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REVIEW-SYMPOSIUM

Overview of oxidative stress and the role of micronutrients in critical illness

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Abstract

Inflammation and oxidative stress represent physiological response mechanisms to different types of stimuli and injury during critical illness. Its proper regulation is fundamental to cellular and organismal survival and are paramount to outcomes and recovery from critical illness. A proper maintenance of the delicate balance between inflammation, oxidative stress, and immune response is crucial for resolution from critical illness with important implications for patient outcome. The extent of inflammation and oxidative stress under normal conditions is limited by the antioxidant defense system of the human body, whereas the antioxidant capacity is commonly significantly compromised, and serum levels of micronutrients and vitamins significantly depleted in patients who are critically ill. Hence, the provision of antioxidants and anti-inflammatory nutrients may help to reduce the extent of oxidative stress and therefore improve clinical outcomes in patients who are critically ill. As existing evidence of the beneficial effects of antioxidant supplementation in patients who are critically ill is still unclear, actual findings about the most promising anti-inflammatory and antioxidative candidates selenium, vitamin C, zinc, and vitamin D will be discussed in this narrative review. The existing evidence provided so far demonstrates that several factors need to be considered to determine the efficacy of an antioxidant supplementation strategy in patients who are critically ill and indicates the need for adequately designed multicenter prospective randomized control trials to evaluate the clinical significance of different types and doses of micronutrients and vitamins in selected groups of patients with different types of critical illness.

Abbreviations: ARDS, acute respiratory distress syndrome; ASPEN, American Society for Parenteral and Enteral Nutrition; ATP, adenosine triphosphate; DNA, deoxyribonucleic acid; ECMO, extracorporeal membrane oxygenation; EN, enteral nutrition; ESPEN, European Society for Clinical Nutrition and Metabolism; GPx, glutathione peroxidase; ICP-MS, inductively coupled plasma mass spectroscopy; ICU, intensive care unit; IL, interleukin; iNOS, inducible nitric oxide synthase; LOS, length of stay; MCT, medium-chain triglycerides; NAC, N-acetylcysteine; NF-κB, nuclear factor-kappa B; NOX, nicotinamide adenine dinucleotide phosphate oxidase; 1,25-OHD, 1,25-dihydroxycholecalciferol, calcitriol; 25-OHD, 25-hydroxycholecalciferol, calcidiol; OR, odds ratio; PN, parenteral nutrition; RCT, randomized controlled trial; RNS, reactive nitrogen species; ROS, reactive oxygen species; RR, relative risk; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; SOD, superoxide dismutase; SOFA, sequential organ failure assessment; SPP, selenoprotein P; SRMA, systematic review and meta-analysis; TNF-α, tumor necrosis factor-alpha; VDR, vitamin D receptor.

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KEYWORDS
critical illness, inflammation, medical nutrition therapy, micronutrients, oxidative stress, selenium, trace elements, vitamin C, vitamin D, vitamins, zinc

1 | INTRODUCTION

Although inflammation and oxidative stress are present but controlled during homeostasis, they are drastically elevated in, and often overwhelm, the patient who is critically ill.[1,2] Reactive oxygen and nitrogen species (ROS/RNS) derive, for example, from activation of phagocytic cells, production by vascular endothelium, release of iron and copper ions and metalloproteins, and ischemia/reperfusion–induced tissue damage. ROS/RNS further trigger the release of inflammatory cytokines from immune cells, activate inflammatory cascades, and increase the expression of adhesion molecules.[3] Inflammation and its sequelae result in an accumulation of granulocytes, leading to greater generation of ROS, which begets the inflammatory response and culminates in organ damage and dysfunction,[4] often necessitating organ support modalities.

Numerous observational studies demonstrate that patients who are critically ill have reduced plasma antioxidants, free electron scavengers or cofactors, and decreased enzyme activities involved in ROS detoxification.[5] During critical illness, antioxidant capacity may be compromised by preexisting deficiencies, increased utilization by the antioxidative acting enzymes and their binding to specific plasma proteins, and inadequate nutrition. In these states, optimizing antioxidative capacity towards balancing antioxidants may be relevant in mitigating the development of multiple organ failure.[6]

Several clinical studies have evaluated the clinical significance of antioxidants as a component of nutrition support or have provided an individualized intervention (pharmacotherapy) to patients who are critically ill.[7–9] The purpose of this narrative review is to (1) describe the basis for and outcomes of the inflammatory response and oxidative stress in critical illness, (2) discuss the rationale for micronutrients in patients who are critically ill, and (3) identify and appraise studies that have tested micronutrients (selenium, zinc, vitamin C, and vitamin D) on various outcomes in patients who are critically ill.

2 | THE INFLAMMATORY RESPONSE DURING CRITICAL ILLNESS

Patients who are critically ill experience a complex systemic inflammatory response syndrome. As part of the inflammatory response, ROS, RNS, and both proinflammatory and anti-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1-beta (IL-1β), interleukin-6 (IL-6), and interleukin-8 (IL-8) are released. Their release, in turn, triggers immune defense responses, such as leukocyte extravasation, intravascular leukostasis, immune cell trafficking, regulation of cell death, vasodilation, and capillary leak. Clinically, these inflammatory responses may manifest as organ dysfunctions, including hemodynamic instability and coagulopathy, which are associated with a protracted intensive care unit (ICU) stay. To counter the effects of the proinflammatory mechanisms, a compensatory anti-inflammatory response is activated in parallel. Under normal circumstances, there is a balance between inflammation and anti-inflammation, which supports the healing process and defends against secondary infections. However, a robust and sustained inflammatory response can overwhelm the anti-inflammatory response, which may compound organ damage and have deleterious outcomes for patients who are critically ill.[10,11]

3 | TARGETING THE INFLAMMATORY RESPONSE—A ROLE FOR MICRONUTRIENTS?

Micronutrients, such as vitamins and trace elements, are essential for maintaining the physiologic functions of the mitochondria, for example, the provision of cellular energy through the production of adenosine triphosphate (ATP) and the regulation of cell signaling, differentiation, and death.[11–13] Because of their antioxidative and anti-inflammatory properties, several micronutrients play a key role in maintaining redox homeostasis and, thus, in preventing oxidative stress.[11,14] On the one hand, trace elements such as copper, iron, manganese, selenium, and zinc act as important cofactors of antioxidative enzymes, for example, catalase, glutathione peroxidase (GPx), and superoxide dismutase (SOD). On the other hand, vitamins E, C, and D, respectively, and beta-carotene (pro-vitamin A) regulate nonenzymatic antioxidative reactions by directly scavenging, inactivating, and eliminating radicals and interrupting oxidative (chain-) reactions.[7,14] Several observational clinical studies demonstrated that (1) patients often show deficient blood levels of micronutrients even before ICU admission, which (2) further decrease below reference ranges during critical illness, and thus significantly aggravate the inflammatory response. However, especially in the presence of inflammation, low plasma levels may also result from recirculation of micronutrients to other organs, shift in different compartments in the human body, or binding to the endothelium (as it is known for selenoprotein P [SPP]). Therefore, low micronutrient levels in the plasma may not necessarily be interpreted as depletion or deficiency that result from an increased consumption. The concomitant measurement of plasma micronutrient status and markers of inflammation, for example, C-reactive protein (CRP) should be considered in parallel (CRP ≥ 20 mg/L as sign for inflammation may affect micronutrient status).[15,16] Low micronutrient status at ICU admission and impaired micronutrient delivery, for example, due to

purposeful or unintentional provision of reduced energy, may accentuate antioxidant depletion. Consequently, radicals may bind to lipids (lipid peroxidation), proteins (inactivation of enzymes), and deoxyribonucleic acid (DNA; modifications in DNA bases, strand breaks, and linkages), culminating in cell death, which accentuates the oxidant load.[14] Based on these preclinical observations, several randomized controlled trials (RCTs) tested antioxidant (trace elements, vitamins) supplementation on various outcomes in patients who are critically ill.[8,17–21] The evidence from antioxidant trials in patients who are critically ill has been aggregated and meta-analyzed[22] and demonstrates that supplementation of combined antioxidants was associated with a reduction in overall mortality and duration of mechanical ventilation, may be associated with a reduction in overall infectious complications, but had no effects on ICU or hospital length of stay (LOS). However, results from a trial sequential analysis of RCTs with a low risk of bias showed no effect of antioxidants.[8]

Based on existing evidence demonstrating conflicting results, the European Society for Clinical Nutrition and Metabolism (ESPEN) and the American Society for Parenteral and Enteral Nutrition (ASPEN) do not recommend routine supplementation of pharmacological doses of selenium, zinc, or vitamins in patients who are critically ill.[23,24] However, in cases where a true micronutrient deficiency exists, the ESPEN guideline recommends (nonpharmacological) supplementation for adequate substrate metabolism and optimal immune function.

How can we adjudicate the discrepancy between the findings in preclinical studies and negative findings from RCTs? First, because no two patients who are critically ill are alike, it will be prudent to identify which patients, who are critically ill, may benefit from micronutrient therapy. Second, the optimal supplementation strategy, including timing, dosage, duration, and the role of combination therapy, remain unclear.[10]

Unfortunately, only a few studies report about the molecular mechanisms, the inflammatory or immune activity in response to a treatment with micronutrients or vitamins. High-costs, complex and time-intense analysis, lack of uniformly recommended and standardized inflammatory measurements significantly limit the availability of such data. The lack of such findings makes it more difficult to answer the question if an evaluated anti-inflammatory treatment shows biologically relevant effects but is often insufficient to translate into clinically relevant findings.

Today, only limited knowledge exists about the most appropriate measurement methods for these micronutrients, which are often complex, not established in routine clinical testing, and time-intense and rarely accessible laboratory measurements. These limit its daily use in patients who are critically ill. In addition to the measurements of specific micronutrients or vitamins,[25] specific biological surrogate parameters have been introduced to allow more adequate assessments and use in clinical practice and to focus more on the biological response mechanisms. As several trials in the past failed to demonstrate any positive effects of antioxidant interventions, future studies should include possible biomarkers to measure the biological response of the intervention of interest and evaluate if it translates into a significant biological response, which further could translate into clinical meaningful outcomes.

4 | ROLE OF MICRONUTRIENTS/ ANTIOXIDANTS IN CRITICAL ILLNESS

Under physiologic (healthy) conditions, a certain level of oxidants production (eg, ROS, RNS) is essential to regulate important mechanisms such as activation of signaling pathways, cell differentiation and proliferation, activation of immune cells (eg, lymphocytes, monocytes, T-cells), and adaptation of metabolism.[12] In these states, the balance between oxidants and reductants (redox homeostasis) is maintained through the functionality of the endogenous antioxidative mechanisms, which are guaranteed by adequate intake of micronutrients as recommended for healthy individuals.[12] However, in critical illness, the balance between oxidants and reductants is disturbed. On the one hand, there is an increase in oxidants following induction of pro-oxidant enzymes such as nicotinamide adenine dinucleotide phosphate oxidase (NOX) and inducible nitric oxide synthase (iNOS) and an increased production of ROS and RNS by leukocytes and anaerobic cell metabolism. On the other hand, the levels of antioxidants decrease because of increased loss (eg, due to the necessity of medical treatments such as renal replacement therapy, extracorporeal membrane oxygenation [ECMO], drainages, medication), redistribution, and use for immunologic and metabolic reactions.[14] In consequence, oxidative stress during critical illness leads to functional and structural modifications of the mitochondria, which further may trigger the production of ROS and RNS and lead to organ dysfunctions.[12] Although inflammation, oxidative stress, and mitochondrial dysfunction represent an attractive therapeutic target in critical illness for treatment with micronutrients and vitamins, justification for providing doses beyond recommended dietary allowance is lacking. The reasons for these disappointing results are speculative and could be due to the earlier discussed heterogeneity of included patients who are critically ill (eg, variety in underlying disease: trauma, burn, surgery, etc). Moreover, as discussed earlier, it remains unknown if the variance in dosing, timing, combination, or delivery of antioxidants were optimal. Importantly, Jain et al speculated that adverse off-target effects may have contributed to their failure, as ROS are critical signaling molecules for cell homeostasis and adaptation to stress (eg, hypoxia), processes that may be neutralized with antioxidants. Patients with sepsis commonly show a period of relative immunosuppression after the initial cytokine storm, during which they are at increased risk of nosocomial infection or viral reactivation. Regarding the importance of ROS in activating lymphocytes and monocytes, it thus remains speculative if the ROS production contributes to positive effects and the desired

variability in inflammatory responses and immune competence. Therefore, the timing about when to perform such optimizing strategies seems to play a crucial role but often remains an underrecognized aspect. The initiation of any antioxidant treatment may simply have been too late initiated in recent studies to target the overwhelming cytokine storm and to ultimately translate in any clinically meaningful effects. More precisely, the use of antioxidants may be beneficial during the initial acute phase of exaggerated inflammatory responses to inhibit the overwhelming inflammatory response but too late and even detrimental during periods of relative immunosuppression (Figure 1). Furthermore, the role of autophagocytosis within the healing and recovery process during critical illness, which might be suppressed through therapy with micronutrients, still remains an important and debatable issue.[26]

Patients undergoing major surgical procedures represent a specific cohort of interest of patients who are critically ill as it can be predicted that these patients will experience a scheduled intense inflammatory response that affects multiple organs and may result in the development of organ dysfunctions. As this represents a predictive insult, it opens the chance for a preoperative preemptive optimization strategy to replenish the antioxidative capacity, enhance the body's immunological defense mechanisms, and to attenuate the inflammatory response. In fact, smaller studies indicated beneficial effects of perioperatively administered immune modulating agents, whereas adequately designed clinical trials in patients with major surgical traumas are still needed to evaluate if this hypothesis translates into clinically meaningful effects.

To date, there is still limited knowledge on potential disease-related greater micronutrient needs to maintain redox homeostasis and, thus, there exist no specific recommendations for an adequate intake in patients who are critically ill. However, for several years, targeted approaches to optimize micronutrient status and, thereby, maintain or restore redox homeostasis to improve patient outcomes have been gaining increasing attention in clinical research. In this context, the vitamins C and D, as well as the

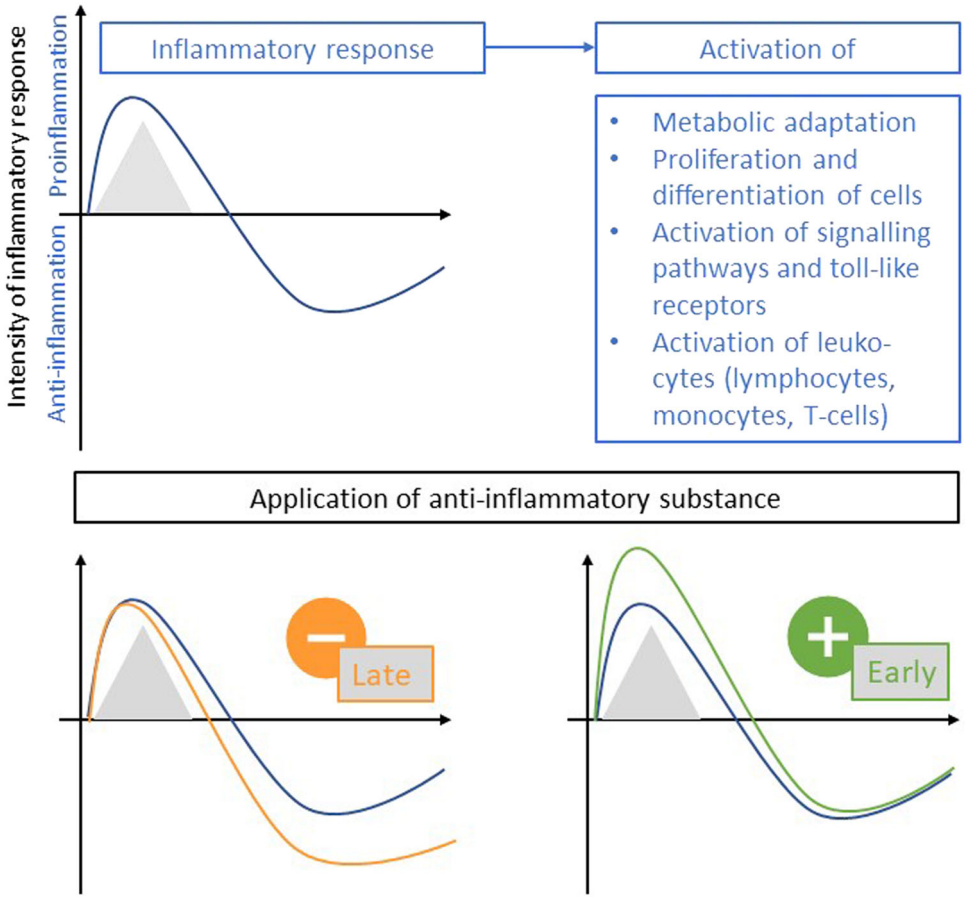

FIGURE 1 Inflammatory and immune response in acute critical illness and hypothetical influence of early and late antioxidant supplementation. The early period of the inflammatory and immune response is characterized by hyperinflammation with release of proinflammatory markers, which activate various beneficial pathways (eg, metabolic adaptation, proliferation and differentiation of cells, activation of signaling pathways and toll-like receptors, and activation of leukocytes). This response is followed by a rapid decrease of inflammation resulting in a phase of immunosuppression, where anti-inflammatory mechanisms play a predominant role. Whereas a late start of anti-inflammatory strategies seems to reduce the activation of signaling processes involved in adaptive and innate immunity, early approaches might be beneficial for optimal regulation of endogenous defense mechanisms

trace elements selenium and zinc, are of special interest and discussed in the following chapters.

5 | VITAMIN C

Vitamin C (ascorbic acid) is an essential, water-soluble vitamin acting as cofactor in several enzymatic reactions and having antioxidative properties. In general, vitamin C is essential for several physiological functions (Figure 2) such as the synthesis of catecholamines, functionality of the immune cells, preservation of endothelial barrier, synthesis of collagen, cortisol, neurotransmitters (eg, noradrenalin, serotonin), and peptide hormones (eg, vasopressin), and the metabolism of iron and folic acid.[14,27] As an antioxidant, vitamin C may further limit the formation of ROS by inhibiting NOX and iNOS. Moreover, vitamin C directly acts as scavenger or quencher of radicals. In this context, vitamin C also plays a key role in the regeneration of alpha-tocopherol (vitamin E) from alpha-tocopheroxyl radicals, which are generated through binding of lipid peroxyl radicals and, thereby, stopping the lipid peroxidation chain reaction. Even though this latter process generates a mild pro-oxidative ascorbyl radical, the benefit of eliminating the much more harmful lipid peroxyl radicals predominates. Furthermore, vitamin C is a substrate of the ascorbate peroxidase (conversion of hydrogen peroxide into water) and prevents the adhesion of phagocytes and concomitant endothelial damages through ROS.[14,28]

In general, vitamin C status can be determined either by measurement of plasma or leukocyte levels using enzymatic and chromatographic assays or by measurement of the oxidation-reduction potential.[29] However, status measurement has not yet been implemented in routine clinical practice due to the limited practicability of analytical procedures in daily care and the difficulty in interpreting the results in the context of a pathophysiologic picture of biochemical markers.

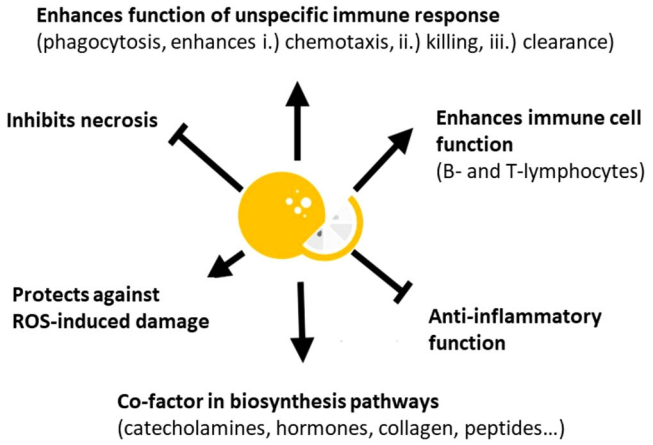

FIGURE 2 Physiological functions of vitamin C. Due to its pleiotropic functions, vitamin C regulates several mechanisms involved in the response to inflammation and oxidative stress. ROS, reactive oxygen species

As the human body is unable to synthesize vitamin C, dietary intake via fruits and vegetables is essential to maintain physiological functions. For healthy adults, a reference value for vitamin C intake of 95–125 mg/day is recommended to keep plasma levels of ≥50 mcmol/L (adequate status).[30] In contrast, low vitamin C levels in patients who are critically ill have been frequently reported in clinical trials, especially in those with sepsis and cardiac surgery.[31–33] Higher dosages might be needed to counteract disease-related depletion and deficiencies. Recently, the "ESPEN Micronutrient guideline" recommends providing ≥100 mg vitamin C/day/1,500 kcal enteral nutrition (EN) and 100–200 mg/day through parenteral nutrition (PN).[15] Moreover, higher dosages of 200–500 mg/day may be indicated during chronic oxidative stress (eg, diabetes, heart failure, dialysis), whereas for patients who are critically ill an intravenous dosage of 2–3 g/day may be indicated during acute inflammatory phases.[15]

Nevertheless, as knowledge on the optimal vitamin C dosage and application timing to counteract depletion and deficiencies during critical illness in general and especially in specific patient populations (eg, cardiac surgery, burn) is still limited and previous research findings highly debatable, these aspects are of special interest in current research.

A few systematic reviews and meta-analyses (SRMAs)[34–37] published recently evaluated the effects of intravenous high-dose vitamin C, either as monotherapy or combined with other antioxidative substrates (eg, thiamin, hydrocortisone), on diverse outcome parameters. Therein, no significant effects of intravenous high-dose vitamin C monotherapy on short-term mortality, but a trend towards reduction in overall mortality was observed. Moreover, high-dose vitamin C monotherapy was associated with a decrease in the duration of vasopressor use and the Sequential Organ Failure Assessment (SOFA) score (at 72–96 h).[35,36] Furthermore, a combined supplementation of high-dose vitamin C and other antioxidants showed improvements in SOFA score (at 72 h)[34] but did not significantly affect long-term mortality.[37] Overall, no effects of high-dose vitamin C either as monotherapy or combined with other antioxidants on further patient outcomes such as development of acute kidney injury,[34] days without mechanical ventilation,[35] ICU and hospital LOS could be observed.[35–37] But, due to great heterogeneity in study methodology such as patient population (eg, general surgical, trauma, head injury, sepsis), intervention (monotherapy vs antioxidant mixture), and dosage (500–24,000 mg/day) of the studies included in the SRMAs, the results should be considered with caution. Nevertheless, the SRMAs support a potential beneficial role of high-dose intravenous vitamin C monotherapy in routine clinical practice to improve patient outcome.[38]

To strengthen the evidence on these metrics, several RCTs evaluating the effects of an intravenous vitamin C monotherapy to improve the clinical outcome of specific patient populations, for example, septic patients (LOVIT, NCT03680274), burn patients (VICToRY, NCT04138394), and cardiac surgery patients (advanceCSX, EudraCT-Number: 2019-001086-32), have already been planned and at least partially started recruitment.

6 | VITAMIN D

Vitamin D is an essential, fat-soluble micronutrient, that is mainly synthesized endogenously in the skin from cholesterol by exposure to sunlight. Vitamin D is found in fatty fish, specific mushrooms, and eggs, but dietary intake cannot adequately cover the individuals' need. Besides its typical functions in bone metabolism by regulating calcium homeostasis, vitamin D also plays a key role in many endocrinologic and immunologic mechanisms. The nuclear vitamin D receptors found on macrophages, B- and T-cells, and organs have gene-regulating functions and, thereby, vitamin D affects the immune system's response to acute systemic inflammation and infection, the functionality and metabolism of muscles, cardiac functions, and the integrity of the lung epithelial cells.[39,40] In the patient who is critically ill, vitamin D levels are significantly reduced due to missing sunlight, which is essential for the endogenous synthesis of cholecalciferol (vitamin D_3) from 7-dehydrocholesterol in the skin, and the necessity for specific EN/PN products low in vitamin D by nature. Consequently, there occurs a decrease in inactive (25-hydroxycholecalciferol, calcidiol) and active (1,25-dihydroxycholecalciferol, calcitriol) vitamin D, which further might impair physical functions of several organs such as the muscles, lung, kidney, heart, nerve system, and immune system (Figure 3).[28]

In general, vitamin D status is determined by chromatographic analysis of serum (or plasma) concentration of total 25-hydroxyvitamin D (25-OHD, inactive form/precursor of active 1,25-dihydroxyvitamin D [1,25-OHD]), which has been established as valid biomarker implemented in routine laboratory analysis in clinical practice.

For healthy adults, the estimated value on adequate intake of vitamin D is defined as 20 mcg/day, in the case of inadequate endogenous synthesis, to maintain a serum 25-OHD level of at least 50 nmol/L.[41] Although seasonal vitamin D hypovitaminosis is frequently observed in the general (healthy) population, low 25-OHD levels have been shown commonly in patients in the ICU, either preexisting at ICU admission or developing during medical treatment, for example, due to nonexposure to sunlight, medical treatment, and nutrition therapy via EN and PN. In general, vitamin D deficiency during critical illness has frequently been shown to be associated with poor clinical outcome (eg, longer duration of respiratory support and ICU LOS, increased severity of lung injury).[39,42] Therefore, current clinical nutrition guidelines recommend that EN should provide ≥1,000 IU vitamin D/day/1,500 kcal (25 mcg) and PN ≥ 200 IU (5 mcg).[15] Moreover, supplementation of high-dose vitamin D (500,000 IU) as bolus within the first week of ICU admission or, alternatively, 50,000 IU/week over a period of 8 weeks is indicated in the case of 25-OHD serum levels <12.5 ng/ml and <50 nmol/L, respectively.[15,24] In addition, 4,000–5,000 IU/day (100 mcg) over a period of 2 months should be given in patients with recurrent 25-OHD levels of 40–60 ng/ml.[15]

A meta-analysis published in 2017 including seven RCTs (n = 716 patients) showed significantly lower mortality risk (odds ratio [OR], 0.70; 95% CI, 0.50–0.98; P = 0.04) in patients receiving vitamin D compared with placebo and, thus, indicates benefits on patient outcome.[43] Accordingly, in 2018, an SRMA including six RCTs (n = 695 patients) showed no benefits of daily vitamin D doses >300,000 IU on patient clinical outcome (eg, mortality, ICU and hospital LOS, infection rates, ventilator-free days) compared with

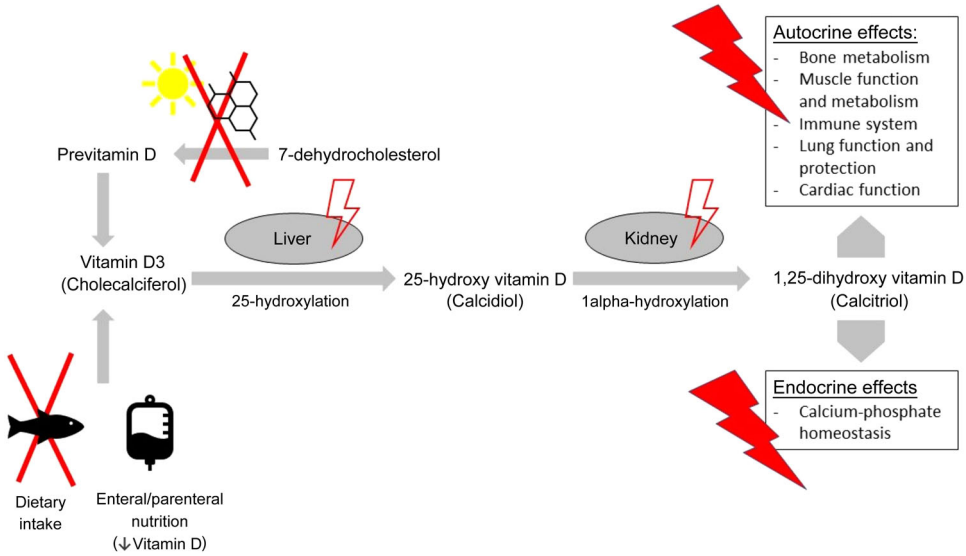

FIGURE 3 Alterations in vitamin D metabolism and impairments in organ functions during critical illness. Patients who are critically ill frequently show decreased vitamin D levels resulting from the significantly differing diet (low vitamin D) and from the missing exposure to sunlight, which is essential for the endogenous synthesis of cholecalciferol (vitamin D3) from 7-dehydrocholesterol in the skin. In the following, there occurs a decrease in inactive (25-hydroxycholecalciferol, calcidiol) and active (1,25-dihydroxycholecalciferol, calcitriol) vitamin D, which further might impair physical functions of several organs (eg, muscles, lung, kidney, heart, nerve system, and immune system)

placebo. To further strengthen the evidence on the role of high-dose vitamin D supplementation during critical illness in improving overall patient outcome, several RCTs have been performed or are still ongoing. Exemplarily, in 2019, the "Vitamin D to Improve Outcomes by Leveraging Early Treatment (VIOLET)" study was published, which investigated the effects of an enteral bolus of 540,000 IU vitamin D compared with placebo on patient outcome (eg, 90-day mortality, ventilator-free days, and development of acute respiratory distress syndrome [ARDS]) in patients with serum levels <20 ng/dl. Despite an increase in serum vitamin D levels (baseline: all patients, 11 ng/dl; day 3: intervention, 47 ng/dl; placebo, 11 ng/dl), no effects on the aforementioned outcome parameters could be observed.[44] Currently, several RCTs investigating vitamin D in patients who are critically ill are still running, for example, the "Effect of High-dose Vitamin D_3 on 28-day Mortality in Adult Critically Ill Patients (VITDALIZE)" study, which analyzes the effects of combined vitamin D and medium-chain triglycerides (MCT) compared with MCT alone on 28-day mortality (primary outcome).[45] However, based on current evidence, high-dose enteral vitamin D supplementation should not be routinely provided to critical illness, but parenteral vitamin D supplementation might be promising.

7 | SELENIUM

As essential micronutrient in mammals, selenium plays a key role in the synthesis of selenocysteine, which is indispensable for the functionality of selenoproteins involved in several endogenous antioxidant defense mechanisms.[46] In specific, selenium is involved in the functionality of antioxidant enzymes (eg, catalase, SOD, GPx) and, thus, contributes to the neutralization of ROS/RNS. Through binding to the selenoproteins, the capacity of selenium to act as antioxidant increases leading to modulation of ROS by inhibition of the nuclear factor-kappa B (NF-κB) cascade and following suppression of interleukins and TNF-α, thus, influencing the inflammatory response (Figure 4).[47]

In general, actual selenium status can be determined through serum/plasma levels using fluorometric methods (eg, carbon furnace atomic absorption spectroscopy assay, inductively coupled plasma mass spectroscopy [ICP-MS]) as well as enzymatic measurement of GPx activity in plasma, erythrocytes, thrombocytes, or whole blood, and the concentration of SPP, the major selenoprotein in serum/plasma, accounting for about 60% of the total plasma selenium.[48]

For healthy adults, the estimated values for selenium intake are 70 mcg/day (men) and 60 mcg/day (women), respectively.[49] In patients who are critically ill, significant selenium deficiency resulting in inadequate endogenous antioxidative capacity has been described manifold.[50] Moreover, several observational studies have shown an association of the systemic inflammatory response with reduced plasma selenium concentration and plasma GPx activity being inversely correlated with the severity of illness and clinical outcomes.[51] Thus, current clinical nutrition guidelines recommend that EN should provide 50–150 mcg selenium/day/1,500 kcal and PN

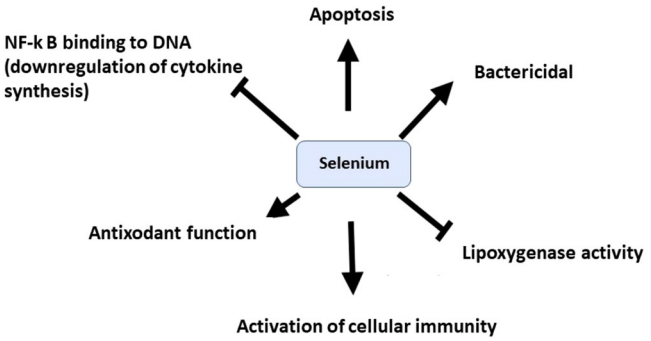

FIGURE 4 Antioxidative/anti-inflammatory defense mechanisms of selenium. Due to its pleiotropic properties, selenium is involved in diverse antioxidative and anti-inflammatory defense mechanisms (arrows: induction; blunt ends: inhibition). DNA, deoxyribonucleic acid; NF-κB, nuclear factor "kappa-light-chain-enhancer" of activated B-cells

60–100 mcg/day. Moreover, in the case of plasma selenium levels <0.4 mcmol/L (<32 mcg/L) 100 mcg selenium/day should be administered until normal levels have been achieved.[15]

However, especially patients with burn, major trauma, and cardiac surgery, or those receiving renal replacement therapy may have higher requirements, but knowledge on the adequate intake amounts in these patients is still limited.[15] Therefore, the effects of selenium supplementation in patients who are critically ill are still subject of current research and should be monitored even through a prolonged ICU stay, if possible. In 2019, an RCT (n = 40 patients with ARDS) investigating the effects of sodium selenite on serum selenium levels, inflammation, and pulmonary function compared with placebo was published.[52] The results indicate that selenium supplementation modulates inflammatory responses and improves lung functions and thus, may beneficially affect patient clinical outcome.[52] Recently, an SRMA[53] showed that intravenous selenium supplementation, either as monotherapy or combined with other antioxidants, had no effects on mortality and ICU or hospital LOS, but may be associated with a reduction in infectious complications and days on mechanical ventilation in patients who are critically ill. However, due to a great methodological heterogeneity (eg, enteral vs parenteral route, high vs low dosage, septic vs nonseptic patients, monotherapy vs combined supplementation with other antioxidants), the effects of selenium supplementation in patients who are critically ill remain debatable.[54] But, as selenium supplementation may show different effects on patient clinical outcome depending on underlying disease and severity of illness, there is an urgent need to strengthen the evidence on these metrics by focusing on specific patient populations and using more comparable study procedures.

In this context, to date, the "Sodium Selenite Administration in Cardiac Surgery (SUSTAIN)" trial is the largest RCT (NCT02002247) evaluating the effect of high-dose perioperative selenium in high-risk cardiac surgery patients and resulting data are expected to be published soon.[50]

8 | ZINC

The essential trace element zinc is needed for maintaining physiological immune system functions, metabolic control (ie, glucose), neurocognitive mechanisms, and the response to oxidative stress. As cofactor of >300 enzymes, zinc is essential for DNA synthesis, proliferation of cells, synthesis of proteins, and the integrity of the cell membrane.[14]

Measurement of zinc status can be performed in whole blood, plasma, serum, urine, and hair using ICP-MS or atomic absorption spectroscopy.

For healthy adults, the reference values are set at 7–10 mg/day (women) and 11–16 mg/day (men), respectively, depending on the concomitant daily phytate intake.[55] In patients in the ICU, low zinc status has frequently been observed, for example, resulting from preexisting deficiencies at admission, following the inflammatory response during the acute phase of critical illness, and occurring due to treatment-related loss/increased needs (eg, through drains and exudates),[14,56] and might be associated with worse clinical outcome (eg, increased 28- and 90-day mortality).[57] Accounting for the disease- and treatment-related increased losses/needs, current clinical nutrition guidelines recommend that EN should provide ≥10 mg zinc/day/1,500 kcal and PN 3–5 mg/day (in the case of normal losses). Furthermore, in patients with increased gastrointestinal losses due to diarrhea, fistula, and stomas, intravenous zinc administration can be increased up to 12 mg/day for as long as needed to achieve an adequate status.[15] Although there are already given recommendations for burn patients (30–35 mg zinc/day intravenously over 2–3 weeks),[15] no suggestions for other specific patient populations (eg, septic and surgical patients) are available to date.

However, due to its functional properties (ie, for maintaining redox homeostasis), there is an urgent need for further high-quality research investigating these metrics as knowledge on zinc requirements during critical illness and especially in different patient populations is still limited. Recently, the current evidence on zinc supplementation (monotherapy or combined with other antioxidants) in patients who are critically ill, has been aggregated and meta-analyzed.[58] The results indicate that intravenous zinc supplementation may be associated with reduced overall mortality in patients who are critically ill.[58] But the interpretation of these results might be limited by methodological differences of the included trials, for example, small sample size, predominantly including patients with burns and head trauma, overall zinc delivery (different dosages, monotherapy vs micronutrient mixture). Therefore, to strengthen the evidence on the effects of (high-dose) zinc supplementation in different populations of patients who are critically ill, further high-quality RCTs are warranted. But until more valid data will be available, high-dose zinc monotherapy (or combined administration with other micronutrients) should not be performed routinely in clinical practice.

9 | SPECIFIC PATIENT COHORTS AT RISK

9.1 | Burn patients

Burn physiology makes patients with a severe burn a very compelling target for interventions with antioxidant compounds, especially as increased endothelial permeability is believed to play a fundamental role in the large fluid requirements during resuscitation in this population.[59,60] High doses of vitamin C supplementation during initial fluid resuscitation have been studied in patients with a severe burn and have shown mixed results.[59–66] Small retrospective studies have suggested clinical benefit (eg, improved inflammatory markers, decreased early and overall fluid requirements) with early administration of vitamin C and trace elements in patients with a severe burn.[62–66] Additionally, a nationwide cohort sample from Japan (157 patients receiving at least 10 g of vitamin C within 2 days of burn unit admission vs 628 contemporaneous patients) showed overall improvement in survival when patients received >10 g vitamin C (relative risk [RR], 0.79; $P = 0.0006$). However, the survival advantage seemed to disappear when looking specifically at the patients within this group that received the higher doses of vitamin C > 24 g (RR, 0.68; $P = 0.068$). The latter highlights the challenges of interpreting these retrospective studies.[60] Moreover, clinical trial data have shown no survival benefit after administration of high doses of vitamin C in burn patients, although some benefits regarding decreased volume of fluid resuscitation has been reported.[61,65] It is important to highlight, however, that the numbers of patients on these trials were very small and limited power for diverse secondary outcomes cannot be excluded. Therefore, definitive conclusions for this population cannot be drawn.

9.2 | Patients with severe acute respiratory syndrome coronavirus type 2

Ample evidence supports the use of antioxidants in the management of some respiratory illnesses of viral origin.[67,68] In this context, use of antioxidants to improve outcomes in patients with severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) has been suggested and extensively studied. The most studied antioxidants have been vitamin C and D. For vitamin C, a recent observational study and subsequent meta-analysis ($n = 11$ studies) by Gavrielatou et al compiled approximatively 1,800 patients with coronavirus disease 2019 (COVID-19) (vitamin C supplementation: $n = 515$; control: $n = 1,292$) and showed no significant survival benefit after the administration of high doses of vitamin C when compared with the standard of care.[66] Vitamin D supplementation on the other hand seems to be more promising. In a meta-analysis including eight articles (vitamin D supplementation: $n = 786$; control: $n = 1,536$), the authors found a significant improved rate of ICU admissions, a decreased need for mechanical ventilation, improved 14-day and in-hospital mortality for the intervention group, suggesting that the vitamin D supplementation could be very

effective as an adjuvant therapy in patients with COVID-19.[68] Other antioxidants have been studied, including N-acetylcysteine (NAC). A recent retrospective cohort from Spain reported 2,071 patients treated with this intervention and compared with 17,137 concurrent patients hospitalized with COVID-19 diagnosis and not receiving NAC. The authors observed a significantly lower mortality (OR, 0.56; 95% CI, 0.47–0.67) associated with treatment with high doses of NAC (600 mg orally every 8 h), even after adjusting for comorbidities and steroid administration.[69] Interestingly, however, the duration and compliance with therapy was not reported in this study, making understanding these data a bit complicated. Currently, there are multiple studies underway that, we hope, can bring more clarity to the utility of the NAC administration for these patients.[70] Regarding zinc, a meta-analysis ($n = 4$ studies) including 761 patients receiving zinc supplementation compared with 712 receiving standard care showed a slight increase in the length of ICU stay and no improvement in the overall survival for the study group, suggesting that there is no evidence to support zinc supplementation in hospitalized patients with COVID-19.[71] Generally, the use of natural bioactive compounds (eg, zinc + polyphenols) is subject of current research and might be a promising approach to affect the immune system's response to illness.[72,73]

9.3 | Patients on ECMO or cardiac surgery

ECMO therapy is proposed to lead to multiple alterations in serum inflammatory markers, as well as in the overall free radical activity, with an associated decreased bioavailability of micronutrient and trace elements.[73,74] Antioxidant supplementation has been proposed to ameliorate this proinflammatory state.[21,73] Among the antioxidants studied the evidence supporting vitamin C supplementation, especially in cardiac surgery patients, is the strongest, revealing shorter ICU and hospital LOS, a decrease in mechanical ventilation requirement, and lower incidence of atrial fibrillation.[75]

9.4 | Outlook

Due to their physiological functions in the human biology, micronutrients play a key role in maintaining the redox and inflammatory homeostasis and, thereby, might be promising to positively affect the stress response during critical illness. Moreover, significant micronutrient repletion/deficiencies have been observed manifold in routine clinical care. But as detailed above, investigations on the micronutrient needs in patients who are critically ill, and especially in specific subgroups, are still lacking and under current investigation. Recommendations for micronutrient use during ICU stay are still currently limited to recommendations to overcome deficiencies. Therefore, there is an urgent need for well-designed and adequately powered RCTs focusing on specific patient populations (eg, burn or cardiac surgery patients), application (monotherapy vs mixture, EN vs PN), dosing (high vs low), and timing (early vs late phase) in a more comparable way to strengthen the evidence on these metrics (Figure 5).

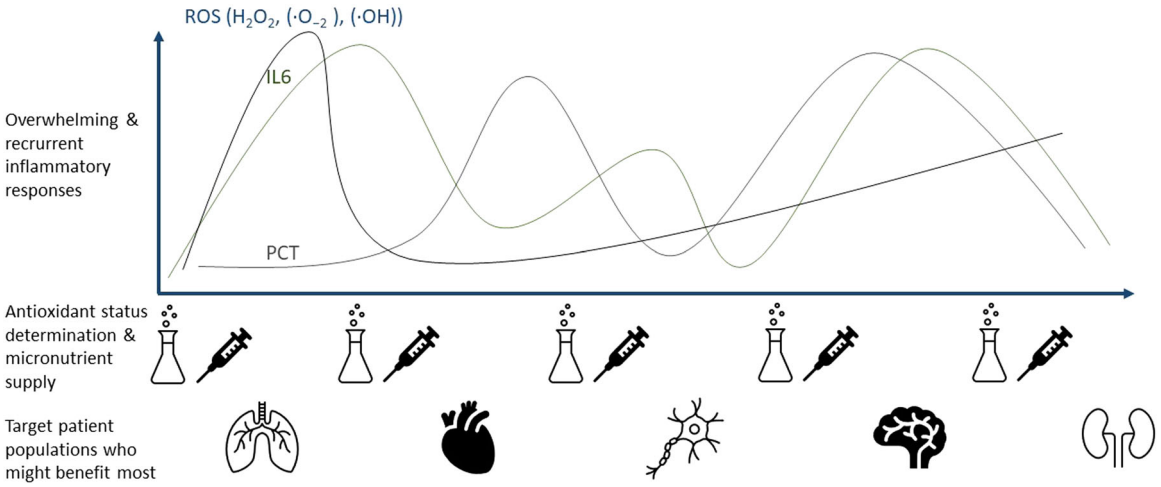

FIGURE 5 Perspectives/targets of future research on the role of micronutrients in oxidative stress in critical illness. During critical illness, the patients are exposed to an overwhelming and recurrent inflammatory response that may lead to the development of organ dysfunctions. Due to their antioxidative properties, micronutrients might contribute to reduce inflammatory responses and to restore redox homeostasis. For this reason, a frequent concomitant measurement of micronutrients and the inflammatory response (for example by C-reactive protein) should be established especially in patients with prolonged intensive care unit length of stay, so that existing deficiencies can be compensated accordingly to optimize the anti-inflammatory and antioxidant defense mechanisms. Further research is needed regarding antioxidant status determination (frequency, surrogate parameters), targeted micronutrient supply (timing, dosage, frequency, monotherapy vs mixture), and target patient populations that might benefit most from micronutrient therapy. IL-6, interleukin-6; PCT, procalcitonin; ROS, reactive oxygen species

10 | CONCLUSION

Micronutrients represent essential antioxidative and anti-inflammatory components for maintaining the inflammatory and redox homeostasis in health and disease. Especially during critical illness, micronutrient deficiency and its association with deleterious outcomes have been observed manyfold, indicating a key role in the metabolic and immunologic stress response. Based on current evidence, restoring the balance between reductants and oxidants early during the ICU stay might be beneficial to improve overall patient outcome, whereas strong evidence for pharmacotherapy with excess loading with either single antioxidative compounds or antioxidant cocktails is still missing, even though data on vitamin C still lend some promise.[38] Despite the clear biological rationale about the key role of micronutrients within human biology and the bodies' inflammatory, antioxidant, and immune defense, results of adequately designed large scale RCTs in specific subpopulations of patients who are critically ill are urgently needed to clarify potential beneficial effects of high-dose antioxidants on the outcomes of patients who are critically ill.

AUTHOR CONTRIBUTIONS

Ellen Dresen and Christian Stoppe equally contributed to the conception and design of this manuscript. Ellen Dresen, Jose M. Pimiento, and Christian Stoppe drafted the manuscript. Ellen Dresen, Jose M. Pimiento, Jayshil J. Patel, Daren K. Heyland, Todd W. Rice, and Christian Stoppe critically revised the manuscript and agree to be fully accountable for ensuring the integrity and accuracy of the work. Ellen Dresen, Jose M. Pimiento, Jayshil J. Patel, Daren K. Heyland, Todd W. Rice, and Christian Stoppe read and approved the final manuscript.

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CONFLICT OF INTEREST

All authors declare no conflict of interest related to the topic of this manuscript. Jose M. Pimiento, Jayshil J. Patel, Daren K. Heyland, Todd W. Rice, and Christian Stoppe had talks on parts of this topic at the *ASPEN 2022 Nutrition Science & Practice Conference*. The content of this article was presented during the course, Comprehensive Nutrition Therapy: Tactical Approaches in 2022 (March 25, 2022), which was organized by the ASPEN Physician Engagement Committee and preceded the ASPEN 2022 Nutrition Science & Practice Conference. The author(s) received a modest monetary honorarium. The conference recordings were posted to the ASPEN eLearning Center https://aspen.digitellinc.com/aspen/store/6/index/6.

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