased ferritin and hepcidin levels. Anemia of inflammation in patients with non–iron deficiency anemia develops within 8 days of ICU admission.[165]

Low plasma iron levels and iron deficiency are associated with worsening of chronic cardiac dysfunction.[166] Decreased hepcidin levels are associated with ICU mortality.[167–169] At ICU discharge, hemoglobin (Hb) < 100 g/L affects up to 53.3% of patients and persists in 46% at hospital discharge and up to 12 months later.[170] Post-ICU anemia correlates with increased ICU readmission rates, prolonged hospital length of stay, increased mortality, and lower quality of life[168,170] (see Table S20).

Clinical studies testing high doses

Anemia management in ICU patients has been extensively reviewed.[171] Intravenous iron is the only efficient strategy in the ICU, because enteral iron absorption is low and further reduced by ongoing inflammation.[172] Intravenous iron increases Hb levels gradually, with clinical results not earlier than 10–30 days from iron administration, thus reducing red blood cell transfusions in ICU.[171]

One gram of IV ferric carboxymaltose administered close to ICU discharge under hepcidin guidance was associated with improved 90-day and 1-year survival rates[173] in 405 ICU patients with anemia (see Table S21). An RCT including 140 patients with anemia (Hb <100 g/L) tested early IV iron administration: iron therapy was associated with reduction of red blood cell units (97 vs 136) and only increased Hb levels at ICU discharge[164] and reduced 90-day ICU readmission rates[174] but did not improve survival. These RCT results suggest that iron therapy's effectiveness improves as inflammation fades and biomarkers guide a tailored prescription. Iron is tightly regulated by evolutionarily conserved mechanisms during infections.[175,176] In contrast to the non-ICU settings,[172] IV iron did not increase ICU infection rates.

Congruent results have been seen after major surgery. Better efficacy of perioperative iron therapy was shown in two RCTs. In the first RCT of patients undergoing elective coronary artery bypass grafts (a noninflammatory model of disease), iron therapy improved Hb levels and blood transfusion rates.[177,178] In the second RCT investigating patients undergoing elective oncologic abdominal surgery, only 2- and 6-month hospital readmission rates were reduced, with no impact on survival and red blood cell transfusions.[179] Finally, in a multicenter RCT including 1137 patients with cardiac failure (left ventricular ejection fraction <45%) and iron deficiency, iron derisomaltose supplementation (bodyweight-adapted dose) was associated with a lower risk of hospital admissions for heart failure and cardiovascular death.[180]

Implementation in clinical practice

Hepcidin levels are crucial for the differentiation of iron deficiency anemia and anemia of inflammation and should become more readily available. In critically ill patients with Hb <100 g/L who have passed the hyperacute inflammatory phase of their disease (imminent ICU discharge), 1 g IV ferric carboxymaltose (or similar product) administration might be considered, preferably under the guidance of hepcidin measurements.

Selenium

Main form and function

The selenium (Se) member of the oxygen family, called the Janus atom (antioxidant and oxidant properties) is always included in molecules, being required for the synthesis of the amino acid selenocysteine, an essential component of at least 25 selenoproteins in human tissues. Total body Se is 10–15 mg.[181] In cellular studies, selenite (Na_2SeO_3) <1 µmol/L expressed as Se concentration (see Figure 3) acts as an Se donor. The amino acid selenocysteine is required for vital antioxidant selenoenzymes. US tolerable uptake intake limit and low adverse effect levels of Se are 400 and 900 µg/day, respectively, and no side effect has been reported in a few studies (see Table S22) at doses of 1 or 2 mg of Na_2SeO_3 in 30 min infusions one or two times at day 1 in ICU patients. Plasma contains 2% of Se (0.3 mg): 60% into selenoprotein-P (SELENOP), a key antioxidant enzyme binding to endothelium under acidosis and protecting it especially against peroxynitrite[181–184] (see Figure 3); 30% into glutathione peroxidase (GPX3); and 10% into albumin (nonactive selenomethionine).

Plasma concentrations in critically ill patients

At ICU admission, average plasma Se and SELENOP and later GPX3 concentrations are generally low and correlate with severity in sepsis (bacterial and viral, such as COVID-19) and systemic inflammatory response syndrome (major surgeries, trauma, and burns).[185–189] These low concentrations have led to the hypothesis that high-dose Se, through intravenous Na_2SeO_3, could restore key antioxidant selenoenzymes. In animal models, a considerable decrease of plasma Se and SELENOP occurs a few hours after the onset of sepsis, whereas GPX3 does not decrease. Simultaneously a major downregulation of liver SELENOP synthesis is observed with Se redistribution[190–194] (see Figure 3).

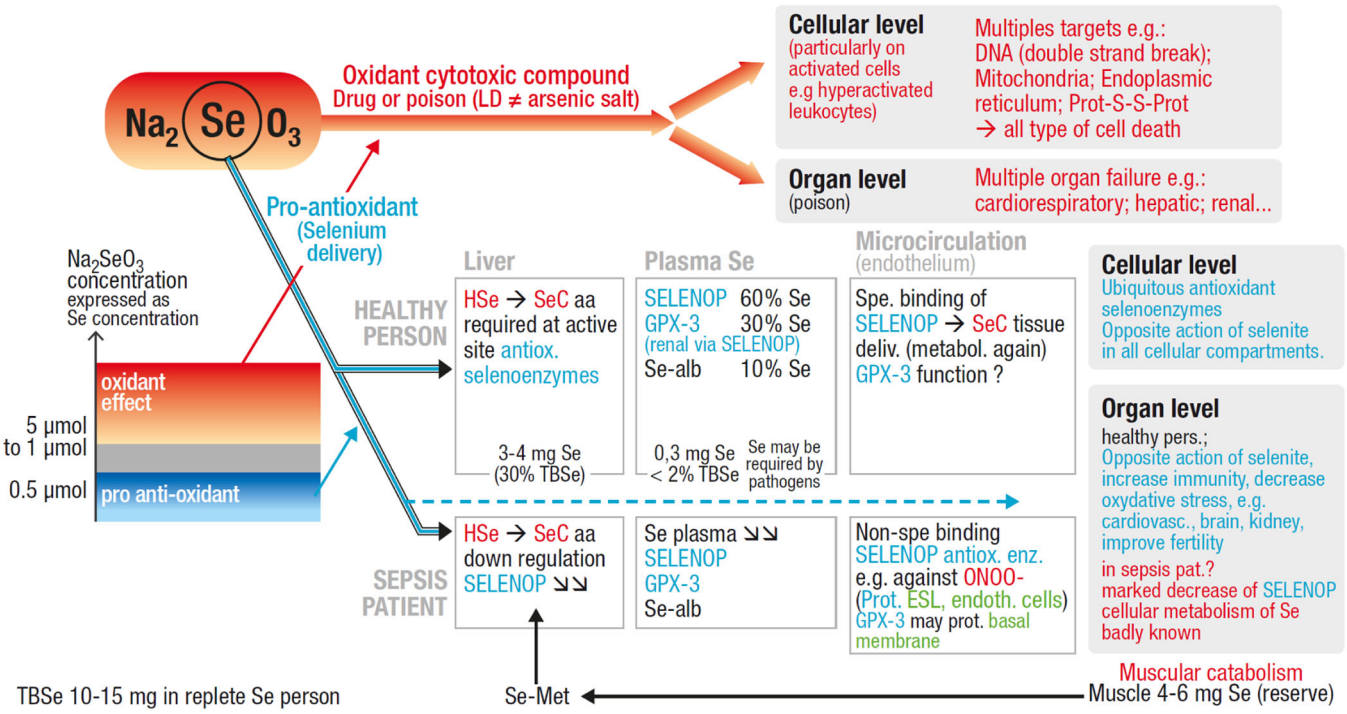

FIGURE 3 Dual selenite action (quantum selenium biochemistry). Red indicates an oxidant molecule or activated structure or cell; blue indicates an antioxidant; and green indicates protected structures. At concentrations above the toxicity threshold (see lower left quadrant), selenite (Na_2SeO_3) induces redox cycles producing oxidative damages in almost all vital structures including DNA. The more the cells are activated, the greater the penetration of selenite and the corresponding damage. At concentrations below the toxicity threshold, selenium (Se) from Na_2SeO_3 can be incorporated into selenocysteine (SeC) in the last step of Se metabolism. Its metabolism (metabol.) is complex, most probably because of the oxidative toxicity of SeC. It is genetically controlled and energy consuming. Sec is required at the active site of vital antioxidant (antiox.) selenoenzymes. In plasma, SELENOP has a dual function: (1) in oxidative stress: antioxidant enzyme, notably against peroxynitrite (ONOO-), protecting ESL and endothelial cells; (2) in healthy conditions: transport of SeC from the liver to the tissues where it is delivered (deliv.) and metabolized again. In the acute phase of sepsis, liver SELENOP synthesis and secretion has been observed as strongly downregulated and nonspecific binding increase leading to markedly concentration decrease. GPX-3 may protect the basal membrane. It is synthetized by the kidney, normally thanks to SELENOP. During sepsis, because of protein catabolism, there is a release of selenomethionine (reserve pool of Se without biological action). Liver content is about 30% of TBSe, and muscle is about 40% in a reserve form (Se-Met). GPX-3, plasma glutathione peroxidase; ESL, endothelium surface layer; SELENOP, selenoprotein-P; Se-Met, selenomethionine; TBSe, total body Se content. Adapted with permission from Forceville X, Van Antwerpen P, Annane D, Vincent JL. Selenocompounds and sepsis-redox bypass hypothesis: part B-selenocompounds in the management of early sepsis. *Antioxid Redox Signal*. 2022;37(13-15):998-1029.

Clinical studies testing high doses

Meta-analyses, multiple phase 2 trials (except one), and two phase 3 trials using Na_2SeO_3 (see Table S22) assumed that Na_2SeO_3 only acts as an Se supplier, even in bolus at high doses. Some technical problems have led to misinterpretation: because of incorrect wording in micorgrams of Na_2SeO_3, instead of micrograms of Se as Na_2SeO_3, the indicated dose is half of that administrated, which has not been adequately considered in recent meta-analysis.[195,196] Na_2SeO_3 (selenite) is also one of the most oxidant selenocompounds, which might be cytotoxic against hyperactivated leucocytes (Figure 3). Its acute toxicity may increase in sepsis.[181,191,197–200] Two phase 2 multicenter RCTs were conducted in similar patients with septic shock (70% mortality). In the first, 1 mg Na_2SeO_3 was delivered in 30 min bolus followed by 1 mg/day continuously until day 14, resulting in a tendency to mortality decrease.[201] In the second, to assess the chemotherapeutic oxidant drug effects of Na_2SeO_3, Na_2SeO_3 corresponding to 4 mg Se was administrated continuously at day 1—targeting cytotoxic blood concentration (which generated ethical debate before approval)—followed by 1 mg/day until day 10, inducing neutral results even at day 1.[197,200] Peritonitis in a ventilated sheep study later confirmed that cytotoxic blood concentrations could only be achieved with bolus.[191] Two high-quality phase 3 RCTs with an initial 30–20 min bolus of Na_2SeO_3 obtained a neutral effect (Table S22). The first, in ICU patients with sepsis, used the same scheme as the first phase 2 multicenter RCT.[202] The second was in patients undergoing cardiac surgery with cardiopulmonary bypass who were randomly assigned to receive a bolus of 2 mg Na_2SeO_3 within 30 min before surgery and a bolus of 2 mg Na_2SeO_3 after surgery, followed by a daily administration of 1 mg/day during the patients' ICU length of stay. The Se administration led to an increase of Se, which did not translate into an increase of GPX3 activities, which demonstrated a failure of translation that needs further investigation.[203]

Implementation in clinical practice

The dietary-recommended intake of 55 (20–90) mcg/day Se is required during ICU stay. However, additional Se supplementation in ICU patients is not supported by the evidence, except for the correction of identified Se deficiency and increased losses (ie, acute diarrhea, high flow fistula, or CRRT).[147,204,205]

Zinc

Main form and function

Zinc is the second most abundant trace metal in the human body and is critical for cell proliferation, immune function, oxidative stress, apoptosis, and wound healing. It is a catalytic cofactor of >300 enzymes,[101] can inhibit viral replication,[206] and modulate inflammation[207] and oxidative stress.[208] Normal plasma zinc concentrations in health are described elsewhere.[101] Although analyzing and interpreting plasma zinc concentrations requires consideration of several other factors, such as inflammation,[2,4] 12% of clinicians surveyed reported that they measure zinc concentrations once per week, with 3% routinely prescribing zinc complements and supplements.[5]

Plasma concentrations during critical illness

The bioavailability of zinc is affected by various mechanisms beyond this review's scope. In general, there is reduced enteral absorption and greater buffering of intracellular and extracellular zinc that leads to a marked reduction in free (ie, active) zinc (see Figure 4).[209–212] During critical illness, plasma zinc concentrations decrease rapidly and are substantially lower than in health.[150,213] Reductions are more severe in patients with sepsis and one or more organ failures,[210,214,215] proportional to the inflammatory response.

In observational studies, reductions in plasma zinc concentrations have been associated with the development of ARDS[216] and increased mortality.[215,217–220] In studies of patients with COVID-19, associations between zinc concentrations and outcomes have been inconsistent, with one study reporting an association between lower zinc concentrations and the need for ICU admission.[221] In contrast, another study reported no association between zinc concentrations and outcomes, including hospitalization and ICU admission.[222]

Clinical studies testing high doses

Most trials that have evaluated the use of zinc supplements have studied zinc as one of several MNs administered.[137] There are only two zinc supplementation trials during ICU admission,[223] which limits the capacity to describe the effect of zinc supplementation (see Table S23). In a single-center parallel group blinded randomized trial of 100 patients with severe head trauma, patients received enteral zinc sulphate (120 mg) or placebo daily for 15 days.[224] This zinc pharmacological dose supplementation markedly increased plasma concentrations and urinary excretion of zinc. Another single-center parallel group blinded randomized trial was conducted among 68 patients with severe head trauma who received exclusive PN.[225] The intervention was zinc supplementation (12 mg of zinc IV for 15 days followed by 22 mg of enteral zinc from day 15 to 3 months) and the comparator was 2.5 mg of zinc IV for 15 days followed by placebo from day 15 to 3 months. Although plasma zinc concentrations initially reduced over time in both groups, these improved after day 10 with no statistical difference in zinc concentrations between groups. Those receiving the intervention did excrete more zinc in their

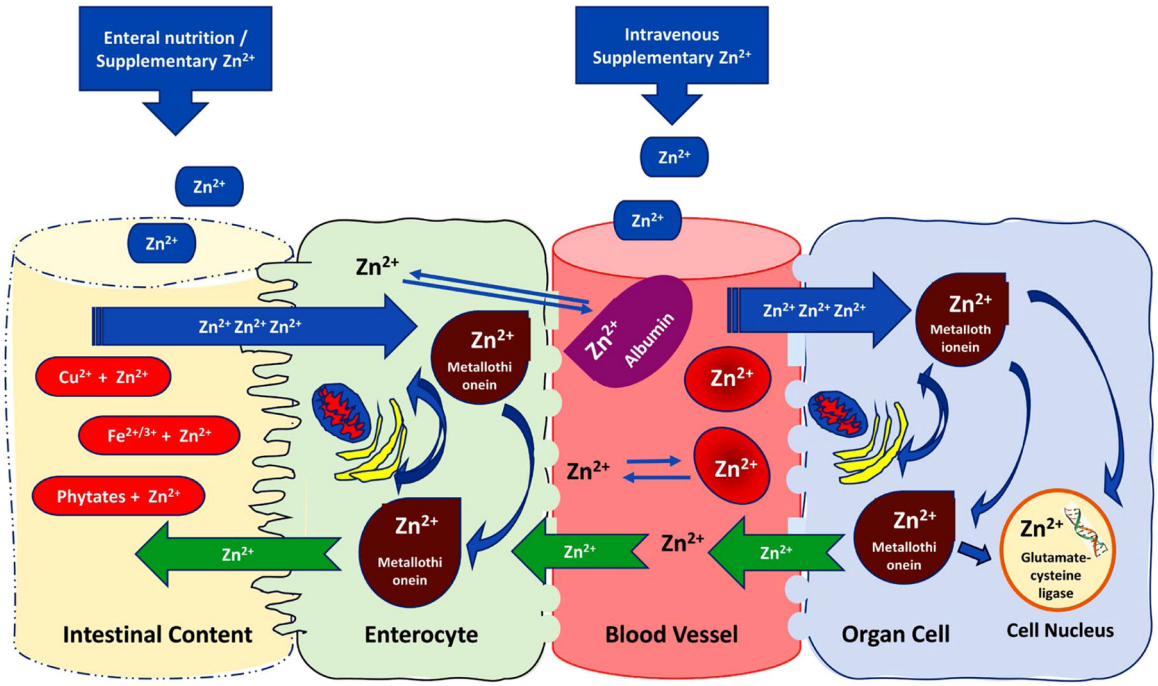

FIGURE 4 Regulatory mechanisms that affect zinc bioavailability.

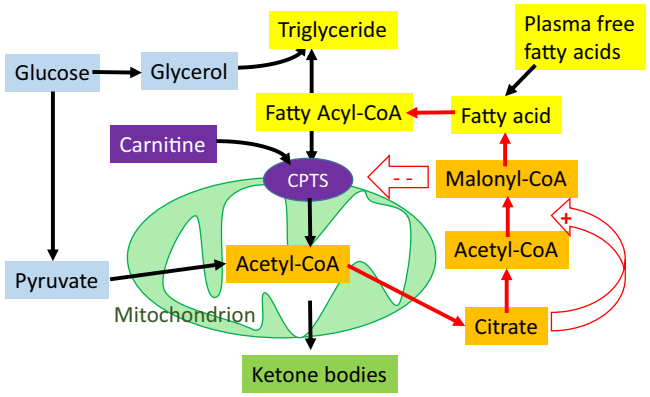

FIGURE 5 The carnitine system. CPTS, carnitine palmitoyl transferase system. This figure is created by the authors of this article but is, with permission, partially based on Foster.[229]

urine. A recent meta-analysis reported no difference in mortality with zinc supplements when combining these trials with limited confidence in the results ($n = 168$, relative risk=0.73 [95% CI, 0.41–1.28]).[223] Providing 120 mg of zinc in combination with 1200 IU of vitamin E 1 day before surgery, followed by a daily regimen of 30 mg of zinc and 200 IU of vitamin E during the postoperative phase for 3 weeks, led to a reduction in both duration of hospital stay and inflammatory response. However, it did not affect mortality rates in patients undergoing coronary artery bypass graft surgery, as reported on the ClinicalTrials.gov website (NCT05402826).[226] An RCT in patients positive for COVID-19 (190 ambulatory and 280 hospitalized) tested 25 mg of elemental zinc oral ($n = 231$) vs placebo. Zinc was associated with a reduction of ICU admissions (5.2% vs 11.3%), shorter hospital stay (difference 3.5 days), and lessened mortality (6,5% vs 9.2%).[227]

Implementation in clinical practice

The existing evidence does not support the use of single zinc supplements for patients who are admitted to the ICU without risk factors for zinc deficiency and who are tolerating enteral nutrition.

Carnitine

Main form and function

Carnitine is a small quaternary ammonium compound found in tissues with high energy needs, such as striated muscle, liver, and myocardium.[228] The carnitine palmitoyl transferase system (CPTS) shuttles long-chain fatty acids across mitochondrial membranes, allowing their oxidation (see Figure 5). There is no recommended intake for the general population because endogenous synthesis from L-lysine and L-methionine by the kidney and liver, with vitamin C and iron as cofactors, is sufficient for health.[230] Genetic carnitine deficiency provokes infantile muscle weakness, cardiac failure, and hypoglycemia.[228] Critical illness provokes cellular stress and increases the risk of carnitine deficiency.[231–233]

Plasma concentrations in the critically ill

In symptomatic cases attributed to absolute carnitine deficiency in prolonged critical illness, free carnitine levels ranged from 3.2 to 21.72 μmol/L, the limit being defined at 20 μmol/L[3,231–233] (see Table S25). Concentrations <36 μmol/L in 15 of 64 emergent ICU admissions were not associated with compromised outcomes and should not be considered "deficiencies."[234] Serum levels are supposed to reflect preponderantly cardiac muscle carnitine status.[235]

Relative carnitine deficiency, an increased ratio (>0.4) of acylcarnitine over free carnitine, may occur when intramitochondrial energy provision exceeds oxidative capacity. Citrate inhibits the CPTS (see Figure 5, red arrows) via Malonyl-Co-enzyme-A, redirecting free fatty acids toward lipogenesis. An increased acylcarnitine over free carnitine ratio, potentially indicating relative deficiency, persists longer in patients requiring RRT.[234] In a post-ICU follow-up cohort, a ratio >0.4 occurred in 30% of patients, with increased short-chain acyl-carnitine levels potentially reflecting protein catabolism in long-stay patients.[236] The life-threatening "propofol infusion syndrome," characterized by elevated urinary acylcarnitine, encephalopathy, renal failure, rhabdomyolysis, metabolic acidosis, and hepatosteatitis, might be an extreme manifestation of relative carnitine deficiency.[237,238]

Clinical studies testing high doses

In early critical illness

Pilot RCTs of L-carnitine supplementation of 1.5–18 g per day by the enteral or parenteral route in ICU patients are summarized in Table S26. Carnitine appeared to be well tolerated in all RCTs. For potential side effects, we refer to the ESPEN MN guidelines.[2]

In prolonged critical illness

L-carnitine treatment may improve outcomes in chronic disease states, such as heart failure and kidney and liver disease.[239–241] Doses >2 g/day for 12 weeks may be more likely to generate effect. In prolonged critical illness, poor intake (absence from standard PN solutions), synthesis (liver or kidney failure, low protein/vitamin C intake, or drugs, such as valproate), and losses with CRRT increase the risk of low carnitine plasma concentrations.[242] Hallmarks indicating potential deficiency, such as hypertriglyceridemia, muscle weakness, and liver dysfunction, may be easily overlooked in the ICU. Carnitine supplementation (ranging from 0.5 to 1 g/day to 100 mg/kg/day) has been reported to lead to rapid symptom relief in cases of suspected deficiency.[3,231,233,242]

The wide range of reported carnitine deficiency incidence in prolonged critical illness (5%–70%) might be related to quantification technologies.[243,244] In the pediatric ICU, this incidence doubles during extracorporeal membrane oxygenation treatment (41 vs 21%).[245] Free carnitine levels are largely normal 1 week after ICU discharge.[236,246] There are no RCTs evaluating carnitine in prolonged critical illness.

Implementation in clinical practice

Despite a lack of solid evidence, plasma carnitine levels can be determined on suspicion of deficiency and, if <20 μmol/L, corrected, starting at 0.5–1 g carnitine/day.[242]

FUTURE RESEARCH

Failure for successful translation

Despite promising preclinical data, and those received from smaller single-center RCTs, early high-dose administration of single or combined vitamin and trace elements in critical illness have not shown hard clinical benefits, as reflected by the most recent updated ESPEN guidelines[247] and shown in the previous sections. The one-size-fits-all approach of studies thus far, with administration of the same dose during the same period of time to all patients, did not yield beneficial results. RCTs in mixed heterogeneous ICU populations or more targeted groups, such as patients with sepsis or following cardiac surgery, generated substantial evidence based on several patients against this mode of pharmaconutrition interventions or repletion strategies of presumed early deficiencies, unlikely to be refuted soon.[41,92,119,203,248] Possibly, the lack of benefit may be explained by the huge variation between critically ill patients in MN status owing to large differences per patient in factors contributing to MN deficiency, such as metabolic consumption and losses of MNs owing to, for example, CRRT, drains, and medication. This new knowledge allows us to move on toward novel directions in MN research for the critically ill, focusing on the following.

Patient population of interest

Although significant research activities and clinical trials show rather broad inclusion criteria, a more differentiated view may yield larger clinical benefit at the cost of reduced generalizability. Based on these assumptions, other, more homogeneous, critically ill populations should be studied in the future, combining the investigation of MN status with a unique pathological process, such as patients after cardiac arrest or trauma. Given the complex relationship between MN status and disease evolutions, translational interventional trials might prove most effective in generating new insights because they allow the detection of causal relations between targeted interventions and patient-centered clinical outcomes and the mediating cellular-biological processes.

Time dependency of the intervention

Another important issue might be the time course of critical illness. For example, it has been shown that surgical ICU patients often need a high degree of organ support, especially during the first period after

surgery, which then decreases much faster when compared with medical ICU patients.[249] Assuming a time-dependent production and release of reactive oxygen species (ROS) after an insult, the benefit of any MN administration strategy may depend on the relative ROS level in the early acute inflammatory phase.[101] After the initial cytokine storm, a period of relative immunosuppression[250,251] is often observed. Therefore, the timing of the tested immune-modulatory strategy is of relevance. Concerning timing, it is relevant that MN deficiencies may contribute substantially to the phenotype of prolonged critical illness. To optimize the treatment of patients with a prolonged ICU stay, developing and validating strategies to prevent, detect, and treat potentially rare but debilitating deficiencies in multicentric clinical collaboration is crucial.[232] Animal models of prolonged critical illness might be of great value in this regard.

Personalized approach

It is possible that not all patients show the same response to an anti-inflammatory intervention, so the future concept of a personalized therapy adapted to interindividual biological phenotypes aiming to identify patients with the highest likelihood to respond to an intervention may yield clinical benefit if feasible and after robust validation. As part of this, improvements in the analysis of MNs (measurements in circulating cells and functional metabolic tests) and the development of innovative diagnostic approaches, which are easy to use at the bedside (such as new biomarkers measured by point-of-care devices), are urgently required to study more personalized approaches. All must be validated against relevant clinical end points before integration in prospective interventional studies.

To optimize the personalized approach, all relevant factors for dosing and timing could be integrated into pharmacokinetic modeling for MNs. Pharmacokinetic modeling software has been developed to predict and graphically display patient-specific antibiotic plasma concentrations in real time[252]; it provides direct and continuous individualized dosing advice. Feedback from antibiotic plasma levels is optional. A similar MN pharmacokinetic modeling program could be developed to optimize MN administration in the future. Factors affecting MN status between patients and over time in a single patient (such as shifts in fluid balance, organ-replacement therapies, premorbid nutrition status, increased metabolism, decreased intake, and disease-specific risks) could be integrated into the models. After the most optimal model is validated, pharmacokinetic modeling could be integrated into prospective interventional studies to confirm the efficacy and safety of such program. Finally, the (in)ability of an extremely ill patient to use high amounts of administered MNs probably should be taken into account when designing a personalized approach to MN management. An increasing number of studies demonstrated, for example, that patients with a high degree of injury (eg, a high SOFA score) or AKI were harmed by additional administration of not only MNs but also protein, so a more careful approach might be useful in these patients.[248,253–255]

MNs of special interest

Based on the different characteristics of each MN, it seems challenging to identify unique research priorities or MNs of particular interest. However, several MNs, such as vitamins B_2 and B_3 and carnitine have been rarely studied despite some promising effects (B_2 and B_3 on mitochondrial function and AKI and carnitine on energy metabolism and tissue catabolism in prolonged critical illness), which may deserve more attention in future, especially in patients with multiorgan failure.

Vitamin C

Currently, a controversial discussion exists about the potential value or harmful effects of vitamin C as a recent large-scale RCT in patients with sepsis and COVID-19 challenged current beliefs about its potential clinical significance.[92] Some methodological limitations and challenges were identified in these studies, which may have been underrecognized, as well in other studies of MNs and will need more attention in future studies. For example, the type of patient population with their respective comorbidities and comedications, the timing of the intervention in relation to the critical illness, the additional use of corticosteroids, the extent of inflammation and oxidative stress, and the combination with other medications.[93,256] Giving the above cited evidence, we suggest to first unravel the cellular-biochemical mechanisms and epidemiological patterns behind an eventual lethal effect of vitamin C in certain patient populations through animal experiments and post hoc analyses of existing trials. Thereafter, candidate biomarkers or scores identifying patients likely to benefit from vitamin C–based interventions can be validated in cautiously designed translational clinical trials. Such strategies might be based on specific biomarkers or patient profiles.

Vitamin D

Novel approaches for patient selection using subphenotypes, metabolic phenotypes, and metabolomic endotypes have been used when studying vitamin D. This strategy has shown promise in identifying disease mechanisms in patient subgroups who may benefit from specific interventions.[257–261] Focusing on the most deficient patient, using a maintenance dose or a different vitamin D route could also be explored.

Vitamin E

Future vitamin E research could focus on the precision of vitamin E measurement methodology (plasma, lipid ratio, or red blood cells) and defining the reference level before testing new research methodologies enriched by its status and quantification (with standardization!) of oxidative stress in adequately powered RCTs. Because of possible

additive effects, this may end with different dosages and combinations with other antioxidants.

Iron

The fine regulation of iron-related molecules and their implications in the pathologies of several acute diseases is not entirely understood, so our ability to modulate iron metabolism to improve clinical outcomes is poor. Deepening our understanding of iron metabolism will lead to the identification of novel biomarkers and, together with the implementation in clinical practice of the already existing hepcidin and sTfR, they might lead to a more accurate identification of the right patients and timing having benefit from iron supplementation.

Selenium

Future RCTs could evaluate the effect of Se supplementation by Na_2SeO_3 in specific subgroups. More research might identify phenotypes of patients who might be responsive to a Se supplementation and identify potential confounding factors, which may inhibit the increase of GPX3 activity in patients. The high-dose trials having been disappointing, dose finding with lower doses is required.

In contrast, using Na_2SeO_3 as a cytotoxic drug against hyperactivated leukocytes may be a potential treatment in early sepsis, combined with previous endothelial-protective effects by recombinant SELENOP infusion to increase the margin of safety.[181] Preclinical development for effectiveness and safety should be done before RCTs according to general drug development rule.

Carnitine

The potential contribution of hypocarnitinemia to the burden of prolonged critical illness needs to be estimated in observational studies to inform future targeted interventions guided by risk factors and/or serum levels and may then contribute to the recommendation by the American Society for Parenteral and Enteral Nutrition to include carnitine in multivitamin preparations, made almost 10 years ago.[262,263] Early administration of high-dose carnitine in acute critical illness, selective detection, and correction of carnitine deficiency in suspected long-stay ICU patients and the potential diagnostic role of carnitine as a metabolic read-out of energy metabolism and tissue catabolism[235] all merit future translational research.

Combination of MNs

Investigating combinations of different MNs is another research priority. However, as tested in REDOXS[248] and METAplus,[255] combination therapy was not successful and potentially harmful at high non-nutrition doses. Potential interactions might explain this or even neutralize the effects of different agents, as known for combining different antioxidants such as selenium and vitamin C. Guidance by new biomarkers and pharmacokinetic modeling could yield new possibilities to find the most optimal combinations for individual patients.

Rebalancing research strategies

We have made an overview of the currently ongoing trials in Tables S4, S12, S14, S17, S24, and S27. Overall, the group aims to contribute to novel research strategies and priorities based on the unexpected results of some of our previous clinical trials, our best understanding of mode of action of the target nutrients, their biological function in the human body, and the molecular mechanisms of the underlying disease. Further, understanding the role of each nutrient within these mechanisms through methodologically sound, clinically powered translational research, including clinically relevant animal experiments, is required. The ESICM FREM/MN group will happily coordinate and support the urgently required research initiatives to develop more adequate methods to measure the patients' MN status, which represents the base for new innovative and more personalized administration strategies.

CONCLUSIONS

We have summarized the primary forms and functions of essential MNs, their plasma concentrations, and the clinical research conducted among critically ill patients. Additionally, we have provided the clinical implications: high-dose monotherapy of MNs is not recommended. Basal daily needs must be provided, with higher doses in some diseases with identified higher needs, and deficiencies must be treated according to MN guidelines. Furthermore, we have addressed areas for future research regarding specific promising nutrients in our pursuit of a more personalized approach to administering MNs to critically ill patients, above all avoiding iatrogenic harm (Table 3).

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A. M. E. de Man, M. M. Berger, C. Stoppe, J. Gunst, M. Casaer, and A. R. H. van Zanten contributed to the conception and design of the review. All authors contributed to the first draft. All authors contributed to the critical revision and writing of the publication. All authors provided final approval to submit, including accountability for the accuracy and integrity of the publication.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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