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Educational Paper

LLL 44-4 : Micronutrients in acute disease and critical illness

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SUMMARY

Micronutrients (MN), i.e. trace elements and vitamins, are essential components of the diet in relatively small amounts in any form of nutrition, with special needs in critically ill patients.

Critical illness is characterised by the presence of inflammation and oxidative stress. MNs are tightly involved in antioxidant and immune defences. In addition, some conditions, and treatments result in large losses of biological fluids containing MNs: therefore, acute renal injury requiring renal replacement therapy, acute intestinal failure, and major burns and trauma are at high risk of acute depletion of body stores, and of deficiency. MN requirements are increased above standard DRI. Blood level interpretation is complicated by inflammation: some biomarkers assist the status determination.

Due to the acute challenges of critical illness, it of utmost importance to cover the needs to maintain the organism's endogenous immune and antioxidant defences, and capacity to repair tissues. Practical strategies are proposed.

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Abbreviations

AKI	acute kidney injury
CRRT	continuous renal replacement therapy
CRP	C-reactive protein
DRI	Daily recommended intakes
ESICM	European Society of Intensive Care medicine
ESPEN	European Society for Clinical Nutrition & Metabolism
FREM	Feeding, Rehabilitation, Endocrinology & Metabolism section
HF	heart failure
IF	intestinal failure
LLL	Life Long Learning (ESPEN educational program)
LVEF	left ventricular ejection fraction
MN	Micronutrient
RCT	randomized controlled trial

Learning objectives

- To become aware about specific micronutrients (MN) and health issues associated with critical illness.
- To be able to identify and interpret the causes and diagnoses of low blood levels.
- To know the MN that might need monitoring in acutely ill patients
- To develop awareness about the mechanisms underpinning increased MN requirements in selected diseases
- To be able to identify the pathologies and conditions at risk of insufficient status and know how to handle it.
- To address the risks and management of refeeding syndrome.

Key messages

- Micronutrient (MN) status assessment is complicated in critic ally ill patients by the nearly systematic presence of inflammation which causes redistribution of MNs from the circulating compartment, without necessarily reflecting deficiency.
- Suboptimal MN status or deficiency are frequent critically ill patients due to diseases itself, or to the treatments that are required.
- Conditions at highest risk of deficiency are those with acute losses of MNs from biological fluids: acute renal injury requiring renal replacement therapy, acute intestinal failure, and major burns and trauma.
- MNs are major determinants of antioxidant defences (especially ascorbic acid, selenium, vitamin D), and therefore require special attention.
- As MNs work as a web, multiple MN complementation is a physiological approach, while single MN administration should be used only in proven deficiency.

1. Introduction

Micronutrient (MN) data remain sparse in patients with acute conditions requiring urgent medical care, eventually hospitalisation, and even intensive care (ICU) admission. This is primarily due to a lack of awareness about the clinical relevance of MN and limited availability of blood analytics for status determination. This absence was reflected by the answers to a survey conducted by the ESICM-FREM section confirming that MN diagnostics were limited, and that there was no systematic organisation of their monitoring [1]. However MN deficiencies and inadequacies are frequent, and affect the full range of MNs, contributing to poor outcome [2]. Abnormalities of blood levels of *e.g.* zinc are commonly observed especially in presence of an inflammatory response, but association with outcomes remain inconclusive due to low number of laboratory results, as shown by a large observational study investigating Mg, P, and zinc [3]. One challenge in the adoption of MN status markers for clinical management lies with their difficult interpretation that can be confounded by the level of inflammation at the time of the blood sampling [4].

In acute medical and surgical conditions, some degree of inflammation is generally present, being generally intense in critical illness. Inflammation complicates the assessment of the blood levels. Using the surrogate C-reactive protein (CRP) as an indicator of its intensity, low levels for most MNs have been shown to occur as a result of the cytokine-mediated redistribution from the circulating compartment to other organs [5]. Low blood levels therefore do not necessarily reflect a deficiency [4], despite being often misclassified as such [6]. The effects of inflammation on blood levels in response to acute injury or infection is manifests within hours but may also be prolonged in chronic illness.

New standards have been set with the 2022 MN-guideline regarding the wording to be used to describe the patient's status [4]: it is stressed that the diagnosis of deficiency requires

1) Evidence of objective loss (or insufficient MN intakee), AND
2) the presence of clinical signs or symptoms OR Blood/plasma concentrations below reference range together with metabolic effects of inadequacy.

In presence of acute losses (such as exudative losses in burns or high output intestinal fistulae), the word “depletion” applies as there has been no time to develop clinical consequences and signs that require several weeks to manifest.

The present LLL course (44.4) will address conditions for which major MN status alterations have been shown. Table 1 serves for diagnostic orientation regarding the likeliness of MN deficit or deficiency in the conditions that are presented.

For each disease category, “practical considerations” are provided. They do not have the force of recommendations as there is no hard evidence supporting them: they are based on observational studies and practical clinical expertise of the authors (all being members of the ESPEN MN-special interest group).

2. Refeeding syndrome

The transition from fasting to eating is a physiological process that often goes unnoticed until it malfunctions. During fasting, energy is initially supplied by glycogen mobilisation, followed by muscle protein breakdown, and subsequently by lipolysis, which produces free fatty acids used as direct fuel or converted into ketone bodies in the liver [7]. Energy production from fatty acids and ketones requires less phosphate and no thiamine (B1) compared

Table 1
Risk factors for MN depletion or deficiency in different conditions according to the presence of prior malnutrition, active biological fluid losses [4], and inflammation, with the MNs most frequently affected.

Disease	Malnutrition on admission	Biological fluid losses	Level of Inflammation	Likeliness of status alteration	MN at highest risk
AKI on CKD with conservative treatment	often	no	moderate	Deficiencies in case of prior malnutrition	B1, B6, B9, K, D, Cu, Se, Zn
AKI with CRRT	no	Yes (effluent)	moderate	Acute depletion frequent	B1, B3, Cu, Se,
Sepsis – septic shock	no	no	intense	Vit.C may be consumed and depleted	B1, B12, C, D, Fe, Se, Zn
Cardiac failure	often	no	moderate	Deficiencies are frequent	B1, B2, B3, B6, B9, D, Cu, Se, Fe, CoQ10
Cardiac surgery	no	minimal	moderate	No	Se, Zn
Major trauma & soft tissue injury	no	Yes (drains)	moderate to intense	Acute depletion frequent	C, E, Se, Zn
Refeeding syndrome	Chronic or acute	no	Depends on accompanying disease	Depletion and deficit frequent	B1 (all B)
Acute intestinal failure	no	Yes (fistulae, diarrhoea)	elevated	Acute depletion frequent	Zn
Viral infections	Variable	no	intense	In case of prior malnutrition	C, D, Se, Zn
Major burns	no	Yes (exudates)	intense	Acute depletion frequent	C, D, Cu, Se, Zn

Abbreviations: AKI = acute kidney injury, CKD = chronic kidney disease, CRRT = continuous renal replacement therapy.

with glucose phosphorylation. Consequently, serum phosphate, potassium, and thiamine levels remain stable during fasting, even with low intake and depletion of bodily stores, including diuretic effects caused by ketone bodies.

When nutrition begins, insulin not only transports glucose but also moves potassium intracellularly (Fig. 1). Glucose oxidation increases the demand for thiamine and phosphate. Thiamine is crucial for branched-chain amino acid oxidation. Untreated hypokalemia, hypophosphatemia, acute thiamine deficiency, along with hypomagnesemia and sodium overload, can lead to fatal arrhythmias, muscle weakness, and wet beriberi, manifesting as congestive heart failure, lactic acidosis, and acute abdominal symptoms [8]. This dramatic clinical scenario is often overlooked, especially in acute conditions.

Refeeding syndrome was first observed in the Burgundian famine in 1033 and more recently during the Dutch hunger winter [9]. Surprisingly, it can also arise under expert nutrition management and monitoring. A post-hoc analysis of the Swiss EFFORT trial was recently conducted [10,11]: the combination of oral nutrition support and expert dietitian follow-up not only improved protein and energy intake but also reduced morbidity and mortality in acutely ill patients, but refeeding syndrome may have occurred in some patients of the intervention group. Notably, the NRS2002-score, introduced 20 years ago by ESPEN [4], proved to be an excellent predictor of refeeding risk. Subsequently, the authors provided a concise overview of measures to prevent and manage refeeding syndrome, including dynamic strategies for multi-micronutrient, potassium, phosphate, and magnesium supplementation, strict fluid management, and nutrient restriction [7].

In critical illness, hypophosphatemia is common, especially shortly after ICU admission [12]. The timing and necessity of correcting this hypophosphatemia remain uncertain, as indicated by a recent ESICM-FREM section review [13]. European guidelines strongly recommend a temporary reduction in nutritional intake (<500 kcal/day for 48 h) when hypophosphatemia occurs [14]. This recommendation primarily stems from the 'Refeeding-RCT,' where nutrient restriction in patients with absolute hypophosphatemia (<0.65 mmol/L) and relative hypophosphatemia (delta >0.16 mmol/L) led to improved survival, although phosphate levels were promptly corrected with equivalent amounts of phosphate in both study groups [15]. The non-hypophosphatemic patients were not included in the study which makes it challenging to ascertain the specificity of this effect to patients with hypophosphatemia. However, a post-hoc observational study by Van Zanten et al. confirmed that nutrient restriction was associated with improved outcomes in hypophosphatemic patients. Moreover, no such relationship was observed in patients with normal phosphate levels [16]. Furthermore, admission characteristics could not predict patients at risk. Whether these observations should be labelled as 'refeeding syndrome' remains debatable. Transient hypophosphatemia may be more of a marker for 'unpreparedness for early enhanced feeding.' This hypothesis needs confirmation

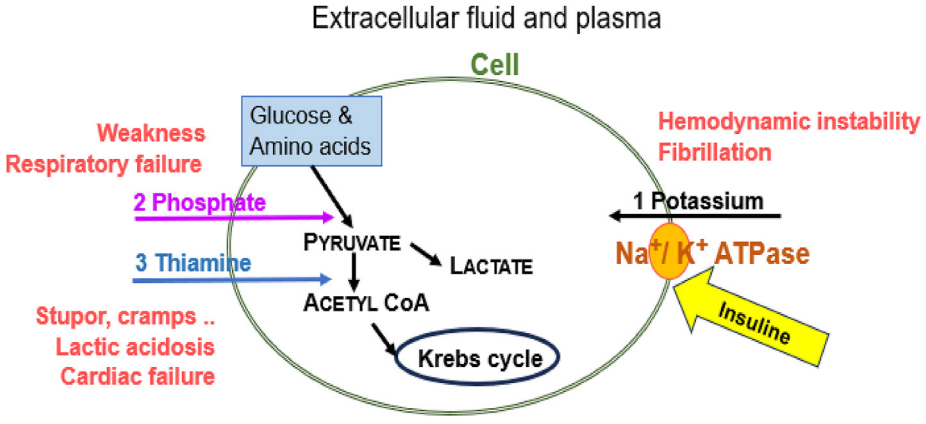

Fig. 1. Pathophysiology of the refeeding syndrome (mitochondrial compartment not shown). In red the clinical manifestations.

through a prospective RCT. The current practices for phosphate monitoring and preventive MN provision in European ICUs vary significantly, potentially leading to the oversight of early hypophosphatemia [1,3].

In conclusion, while the physiology of refeeding in the ICU, hospital, and beyond is still not fully understood, rigorous monitoring and management of MNs, nutrition dosages, and phosphate levels can be lifesaving.

Practical considerations: Table 2 provides the basics of treatment [8]: daily monitoring of blood phosphate belongs to good practice, and enables detecting, whatever the cause, the development of hypophosphatemia, and adapting the nutrition strategy, and repletion doses required to maintain homeostasis. Note that a glucose 5% infusion can be sufficient to trigger hypophosphatemia.

3. Cardiac failure and cardiac surgery

3.1. Cardiac failure

The heart is an organ exposed to a tremendous and prolonged intense activity over lifespan. It is directly affected by malnutrition [17]. With the kidney, heart is the organ with the highest energy consumption per gram of tissue (before brain and liver) [18]. This implies an intense mitochondrial activity and high metabolic level, that generate a massive oxidative stress that required adequate MN levels for efficient control. This implies the necessity for provision of the complete range of micronutrients. The vitamin B family is essential for carbohydrate and amino acid aerobic metabolism and adenosine triphosphate (ATP) production [19]. The selenoenzyme glutathione peroxidase belongs to the intra- and extracellular first line antioxidant defence, and thus requires an adequate provision of selenium ensured [20,21]. Vitamin C has pleiotropic effects affecting several cardiovascular processes. Considering the impact of MNs on the mitochondrial energy production, deficiency diagnosis and correction should be integrated as an additional factor in the heart failure (HF) equation; Bomer et al. [22] suggested "moving our view of the failing myocardium away from an engine out of fuel to a defective engine on a path to self-destruction."

Chronic HF affects approximately 10% of old adults >80 years and is aggravated by MN deficiencies [19,23]. The non-pharmacological management of the condition includes MNs [24]. Selective selenium and thiamine deficiencies may directly cause HF, while vitamins C and E and beta-carotene, are antioxidants that have a protective effect on the vasculature. Vitamins B6, B12 and folate deficiency results in increasing levels of homocysteine as they are required for its transformation into methionine: the high levels are associated with increased oxidative stress. A RCT testing a 9 month intervention with a cocktail (calcium, magnesium, zinc, copper, selenium, vitamin A, thiamine, riboflavin, vitamin B6, folate, vitamin B12, vitamins C, E, and D, and CoQ10) versus placebo [25], showed in that the intervention reduced the left ventricular volumes [−13.1 (17.1)% vs. +3.8 (10.0)%; $P < 0.05$] and increased left ventricular ejection fraction (LVEF) by 5.3%, improving quality of life. Recently the importance of iron deficiency has been stressed, as it affects over 50% of patients with chronic HF and is associated with worsening of clinical evolution [26]. Furthermore, a meta-analysis on in six cardiac trials ($n = 246$) showed that vitamin C increased LVEF on average by 12.0% (95% CI 8.1–15.9%; $P < 0.001$). In six non-cardiac trials ($n = 177$), vitamin C increased LVEF on average by 5.3% (95% CI 2.0–8.5%; $P = 0.001$) [27].

A meta-analysis including 884 RCTs evaluating 27 types of micronutrients and n3-PUFA among 883,627 participants (4,895,544 person-years) showed that supplementation of some but not all MNs may benefit cardiometabolic health. The study highlights the importance of **micronutrient diversity** and the balance of benefits and risks to promote and maintain cardiovascular health in diverse populations [28].

Micronutrient deficiencies may finally contribute to cardiac arrest, but data in this situation are few. A pilot trial testing thiamine 3 × 100 mg/day after cardiac arrest was negative [29].

Practical consideration: in patients with cardiac failure, the potential for MN deficiencies should be addressed, searching for global or specific MN malnutrition. The MNs at highest risk of deficiency are iron, selenium, the vitamin B family, vitamins C and D, and deficits, are present in up to 50% of patients. Deficiencies should be corrected. A pragmatic approached would be to provide multi-MN complements including iron, despite the European and American Societies not yet recommending more than iron administration [22], because of limited trial evidence [30]. The interventions should not be based on single MNs but on a multimodal complementation.

3.2. Cardiac surgery

Different attempts have been made at addressing the additional oxidative stress represented by the surgery. A meta-analysis including 15 trials and 2050 cardiac surgery patients showed that vitamin C might prevent post-operative atrial fibrillation and shorten the duration of hospital stay and ICU stay [31]. In a meta-analysis of seven RCTs, it was shown that intravenous

Table 2
Diagnosis and treatment of refeeding hypophosphatemia in critical illness.

Diagnosis of refeeding hypophosphatemia	
Risk Factors	Typical baseline characteristics, such as low BMI, low intake, or severity of illness or refeeding scores for outpatients and general ward patients, do not predict the emergence of refeeding hypophosphatemia in the ICU.
Monitoring	Measure serum phosphate once or twice daily for 3–5 days post-ICU admission or at least 72 h after nutrition therapy initiation.
Definition nutrition therapy	Nutrition therapy considers Oral, Enteral or Parenteral Nutrition and non-intentional energy (kcals), *e.g.*, glucose/dextrose, propofol, and citrate.
Treatment initiation criteria	If serum phosphate drops below 0.65 mmoL/l (or delta >0.16 mmoL/l) within 72 h of nutrition therapy commencement.
Treatment of refeeding hypophosphatemia	
Energy restriction	Reduce to 500 kcal/24 h or 25% of individual targeted full energy target for 48 h.
Protein intake reduction	Limit to less than 25% of individual targeted full protein target during the caloric reduction phase.
Electrolyte Supplementation	Correct hypophosphatemia, hypokalaemia, and hypomagnesemia until normal ranges are achieved.
Thiamine supplementation	Provide thiamine (vitamin B1) supplements for several days: 100–300 mg/day.
Micronutrient administration	Consider administration of IV or oral/enteral multivitamins and trace element complements (those used for PN) to reach the DRI until a daily energy intake of 1500 kcal of total oral/enteral nutritional intake has been achieved.
Gradual progression	After this energy restriction phase (48 h), gradually progress energy and protein intake to the full target, *e.g.*, in daily steps of 25% per day until the full target has been reached.

administration of vitamin C (1–16 g/day) decreased cardiac troponin levels in periprocedural myocardial injury [32]. A RCT testing a 5-day multi-MN cocktail (Se 270 mcg, Zn 30 mg, Vit C 1.1 g, Vit B1 100 mg) in high risk patients, was associated with a faster resolution of the inflammation response (measured by CRP) but no other clinical improvement [33]. Despite data indicating alteration of selenium status being associated with higher oxidative stress and more organ failures in cardiac surgery [34,35], high dose perioperative selenium intervention has been disappointing with only a modest reduction of postoperative vasopressor requirements [36]. A meta-analysis including seven RCTs with low risk of bias including 2521 patients (65% males) showed no noticeable differences between high dose single selenium and control groups [37]. The most recent selenium RCT (1416 cardiac surgery patients) showed no significant benefit from perioperative administration of high-dose IV sodium selenite (2000 μg followed by 1000 μg for 10 days) [38]. A RCT testing the preop and postoperative administration of a combination of vitamin E (1200 IU then 200IU) and zinc (120 mg then 30 mg) for 3 weeks showed a faster reduction of the inflammatory response and of the oxidative stress (reflected by MDA): a significant reduction of hospital LOS was observed [39].

Prevention of AKI after cardiac surgery is an important issue. Niacin (Vitamin B3) is a precursor of Nicotinamide Adenine Dinucleotide (NAD), which is central to energy metabolism. Impaired NAD+-biosynthesis has been associated with ischemic AKI after major cardiovascular surgeries [40]. At current, a large RCT in cardiac surgery patients is investigating whether niacin supplements can reduce renal damage (NCT04750616).

Practically, Multi-MN, i.e. diversity with moderate MN doses, might be the correct strategy as shown by Witte et al. [25].

4. Sepsis

Sepsis is defined as a life-threatening organ dysfunction due to dysregulated host response to infection, which is reflected by an increasing Sequential Organ Failure Assessment (SOFA) score ≥2 points [41]. Septic shock occurs in a subset of patients with sepsis and comprises an underlying circulatory and cellular/metabolic abnormality that is associated with increased mortality. Septic shock is defined by persisting hypotension requiring vasopressors to maintain a mean arterial pressure of 65 mmHg or higher and a serum lactate level greater than 2 mmol/L (18 mg/dL) despite adequate volume resuscitation.

This condition is characterised by an intense inflammation and major acute phase response due to the associated surge of chemokines. Low to very low MN blood levels are a constant finding in sepsis and septic shock. Numerous publications have shown reduced circulating levels of all MNs during sepsis, except for copper levels that [4], the recent COVID-19 being one more example of low blood levels [42]. In most patients there are no biological fluid losses, hence no real MN deficiency [4]. The fact that infection and inflammation can lead to the misclassification of the patients in terms of trace element status was shown long ago in children [43].

Forceville et al. showed that the selenium levels decreased proportionally to the severity of sepsis and septic shock, i.e. of inflammation [44]. Knowing the importance of selenium in the antioxidant defences [45], and the evidence of increased oxidative stress and mitochondrial dysfunction in sepsis [46], a series of trials attempted to raise selenium status and linked antioxidant defences using high dose selenium. While some studies suggest a reduction of mortality the lack of effect has been confirmed in the latest meta-analysis including 24 RCTs [47].

Ascorbic acid levels are profoundly depressed in critically ill patients [48], and especially in sepsis. A dose finding RCT showed that doses of 50 mg/kg/4 times per day were required to normalise the levels in septic patients [49]. Numerous trials have been conducted after the study by Marik et al. who combined Vitamin C, Thiamine and Hydrocortisone for the Treatment of septic shock [50]: subsequent trials have been disappointing, except for one trial testing high dose ascorbic acid alone [51] showed mortality reduction. A series of other MNs have also been tested, mainly vitamins A, C, D and E, and zinc [52]. Several trials have tested high dose vitamin D, a MN with low status associating with ICU mortality, but with no clear result [53], possibly explained by heterogeneity of the populations.

In summary, the above attempts to treat septic shock with high dose monotherapy MNs are not nutritional interventions but pharmaco-nutrition. High-dose monotherapy is non-physiological. Furthermore, MNs are likely to generate their actions on immune system and tissue healing via a complex web of interactions exceeding the reductionism of a high-dose monotherapy.

Practical considerations: Prevention and correction of deficiencies should be undertaken, but at this stage no complement or supplement can be recommended, while careful attention should be given to cover the basal requirements. Doses of 2–3 g/day of intravenous vitamin C have been shown to normalise blood levels and to be safe [54].

5. Acute renal failure & renal replacement therapy

The incidence of acute kidney injury (AKI) in the ICU has increased during the past decades due to increased severity of illness as well as its better recognition using the KDIGO criteria: it is now recognized as a heterogeneous syndrome that affects acute morbidity and mortality, but also the long-term prognosis [55]. The incidence of AKI ranges from 20 to 50% with lower and higher incidence seen in elective surgical and sepsis patients respectively [56,57].

Continuous renal replacement therapy (CRRT) is being used more frequently in the ICU, due to its better hemodynamic tolerance [58]. CRRT has both direct and indirect impacts on nutritional status beyond the desired removal of toxic elements. Balance studies have been conducted and have shown continuous losses and negative balances of water-soluble MNs such as copper, selenium, zinc, vitamins C and thiamine [59,60].

In addition to the impact of inflammation resulting in MN redistribution, other mechanisms are responsible for changes in blood MN levels such as changes in absorption and extraction, increased utilization, and alterations in protein binding (increase/reduction of MN transport proteins) [61]. Important dietary components encompassing micronutrients, are lost during CRRT, because they are removed or adsorbed on the extra-corporeal circuit. Retrospective studies of critical ill patients have shown that low blood levels of at least one MN was present in 80–90% of those who required CRRT [62,63]. The ESICM-AKI section members conducted a scoping review of 35 publications [61], and showed that during CRRT, losses of several MN and amino acids are associated with low blood levels with a real risk of deficiency for vitamins B1 and C, copper, and selenium.

Osterman et al. conducted a prospective study including 33 critically ill patients with AKI who required (n = 24) or not CRRT [64]. The serial plasma concentrations of vitamins and trace elements were measured for six consecutive days. All trace elements, vitamin C, and folate were detected in the effluent fluid. The plasma levels of zinc, iron, selenium, vitamin D, and vitamin C were below the reference range. However, the low plasma values were observed irrespective of CRRT.

A prospective observational study including 50 critically ill patients with AKI [65], assessed blood levels of several vitamins and

trace elements before, during, and after CRRT. The blood concentrations of vitamin C, selenium, and zinc were below normal range at the beginning of the study. CRRT resulted in a significant additional reduction in vitamin C, selenium, and zinc levels.

The IVOIRE study, a RCT focusing on patients with septic shock and AKI requiring CRRT [66], compared different treatment rates (n = 17 and n = 13 patients with rates of 70 and 35 ml/kg/h, respectively). At the initiation of RRT, the serum levels of both Vitamin A and Vitamin C were below the normal range in 28 (93%) and 30 (100%) patients, respectively. By day 4, the Vitamin A levels had nearly normalized, whereas the Vitamin C levels remained low throughout the entire study period. Furthermore, there was a statistically significant decrease in Vitamin C levels between day 0 and day 4. The dose of CRRT did not have any impact on the blood levels of those MNs.

A study showed that such losses could be attenuated (copper, zinc, folic acid) by the use of refiltering technique compared to high-volume hemofiltration [67].

Practical considerations: there is yet no hard recommendation as to how to address the MN status threats in CRRT. Experts advise to determine blood levels (Cu, Se, B vitamins) in case of prolonged CRRT beyond 2 weeks, and to correct deficiencies based on blood levels [14,61,68]. Some centres have started administering one vial of the PN multi-MN products (trace element and vitamins) per day as soon as the CRRT lasts > one week. This strategy per day is under investigation.

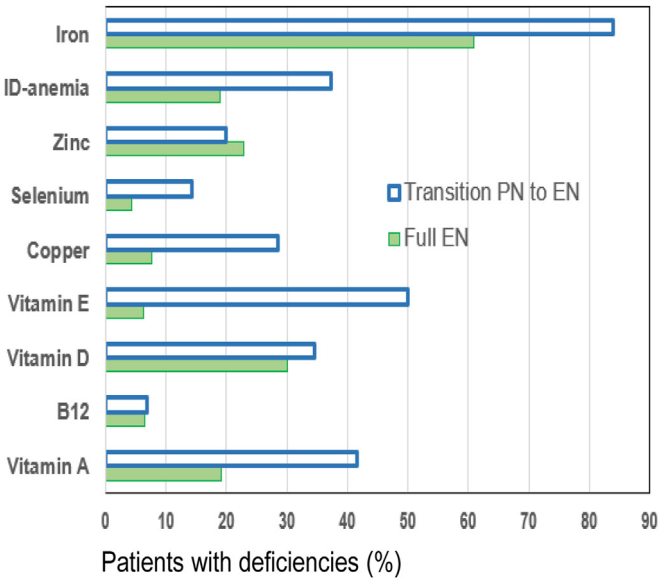

Fig. 2. Prevalence of micronutrient deficiencies in 178 paediatric patients transitioning from prolonged PN to full enteral nutrition. During transition 42.5% of patients had at least one vitamin deficiency, 25% had at least one mineral deficiency, and 27.5% had multiple MN deficiencies. Most common MN status threats were of iron, copper, and fat-soluble vitamins during both periods (adapted from Ubesie et al. [74]) (same figure as Fig. 1 in Module 44-3).

6. Acute intestinal failure

Intestinal failure is defined as "the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth [69]. For Chronic Intestinal Failure (CIF) [70], please see LLL- 44-3.

In the critically ill patients, acute IF is frequently observed and generally transient, with limited MN issues. Acute intestinal failure (IF) can be both the cause, and the consequence of critical illness. Intestinal hypoperfusion, perforation, mechanical obstruction, or ileus (due to major surgery, medication, or toxins) are most common causes. Graft versus host disease, infections (cytomegalovirus or pseudomembranous colitis), auto-immune reactions in the context of immune therapy are less common and more difficult to recognise. The Gastrointestinal Dysfunction Score (GIDS) should be used to define IF based on clinical signs [71].

The obvious consequence of IF for micronutrient management is the risk for insufficient intestinal absorption (due to temporary restriction of enteral nutrition doses) and inadequate absorption due to gastric dysfunction (folate & vitamin B 12), ileal resection or increased losses in bile fistula or diarrhoea [72].

Literature on MN management in IF is scarce with few RCTs, but ESPEN recommendations are straightforward and concise "All micronutrients and electrolytes should be administered from the beginning of nutritional therapy" [73].

In patients presenting with acute on chronic intestinal failure who may have received parenteral nutrition for a longer period of time, deficiency should be suspected affecting B2, B7, B9, B12, A, D, E, K, Cu, Fe, Zn, Carnitine and chromium [4]. A liberal administration of PN doses of MNs is advocated.

Also, the recovery of IF and transition to enteral nutrition constitutes a vulnerable phase for development of micronutrient deficiency, as revealed in a prospective paediatric cohort study (Fig. 2). A retrospective study in 178 patients with IF in transition to enteral nutrition, i.e. receiving between 20% and 100% of estimated nutrition needs, showed multiple low blood levels of MNs, called deficiencies, affecting principally iron, B12 and vitamin D: the study showed the need for routine monitoring and supplementation during this critical transition phase [74]: Of note, inflammation was not assessed (no CRP value was reported), and MN blood values inferior to reference levels were qualified as deficiency which according to our criteria is uncertain but possible. After successful transition the prevalence of low levels decreased. The transition period requires special attention.

Practical consideration: As critically ill patients often present undiagnosed low to very low blood MN levels, with a transient low intake of MNs which remains below the DRI during the phase of nutritional introduction and progression, a pragmatic strategy consisting in the delivery of multi-micronutrient preparations (doses used for parenteral nutrition) during the first days in the ICU is recommended by an expert group of intensivists and is applied in their ICUs [75].

7. Viral infections: SARS-CoV-2 and other viruses

Micronutrients are involved in the continuous progression of the host's immune responses to the virus (Figs. 3 and 4) [76–78]. For a detailed review of the potential immune alterations linked with deficiencies, please see Gombart et al. [79]. The primary defences against the virus are the physical and biochemical barriers of the respiratory tract. Normal epithelial differentiation and growth in these barriers are dependent on adequate levels of vitamin A and Fe [80]. Vitamins A, C, D, and Zinc regulate the fluidity of cell membranes, maintain their integrity, facilitate communication through gap junctions, and promote membrane repair [81–83]. Vitamin E helps reduce/lessen the breakdown of membrane lipids caused by reactive oxygen species [80]. Vitamins A, D, C, as well as the trace elements zinc, iron, copper, and selenium, play a role in regulating the activities of antimicrobial peptides bound to the cell membrane and the microbiota associated with the mucosal surfaces [84,85]. The movement of the mucosa and the control of immune cell functions also coordinate with the integrated pathways of vitamins B6, B9, and B12 [84,86]. Vitamins A, C, D, zinc, iron,

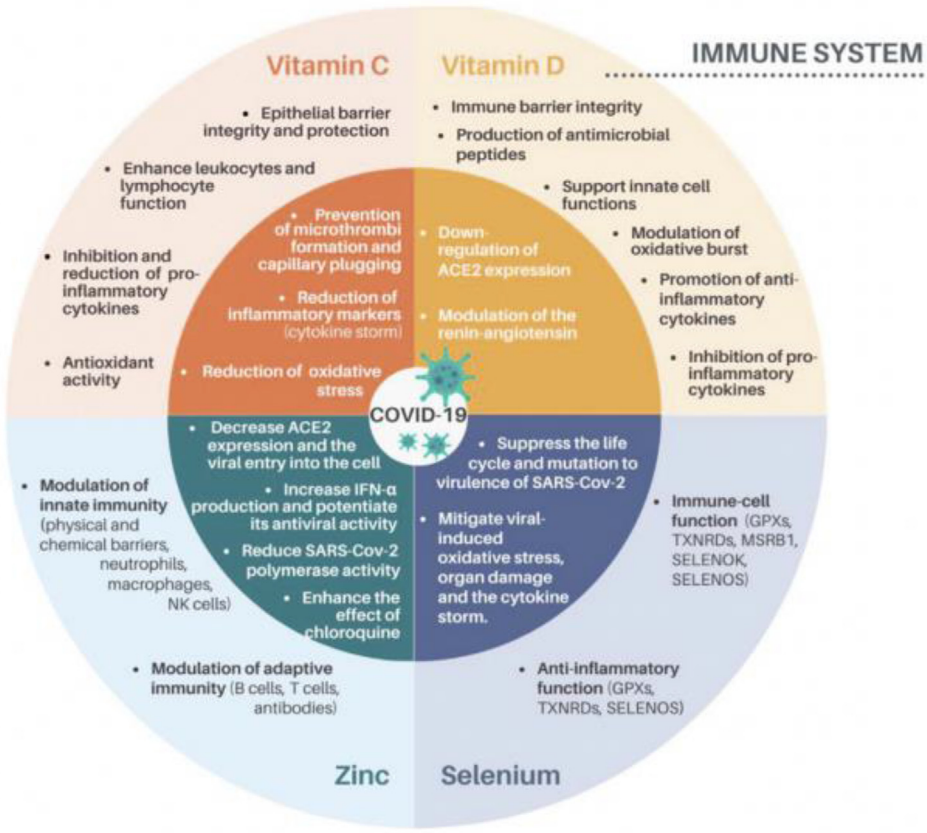

Fig. 3. Four micronutrients (vitamin C, vitamin D, zinc, and selenium) have been shown to be particularly involved in the immune defenses. The figure shows the immunomodulating actions, and the proposed beneficial mechanism in the pathogenicity of COVID-19: reproduced with permission from [77].

copper, and selenium regulate the production of interferons (IFNs) [87,88]. As a result, vitamins A, C, D, E, B6, B12, and folate, along with the trace elements zinc, iron, copper, selenium, as well as the mineral magnesium, constitute a set of nutrients that help enhance the overall range of immune responses between viruses and hosts.

The Coronavirus Disease-2019 (COVID-19) is an infection caused by the coronavirus SARS-CoV-2, which is an enveloped, positive single-strand RNA virus [89]. The typical progression of symptoms includes mild upper respiratory tract symptoms that can develop into non-life-threatening pneumonia and in the worst cases progress to acute respiratory distress syndrome (ARDS), requiring advanced life support [90]. Blood levels of Zn below reference ranges have been shown to be associated with an insufficient immunoglobulin production (IgA and IgA) in an otherwise healthy population [91].

The COVID-19 pandemic was not the first episode showing the interrelation between nutrition and MN status and virus virulence. In 1999, Beck et al. pointed to the importance of selenium and host defence against viruses [92]. In 2001 the same authors demonstrated in an animal model how Coxsackie-B3 virus could become virulent in selenium deficient mice, by reducing their endogenous antioxidant defences reflected by low glutathione peroxidase (GPX) [93], and against influenza [94].

Practical consideration: there is no MN treatment for respiratory viral diseases except zinc for common cold [95], but zinc deficiency prior to disease has been shown to be frequent and reduces immune defence [91]. Covering the basal needs is particularly important for maintenance of immunity.

8. Major burns, trauma, and soft tissue injuries

Extensive injuries, whether in the form of major burns, major trauma, extensive soft tissue destruction such in necrotizing fasciitis, or open abdomen are a specific category of critically ill patients. They are characterised by a destruction of the skin barrier on a variable surface of the body surface area (BSA), associated with biological fluid losses in major burns affecting >20%BSA. Data remain sparse, mostly coming from major burns and trauma with some balance studies.

8.1. Major burns

In major burns, large exudative losses that contain the trace elements copper, selenium and zinc [96] have been shown to cause acute depletion that results from the specific losses contributes to alterations of immunity and metabolism. The patients are characterised by an intense oxidative stress and massive inflammatory response [97]. As shown by randomised trials, the intravenous administration of doses of trace elements that compensates for the losses (i.e. repletion) is associated with significant clinical benefits in terms of improved immunity, attenuation of oxidative stress and inflammation, reduced infectious complications, and better wound healing [98–100]. Other complementation studies have been beneficial as confirmed by a meta-analysis including 8 studies (four RCT and four non-RCT) enrolling a total of 398 patients [101].

Practical considerations: in major burn patients, MNs should be provided intravenously from admission doses corresponding at

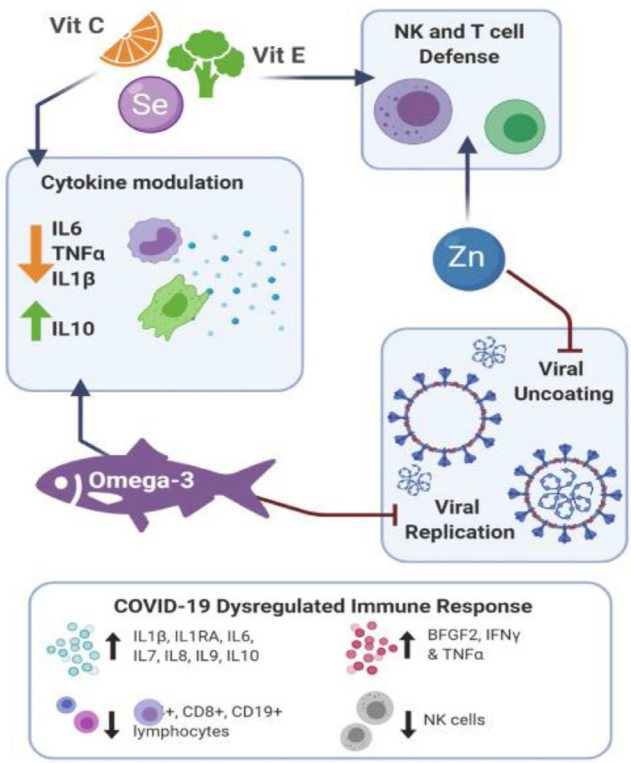

Fig. 4. Protective actions against COVID-19 using vitamin C, vitamin E, zinc, selenium, and omega-3 fatty acids: reproduced with permission from [78].

least to the daily PN doses for 7–30 days, the duration depending on burn size. Whenever possible, daily intravenous copper 3,5 mg, selenium 400 μg and zinc 35 mg repletion doses should be provided for the same duration in addition to DRI [102], a strategy which is recommended by the dedicated ESPEN guidelines [103], and whose benefits are confirmed in meta-analysis [101].

8.2. Major trauma

In major trauma, the fluid losses are less important, mainly resulting from bleeding from various drains [104]. The patients are characterized by an intense oxidative stress [33,105]. In this condition, selenium homeostasis is particularly challenged even affecting Triiodothyronine activation by the type I iodothyronine deiodinase, a selenoprotein that is sensitive to selenium (Se) deficiency [106,107]. A RCT providing repletion doses of a cocktail containing thiamine, vitamin C, Se and Zinc for 5 days was associated with a reduction of the length of hospital stay [108]. A large before and after retrospective cohort study including 4294 major trauma patients (Injury severity score = 21) tested the impact of a high dose combination of MN (ascorbic acid 1000 mg q 8 h, α-tocopherol 1000 IU q 8 h, and selenium 200 mcg qd for 7-days) on major trauma outcome, showed a significant reduction of morality [105]. In the follow up study the authors showed that the high-dose AO protocol was associated with a reduction in respiratory failure and days on mechanical ventilation, and a marked decrease in abdominal wall complications, including abdominal compartment syndrome and of surgical site infections [109].

Wound healing results in increased nutritional requirements. A cross-sectional study conducted in 44 patients with delayed wound healing after trauma showed multiple but variable alteration of status of Vitamin D, ascorbic acid, β-carotene, and selenium, all being inversely correlated to CRP [110]. A RCT conducted in 20 trauma patients with delayed wound healing providing ascorbic acid, alpha-tocopherol, beta-carotene, zinc, selenium and glutamine at nutritional doses was associated with a significant reduction of healing time (35 ± 22 vs. 70 ± 35 days; P = 0.01) [111]. Despite these convincing results, further studies are required.

Practical considerations: after major trauma, MN requirements are increased by the wound healing process. Covering at least DRI is essential, and higher doses (5 times DRI) of ascorbic acid, tocopherol and selenium delivered for 1 week after injury have been proven to improve outcome.

8.3. Soft tissue injuries

Soft-tissue injuries, including fasciitis, are conditions with an intense inflammation, and are likely associated with alterations of MN status but more investigations in this domain are needed. Topical zinc applications have however been used, and appears to be superior to oral therapy due to its action in reducing superinfections and necrotic material via enhanced local defense systems and collagenolytic activity, and the sustained release of zinc ions that stimulates epithelialization of wounds [112].

Streptococcus group A infections may cause devastating soft tissue damage: a review signals that vitamin D deficiency seems to be a risk factor, and that its administration may improve antibacterial defenses by stimulating innate immunity [113].

9. Conclusion

In acutely ill and critically ill patients, MN studies remain sparse or missing. But the link between MN, inflammation and immunity is strongly established. In absence of hard interventions study results, it is essential to remain a clinician, and to assess which mechanism may result in the development of a deficiency before admission, or of an acute depletion during the acute disease phase. Diagnosis will include blood determinations whenever available with the simultaneous assessment of the level of inflammation. The latter complicates the assessment but should not hinder blood determinations, and particularly their repetition at intervals when the condition persists.

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Authors contribution

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Declaration of competing interest

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References

[1] Vankrunkelsven W, Gunst J, Amrein K, Bear DE, Berger MM, Christopher KB, et al. Monitoring and parenteral administration of micronutrients, phosphate and magnesium in critically ill patients: the VITA-TRACE survey. Clin Nutr 2021;40:590–9.
[2] Casaer MP, Bellomo R. Micronutrient deficiency in critical illness: an invisible foe? Intensive Care Med 2019;45:1136–9.
[3] Vesterlund GK, Thorsen-Meyer HC, Moller MH, Brunak S, Strom T, Perner A, et al. Abnormal serum levels of magnesium, phosphate, and zinc in ICU patients-Characteristics, management, and outcomes: the WhyTrace cohort study. Acta Anaesthesiol Scand 2023;67:925–35.

[4] Berger MM, Shenkin A, Schweinlin A, Amrein K, Augsburger M, Biesalski HK, et al. ESPEN micronutrient guideline. Clin Nutr 2022;41:1357–424.
[5] Duncan A, Talwar D, McMillan DC, Stefanowicz F, O'Reilly DS. Quantitative data on the magnitude of the systemic inflammatory response and its effect on micronutrient status based on plasma measurements. Am J Clin Nutr 2012;95:64–71.
[6] Shenkin A, Micronutrients Berger MM. A low blood concentration is not equivalent to deficiency. Clin Nutr 2022;41:2562–4.
[7] Reber E, Friedli N, Vasiloglou MF, Schuetz P, Stanga Z. Management of refeeding syndrome in medical inpatients. J Clin Med 2019;8:2202.
[8] van Zanten ARH. Nutritional support and refeeding syndrome in critical illness. Lancet Respir Med 2015;3:904–5.
[9] Burger GCE, Sandstead HR, Drummond J. Starvation in Western Holland: 1945. Lancet 1945:282–3.
[10] Friedli N, Baumann J, Hummel R, Kloter M, Odermatt J, Fehr R, et al. Refeeding syndrome is associated with increased mortality in malnourished medical inpatients: secondary analysis of a randomized trial. Medicine (Baltim) 2020;99:e18506.
[11] Schuetz P, Fehr R, Baechli V, Geiser M, Deiss M, Gomes F, et al. Individualised nutritional support in medical inpatients at nutritional risk: a randomised clinical trial. Lancet 2019;393:2312–21.
[12] Berger MM, Appelberg O, Reintam-Blaser A, Ichai C, Joannes-Boyau O, Casaer M, et al. Prevalence of Hypophosphatemia in the ICU – preliminary results of an international one-day point prevalence survey. Intensive Care Med 2021;40:3615–21.
[13] Reintam Blaser A, Gunst J, Ichai C, Casaer MP, Benstoem C, Besch G, et al. Hypophosphatemia in critically ill adults and children: a systematic review. Clin Nutr 2021;40:1744–54.
[14] Singer P, Blaser AR, Berger MM, Calder PC, Casaer M, Hiesmayr M, et al. ESPEN practical and partially revised guideline: clinical nutrition in the intensive care unit. Clin Nutr 2023;42:1671–89.
[15] Doig GS, Simpson F, Heighes PT, Bellomo R, Chesher D, Caterson ID, et al. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. Lancet Respir Med 2015;3:943–52.
[16] Olthof LE, Koekkoek WACK, van Setten C, Kars JCN, van Blokland D, van Zanten ARH. Impact of caloric intake in critically ill patients with, and without, refeeding syndrome: a retrospective study. Clin Nutr 2018;37:1609–17.
[17] Anker SD, Ponikowski P, Varney S, Chua TP, Clark AL, Webb-Peploe KM, et al. Wasting as independent risk factor for mortality in chronic heart failure. Lancet 1997;349:1050–3.
[18] Wang Z, Ying Z, Bosy-Westphal A, Zhang J, Schautz B, Later W, et al. Specific metabolic rates of major organs and tissues across adulthood: evaluation by mechanistic model of resting energy expenditure. Am J Clin Nutr 2010;92:1369–77.
[19] Cvetinovic N, Loncar G, Isakovic AM, von Haehling S, Doehner W, Lainscak M, et al. Micronutrient depletion in heart failure: common, clinically relevant and treatable. Int J Mol Sci 2019;20.
[20] Zhang L, Gao Y, Feng H, Zou N, Wang K, Sun D. Effects of selenium deficiency and low protein intake on the apoptosis through a mitochondria-dependent pathway. J Trace Elem Med Biol 2019;56:21–30.
[21] Benstoem C, Goetzenich A, Kraemer S, Borosch S, Manzanares W, Hardy G, et al. Selenium and its supplementation in cardiovascular disease–what do we know? Nutrients 2015;7:3094–118.
[22] Bomer N, Pavez-Giani MG, Grote Beverborg N, Cleland JGF, van Veldhuisen DJ, van der Meer P. Micronutrient deficiencies in heart failure: mitochondrial dysfunction as a common pathophysiological mechanism? J Intern Med 2022;291:713–31.
[23] Witte KK, Clark AL, Cleland JG. Chronic heart failure and micronutrients. J Am Coll Cardiol 2001;37:1765–74.
[24] Yang R, Huang J, Zhao Y, Wang J, Niu D, Ye E, et al. Association of thiamine administration and prognosis in critically ill patients with heart failure. Front Pharmacol 2023;14:1162797.
[25] Witte KKA, Nikitin NP, Parker AC, von Haehling S, Volk HD, Anker SD, et al. The effect of micronutrient supplementation on quality-of-life and left ventricular function in elderly patients with chronic heart failure. Eur Heart J 2005;26:2238–44.
[26] Cohen-Solal A, Philip JL, Picard F, Delarche N, Taldir G, Gzara H, et al. Iron deficiency in heart failure patients: the French CARENFER prospective study. ESC Heart Fail 2022;9:874–84.
[27] Hemilä H, Chalker E, de Man AME. Vitamin C may improve left ventricular ejection fraction: a meta-analysis. Front Cardiovasc Med 2022;9:789729.
[28] An P, Wan S, Luo Y, Luo J, Zhang X, Zhou S, et al. Micronutrient supplementation to reduce cardiovascular risk. J Am Coll Cardiol 2022;80:2269–85.
[29] Pradita-Ukrit S, Vattanavanit V. Efficacy of thiamine in the treatment of postcardiac arrest patients: a randomized controlled study. Crit Care Res Pract 2020;2020:2981079.
[30] Girerd N. Is the correction of micronutrient deficiencies the next step in heart failure management? J Intern Med 2022;291:710–2.
[31] Hemilä H, Suonsyrja T. Vitamin C for preventing atrial fibrillation in high risk patients: a systematic review and meta-analysis. BMC Cardiovasc Disord 2017;17:49.
[32] Rozemeijer S, Hemila H, van Baaren M, de Man AME. Vitamin C may reduce troponin and CKMB levels after PCI and CABG: a meta-analysis. BMC Cardiovasc Disord 2023;23:475.
[33] Berger MM, Soguel L, Shenkin A, Revelly JP, Pinget C, Baines M, et al. Influence of early antioxidant supplements on clinical evolution and organ function in critically ill cardiac surgery, major trauma and subarachnoid hemorrhage patients. Crit Care 2008;12:R101.
[34] Kuhn-Heid ECD, Kuhn EC, Ney J, Wendt S, Seelig J, Schwiebert C, et al. Selenium-binding protein 1 indicates myocardial stress and risk for adverse outcome in cardiac surgery. Nutrients 2019;11:2005.
[35] Wendt S, Schomburg L, Manzanares W, Stoppe C. Selenium in cardiac surgery. Nutr Clin Pract 2019;34:528–39.
[36] Schmidt T, Pargger H, Seeberger E, Eckhart F, von Felten S, Haberthur C. Effect of high-dose sodium selenite in cardiac surgery patients: a randomized controlled bi-center trial. Clin Nutr 2018;37:1172–80.
[37] Rehan ST, Hussain HU, Imran L, Eqbal F, Asghar MS. Perioperative selenium administration in cardiac surgery patients, a way out to reduce post surgical adversities? A meta analysis. Front Cardiovasc Med 2023;10:1235247.
[38] Stoppe C, McDonald B, Meybohm P, Christopher KB, Fremes S, Whitlock R, et al. Effect of high-dose selenium on postoperative organ dysfunction and mortality in cardiac surgery patients: the SUSTAIN CSX randomized clinical trial. JAMA Surg 2023;158:235–44.
[39] Makiabadi E, Nakhaeizadeh R, Soleimani M, Nasrollahzadeh J. Effects of perioperative vitamin E and zinc co-supplementation on systemic inflammation and length of stay following coronary artery bypass graft surgery: a randomized controlled trial. Eur J Clin Nutr 2024;78:120–7.
[40] Poyan Mehr A, Tran MT, Ralto KM, Leaf DE, Washco V, Messmer J, et al. De novo NAD(+) biosynthetic impairment in acute kidney injury in humans. Nat Med 2018;24:1351–9.
[41] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801–10.
[42] Rossetti M, Martucci G, Starchl C, Amrein K. Micronutrients in Sepsis and COVID-19: a Narrative Review on what we have learned and what we want to know in future trials. Medicina 2021;57:419.
[43] Brown KH, Lanata CF, Yuen ML, Peerson JM, Butron B, Lonnerdal B. Potential magnitude of the misclassification of a populations trace element status due to infection - example from a survey of young Peruvian children. Am J Clin Nutr 1993;58:549–54.
[44] Forceville X, Vitoux D, Gauzit R, Combes A, Lahilaire P, Chappuis P. Selenium, systemic immune response syndrome, sepsis, and outcome in critically ill patients. Crit Care Med 1998;26:1536–44.
[45] Helan M, Malaska J, Tomandl J, Jarkovsky J, Helanova K, Benesova K, et al. Kinetics of biomarkers of oxidative stress in septic shock: a pilot study. Antioxidants 2022;11.
[46] Singer M. Mitochondrial function in sepsis: acute phase versus multiple organ failure. Crit Care Med 2007;35:S441–8.
[47] Jaff S, Zeraattalab-Motlagh S, Amiri Khosroshahi R, Gubari M, Mohammadi H, Djafarian K. The effect of selenium therapy in critically ill patients: an umbrella review of systematic reviews and meta-analysis of randomized controlled trials. Eur J Med Res 2023;28:104.
[48] Schorah CJ, Downing C, Piripitsi A, Gallivan L, Al-Hazaa AH, Sanderson MJ, et al. Total vitamin C, ascorbic acid, and dehydroascorbic acid concentrations in plasma of critically ill patients. Am J Clin Nutr 1996;63:760–5.
[49] Fowler 3rd AA, Syed AA, Knowlson S, Sculthorpe R, Farthing D, DeWilde C, et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. J Transl Med 2014;12:32.
[50] Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. Chest 2017;151:1229–38.
[51] Fowler 3rd AA, Truwit JD, Hite RD, Morris PE, DeWilde C, Priday A, et al. Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: the CITRIS-ALI randomized clinical trial. JAMA 2019;322:1261–70.
[52] Aisa-Alvarez A, Soto ME, Guarner-Lans V, Camarena-Alejo G, Franco-Granillo J, Martinez-Rodriguez EA, et al. Usefulness of antioxidants as adjuvant therapy for septic shock: a randomized clinical trial. Medicina 2020;56:619.
[53] Li Y, Ding S. Serum 25-Hydroxyvitamin D and the risk of mortality in adult patients with Sepsis: a meta-analysis. BMC Infect Dis 2020;20:189.
[54] Spoelstra-de Man AME, Elbers PWG, Oudemans-Van Straaten HM. Vitamin C: should we supplement? Curr Opin Crit Care 2018;24:248–55.
[55] Pickkers P, Darmon M, Hoste E, Joannidis M, Legrand M, Ostermann M, et al. Acute kidney injury in the critically ill: an updated review on pathophysiology and management. Intensive Care Med 2021;47:835–50.
[56] Case J, Khan S, Khalid R, Khan A. Epidemiology of acute kidney injury in the intensive care unit. Crit Care Res Pract 2013;2013:479730.
[57] Jiang L, Zhu Y, Luo X, Wen Y, Du B, Wang M, et al. Epidemiology of acute kidney injury in intensive care units in Beijing: the multi-center BAKIT study. BMC Nephrol 2019;20:468.
[58] Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Critical care 2013;17:204.
[59] Berger MM, Shenkin A, Revelly JP, Roberts E, Cayeux MC, Baines M, et al. Copper, selenium, zinc and thiamine balances during continuous

venovenous hemodiafiltration in critically ill patients. Am J Clin Nutr 2004;80:410–6.
[60] Story DA, Ronco C, Bellomo R. Trace element and vitamin concentrations and losses in critically ill patients treated with continuous venovenous hemofiltration. Crit Care Med 1999;27:220–3.
[61] Berger MM, Broman M, Forni L, Ostermann M, De Waele E, Wischmeyer PE. Nutrients and micronutrients at risk during renal replacement therapy: a scoping review. Curr Opin Crit Care 2021;27:367–77.
[62] Fah M, Van Althuis LE, Ohnuma T, Winthrop HM, Haines KL, Williams DGA, et al. Micronutrient deficiencies in critically ill patients receiving continuous renal replacement therapy. Clinical nutrition ESPEN 2022;50:247–54.
[63] Kamel AY, Dave NJ, Zhao VM, Griffith DP, Connor Jr MJ, Ziegler TR. Micronutrient alterations during Continuous Renal Replacement therapy in critically ill adults: a retrospective study. Nutr Clin Pract 2018;33:439–46.
[64] Ostermann M, Summers J, Lei K, Card D, Harrington DJ, Sherwood R, et al. Micronutrients in critically ill patients with severe acute kidney injury - a prospective study. Sci Rep 2020;10:1505.
[65] Gundogan K, Yucesoy FS, Ozer NT, Temel S, Sahin S, Sahin GG, et al. Serum micronutrient levels in critically ill patients receiving continuous renal replacement therapy: a prospective, observational study. JPEN - J Parenter Enter Nutr 2022;46:1141–8.
[66] Schneider AG, Picard W, Honore P, Dewitte A, Mesli S, Redonnet-Vernhet I, et al. Amino-acids and vitamins status during continuous renal replacement therapy, a prospective observational study. Anaesth Crit Care Pain Med ACCPM 2021;40:100813.
[67] Wu B, Ji D, Xu B, Fan R, Gong D. New modes of continuous renal replacement therapy using a refiltering technique to reduce micronutrient loss. Hemodial Int 2019;23:181–8.
[68] Ostermann M, Lumlertgul N, Mehta R. Nutritional assessment and support during continuous renal replacement therapy. Semin Dial 2021;34:449–56.
[69] Pironi L, Arends J, Baxter J, Bozzetti F, Pelaez RB, Cuerda C, et al. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. Clin Nutr 2015;34:171–80.
[70] Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB, et al. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr 2016;35:247–307.
[71] Reintam Blaser A, Padar M, Mandul M, Elke G, Engel C, Fischer K, et al. Development of the Gastrointestinal Dysfunction Score (GIDS) for critically ill patients - a prospective multicenter observational study (iSOFA study). Clin Nutr 2021;40:4932–40.
[72] Wu G, Liu C, Zhou X, Zhao L, Zhang W, Wang M, et al. Short- and long-term complications after living donor ileal resection. Am J Transplant 2022;22:3053–60.
[73] Klek S, Forbes A, Gabe S, Holst M, Wanten G, Irtun O, et al. Management of acute intestinal failure: a position paper from the European society for clinical nutrition and metabolism (ESPEN) special interest group. Clin Nutr 2016;35:1209–18.
[74] Ubesie AC, Kocoshis SA, Mezoff AG, Henderson CJ, Helmrath MA, Cole CR. Multiple micronutrient deficiencies among patients with intestinal failure during and after transition to enteral nutrition. J Pediatr 2013;163:1692–6.
[75] Preiser JC, Arabi Y, Berger MM, Casaer MC, McClave S, Montejo-Gonzalez JC, et al. A guide to enteral nutrition in intensive care units: 10 expert tips for the daily practice. Crit Care 2021;25:424.
[76] Gasmi A, Tippairote T, Mujawdiya PK, Peana M, Menzel A, Dadar M, et al. Micronutrients as immunomodulatory tools for COVID-19 management. Clin Immunol 2020;220:108545.
[77] Pedrosa LFC, Anab Barros, Leite-Lais L. Nutritional risk of vitamin D, vitamin C, zinc, and selenium deficiency on risk and clinical outcomes of COVID-19: a narrative review. Clinical nutrition ESPEN 2022;47:9–27.
[78] Shakoor H, Feehan J, Al Dhaheri AS, Ali HI, Platat C, Ismail LC, et al. Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: could they help against COVID-19? Maturitas 2021;143:1–9.
[79] Gombart AF, Pierre A, Maggini S. A review of micronutrients and the immune system-working in harmony to reduce the risk of infection. Nutrients 2020;12:236.
[80] Maggini S, Óvári V, Ferreres Giménez I, Pueyo Alamán MG. Benefits of micronutrient supplementation on nutritional status, energy metabolism, and subjective wellbeing. Nutr Hosp 2021;38:3–8.
[81] Zoroddu MA, Aaseth J, Crisponi G, Medici S, Peana M, Nurchi VM. The essential metals for humans: a brief overview. J Inorg Biochem 2019;195:120–9.
[82] Chew BP, Park JS. Carotenoid action on the immune response. J Nutr 2004;134:257s–61s.
[83] Pálmer HG, González-Sancho JM, Espada J, Berciano MT, Puig I, Baulida J, et al. Vitamin D(3) promotes the differentiation of colon carcinoma cells by the induction of E-cadherin and the inhibition of beta-catenin signaling. J Cell Biol 2001;154:369–87.
[84] Biesalski HK. Nutrition meets the microbiome: micronutrients and the microbiota. Ann N Y Acad Sci 2016;1372:53–64.
[85] Clark A, Mach N. Role of vitamin D in the hygiene hypothesis: the interplay between vitamin D, vitamin D receptors, gut microbiota, and immune response. Front Immunol 2016;7:627.
[86] Yoshii K, Hosomi K, Sawane K, Kunisawa J. Metabolism of dietary and microbial vitamin B family in the regulation of host immunity. Front Nutr 2019;6:48.
[87] McCarty MF, Iloki Assanga SB, Lewis Lujan L, O'Keefe JH, DiNicolantonio JJ. Nutraceutical strategies for suppressing NLRP3 inflammasome activation: pertinence to the management of COVID-19 and beyond. Nutrients 2020;13:47.
[88] Lee SH, Kwon JY, Kim SY, Jung K, Cho ML. Interferon-gamma regulates inflammatory cell death by targeting necroptosis in experimental autoimmune arthritis. Sci Rep 2017;7:10133.
[89] Lamers MM, Haagmans BL. SARS-CoV-2 pathogenesis. Nat Rev Microbiol 2022;20:270–84.
[90] Heymann DL, Shindo N, Scientific WHO. Technical advisory group for infectious hazards. COVID-19: what is next for public health? Lancet 2020;395:542–5.
[91] Equey A, Berger MM, Gonseth-Nussle S, Augsburger M, Rezzi S, Hodgson ACC, et al. Association of plasma zinc levels with anti-SARS-CoV-2 IgG and IgA seropositivity in the general population: a case-control study. Clin Nutr 2023;42:972–86.
[92] Beck MA. Selenium and host defence towards viruses. Proc Nutr Soc 1999;58:707–11.
[93] Beck MA, Williams-Toone D, Levander OA. Coxsackievirus B3-resistant mice become susceptible in Se/vitamin E deficiency. Free Radic Biol Med 2003;34:1263–70.
[94] Beck MA, Nelson HK, Shi Q, Van Dael P, Schiffrin EJ, Blum S, et al. Selenium deficiency increases the pathology of an influenza virus infection. Faseb J 2001;15:1481–3.
[95] Wang MX, Win SS, Pang J. Zinc supplementation reduces common cold duration among healthy adults: a systematic review of randomized controlled trials with micronutrients supplementation. Am J Trop Med Hyg 2020;103:86–99.
[96] Berger MM, Shenkin A. Trace element requirements in critically ill burned patients. J Trace Elem Med Biol 2007;21:44–8.
[97] Moreira E, Burghi G, Manzanares W. Update on metabolism and nutrition therapy in critically ill burn patients. Med Intensiva 2018;42:306–16.
[98] Berger MM, Baines M, Raffoul W, Benathan M, Chiolero RL, Reeves C, et al. Trace element supplements after major burns modulate antioxidant status and clinical course by way of increased tissue trace element concentration. Am J Clin Nutr 2007;85:1293–300.
[99] Berger MM, Binnert C, Chiolero RL, Taylor W, Raffoul W, Cayeux MC, et al. Trace element supplements after major burns increase burned skin concentrations and modulate local protein metabolism, but not whole body substrate metabolism. Am J Clin Nutr 2007;85:1301–6.
[100] Berger MM, Eggimann P, Heyland DK, Chioléro RL, Revelly JP, Day A, et al. Reduction of nosocomial pneumonia after major burns by trace element supplementation: aggregation of two randomised trials. Crit Care 2006;10:R153.
[101] Kurmis R, Greenwood J, Aromataris E. Trace element supplementation following severe burn injury: a systematic review and meta-analysis. J Burn Care Res 2016;37:143–59.
[102] Pantet O, Stoecklin P, Charriere M, Voirol P, Vernay A, Berger MM. Trace element repletion following severe burn injury: a dose-finding cohort study. Clin Nutr 2019;38:246–51.
[103] Rousseau AF, Losser MR, Ichai C, Berger MM. ESPEN endorsed recommendations: nutritional therapy in major burns. Clin Nutr 2013;32:497–502.
[104] Berger MM, Cavadini C, Chioléro R, Dirren H. Copper, selenium, and zinc status and balances after major trauma. J Trauma 1996;40:103–9.
[105] Collier BR, Giladi A, Dossett LA, Dyer L, Fleming SB, Cotton BA. Impact of high-dose antioxidants on outcomes in acutely injured patients. JPEN J Parenter Enteral Nutr 2008;32:384–8.
[106] Berger MM, Reymond MJ, Shenkin A, Rey F, Wardle C, Cayeux M, et al. Influence of selenium supplements on the post-traumatic alterations of the thyroid axis - a prospective placebo controlled trial. Intensive Care Med 2001;27:91–100.
[107] Berger MM, Lemarchand-Béraud T, Cavadini C, Chioléro R. Relations between the selenium status and the low T3 syndrome after major trauma. Intensive Care Med 1996;22:575–81.
[108] Berger MM, Soguel L, Pinget C, Revelly JP, Schindler C, Chiolero RL. Antioxidant supplements modulate clinical course after complex cardiac surgery, and major trauma. Intensive Care Med 2005;31(suppl 1):S32.
[109] Giladi AM, Dossett LA, Fleming SB, Abumrad NN, Cotton BA. High-dose antioxidant administration is associated with a reduction in post-injury complications in critically ill trauma patients. Injury 2011;42:78–82.
[110] Blass SC, Goost H, Burger C, Tolba RH, Stoffel-Wagner B, Stehle P, et al. Extracellular micronutrient levels and pro-/antioxidant status in trauma patients with wound healing disorders: results of a cross-sectional study. Nutr J 2013;12:157.
[111] Blass SC, Goost H, Tolba RH, Stoffel-Wagner B, Kabir K, Burger C, et al. Time to wound closure in trauma patients with disorders in wound healing is shortened by supplements containing antioxidant micronutrients and glutamine: a PRCT. Clin Nutr 2012;31:469–75.
[112] Lansdown AB, Mirastschijski U, Stubbs N, Scanlon E, Agren MS. Zinc in wound healing: theoretical, experimental, and clinical aspects. Wound Repair Regen 2007;15:2–16.
[113] Guevara MA, Lu J, Moore RE, Chambers SA, Eastman AJ, Francis JD, et al. Vitamin D and streptococci: the interface of nutrition, host immune response, and antimicrobial activity in response to infection. ACS Infect Dis 2020;6:3131–40.