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WHAT'S NEW IN INTENSIVE CARE

Vitamin therapy in critically ill patients: focus on thiamine, vitamin C, and vitamin D

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Introduction

Recent hypothesis-generating studies have sparked new interest in an old concept: adjuvant vitamin therapy in critical illness or "metabolic resuscitation". In this mini-review, we report on the most promising players in this setting: thiamine (vitamin B1), vitamin C, and vitamin D. Their main characteristics are summarized in Table 1 (see also electronic supplementary material, ESM).

Thiamine

Function

Thiamine is the precursor of thiamine pyrophosphate (TPP), the essential coenzyme of several decarboxylases required for glucose metabolism, the Krebs cycle, the generation of ATP, the pentose phosphate pathway, and the production of NADPH [1, 2].

Thiamine and acute illness

Apart from lactic acidosis due to failure of pyruvate to enter the Krebs cycle, two potentially fatal deficiency conditions are known: cardiac (or wet) beriberi, and Gayet–Wernicke encephalopathy. Thiamine deficiency was first described in critically ill patients in the 1980s and is recognized as being associated with mortality [2]. Hypermetabolic states and parenteral nutrition without micronutrients predispose to acute deficiency of thiamine [1]. Thiamine deficiency is present in 20–70% of septic shock patients, depending on the cutoff value used [2]. Analytical issues associated with TPP determination in inflammation complicate the diagnosis of deficiency. High-performance liquid chromatography (HPLC) on whole blood together with erythrocyte determination represents the most reliable method (ESM).

Dose and future

Preventive interventions have shown controversial results. A randomized trial using a single dose of 300 mg thiamine versus placebo before elective cardiac surgery [3] normalized plasma thiamine without affecting postoperative lactate concentrations.

In contrast, the metabolic effects of thiamine justify further investigations in sepsis. A randomized trial conducted in 88 septic shock patients (2×200 mg thiamine/day for 7 days) showed decreasing lactate levels. A significant difference in time to death was observed in favor of thiamine ($P = 0.047$), with lower mortality (13 versus 46% in controls) in the subgroup of patients with deficiency [4]. The post hoc analysis showed that the thiamine group had lower creatinine levels with less progression to renal replacement therapy than the placebo group [5]. In a highly controversial, small before–after trial, a combination of thiamine, hydrocortisone, and vitamin C in sepsis was associated with a large reduction of organ dysfunction [6]; this finding requires validation. In view of the current evidence, the low risks, and the low costs, administration of liberal amounts of thiamine (300 mg I.V. daily in at-risk patients and 100 mg in all other patients during the first 48 h in the ICU) should be considered as it enables metabolic handling of dextrose 5%.

Vitamin C

Vitamin C (ascorbate) has pleiotropic effects. During critical illness, acute deficiency of vitamin C is common (eTable 2, ESM) but generally goes unnoticed because the symptoms mimic critical illness and rapid measurement of plasma concentrations is not available. Acute vitamin C deficiency may contribute to hypotension, exaggerated inflammation, capillary leakage,

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Table 1 The characteristics of thiamine, vitamin C, and vitamin D and the symptoms and management of deficiency

	Thiamine	Vitamin C	Vitamin D
Other names	Vitamin B1	Ascorbic acid	Native forms D3: cholecalciferol D2: ergocalciferol Active form Calcitriol
Molecular characteristics	Water-soluble	Water-soluble	Fat-soluble
Formula	$C_{12}H_{17}N_4OS$	$C_6H_8O_6$	D3: $C_{27}H_{44}O$
Molar mass (g/mol)	265.35	176.12	D3: 384.64
Source	Diet (seeds, legumes, rice, cereals, corns, pork, spinach)	Diet [fruits and vegetables (lost by long cooking)]; supplements	Mainly from skin: synthesis from cholesterol elicited by sun exposure (UVB radiation); diet (fatty fish); supplements
Excretion	Renal Daily loss with CRRT ± 4-5 mg/day	Renal Daily loss with CRRT ± 70 mg/day	Bile/feces and renal Catabolizing enzymes Daily loss with CRRT unknown
Risk of deficiency	Poor diet Alcoholism Hypermetabolism Increased loss (CRRT)	Poor diet Oxidative stress: sepsis, ischemia–reperfusion, trauma, burns, CRRT Increased loss (CRRT)	Low sun exposure Comedication Obesity Dark skin Chronic disease Malnutrition
Stores and time to deficiency	Half-life of 18 days. Stores are rapidly depleted when metabolic demands are high	In otherwise healthy persons, scurvy develops in 4–8 weeks. Stores are rapidly depleted if oxidative stress is high	Half-life of 2–3 weeks Metabolism in acute illness unknown
Functions	Coenzyme for glucose metabolism, Krebs cycle, generation of ATP, pentose phosphate pathway, NADPH production	Donation of electrons Cofactor/co-substrate Anti-oxidant Anti-inflammatory and immune-promoting actions	Classic: regulation of intestinal calcium absorption Nonclassic: cell-specific regulation of transcriptional activity, inhibition of PTH secretion, promotion of insulin secretion, regulatory action on adaptive and innate immunity, inhibition of cell proliferation, stimulation of differentiation
Clinical consequences of deficiency	Lactic acidosis Wet beriberi: high-output cardiac failure Dry beriberi: polyneuropathy, muscle weakness, confusion, ataxia, nystagmus Wernicke–Korsakoff encephalopathy	Scurvy Poor wound healing Lassitude, depression Hypotension Capillary leakage Bleeding Infections	Rickets (children) Osteomalacia (adults) Unspecific or absent symptoms Musculoskeletal pain in some cases
Side effects, toxicity	Unknown	Oxalate nephropathy (ESM) in susceptible persons	Hypercalcemia Acute renal failure Nephrocalcinosis

Table 1 continued

	Thiamine	Vitamin C	Vitamin D
Recommended dose[a]	Healthy persons: 1.5 mg/day Acute critical illness: 100–300 mg/day CRRT: 100 mg/day of therapy to safely compensate effluent losses	Healthy persons: 200 mg/day Acute critical illness: 2–3 g/day iv to correct deficiency (ESM) Chronic critical illness: 0.2–1 g/day? Dialysis/hemofiltration: 0.5–1 g/day Burns: 0.5–1 g/day	Native vitamin D3 or D2 Healthy persons: 600–800 IU/day Risk groups: 1500–2000 IU/day Safe dose: up to 10 000 IU/day Acute critical illness: unknown Dialysis/CRRT: unknown

CRRT continuous renal replacement therapy, *ATP* adenosine triphosphate, *NADPH* nicotinamide adenine dinucleotide phosphate

[a] Recommendations are based on expert opinion after careful appraisal of the literature. Recommended doses are needed for repletion of deficiency or maintenance of safe and normal plasma concentrations during critical illness (ESM)

microcirculatory compromise, oxidative organ injury, and impaired immune defense and wound healing.

Function

Vitamin C is an electron donor, which accounts for its myriad functions [7]. It is cofactor/cosubstrate for the biosynthesis of neurotransmitters (noradrenaline, serotonin), cortisol, peptide hormones (vasopressin), and collagen. Vitamin C is the most potent water-soluble antioxidant. It directly scavenges radicals and recycles other antioxidants, and protects the endothelium by promoting collagen synthesis and maintaining endothelial vasodilation and barrier function [8]. Vitamin C can limit the inflammatory response and ischemia–reperfusion injury, improve host defense, wound healing, and mood, and reduce pain (ESM).

Vitamin C and acute illness

Critical illness abruptly increases vitamin C requirements (ESM). Activated neutrophils accumulate vitamin C, while the adrenals secrete accumulated vitamin C, triggering cortisol production [7]. Although redistributed, vitamin C is likely lost during cell degradation. Furthermore, while some of the oxidized vitamin C is normally recycled, some is lost if reducing mechanisms fail [7]. Additionally, vitamin C is consumed during the synthesis of norepinephrine, peptide hormones, and cortisol.

Dose and future

The optimal dose and plasma concentration of vitamin C remain unknown. Several trials (eTable 2, ESM) using a repletion dose (0.5–3 g/day) reported improved recovery from organ failure [8]. The results of recent preliminary trials (eTable 3, ESM) suggest that a short course of pharmacological doses in severe sepsis (50–200 mg/kg/day or 6 g/day with or without hydrocortisone and thiamine [6]) reduces vasopressor dose and promotes recovery, but the tendency towards lower mortality needs confirmation (eTable 3, ESM) [6, 9, 10]. High doses seem to be safe (ESM). Pathophysiological findings suggest that pharmacological doses of intravenous vitamin C should probably be limited to the early phase, because low levels of radicals are crucial for (intra)cellular signaling.

Vitamin D

Humans can produce vitamin D endogenously under conditions of sufficient UVB exposure. Vitamin D is a precursor to a steroid hormone with a specific nuclear receptor (vitamin D receptor) present in a variety of different cell types and organs.

Function

Vitamin D acts via pleiotropic, cell-specific genomic and nongenomic pathways [11]. Target organs that are particularly relevant in the ICU include muscle, lung, heart, immune system, and kidney. In contrast to vitamin C and thiamine, testing for vitamin D is fast, widely available, and sufficiently reliable.

Vitamin D and acute illness

Depending on definition and population, vitamin D deficiency [usually defined as serum 25(OH)D $\leq$ 20 ng/ml] is present in 30–60% of ICU patients worldwide. Since 2009, observational studies have clearly shown that vitamin D deficiency is linked to excess morbidity and mortality in adults and children in the ICU [12]. Preliminary data using novel methods suggest that glutathione and glutamate pathway metabolism, which are important for redox regulation and immunomodulation, are affected by vitamin D status [13].

So far, worldwide < 700 patients have been treated for vitamin D deficiency in a very limited number of randomized controlled intervention trials, recently summarized in different meta-analyses [14]. The VITdAL-ICU study (n = 475) did not find a difference in the length of hospital stay between groups, but there was a significant reduction in mortality in the predefined subgroup of patients with severe vitamin D deficiency [15]. The most recent meta-analysis concludes that vitamin D in the ICU may be associated with mortality reduction [12].

Dose and future

The optimal native vitamin D dose in critical illness is unknown, but up to 10,000 IU daily is considered safe; the standard dose of 600–800 IU, however, is ineffective in the acute setting. The logical question, "Can vitamin D supplementation during or before critical illness improve outcomes?", is currently the subject of intensive research aiming to include > 5000 patients in the VIOLET study (NCT03096314) and the VITDALIZE study (NCT03188796).

Summary, conclusions and outlook

Vitamin C, vitamin D, and thiamine are promising micronutrients for adjuvant therapy in severe acute illness. We recommend early supplementation to prevent/treat deficiency (Table 1). Due to increased needs, critically ill patients need amounts higher than the daily recommended dose, but pharmacological dosing requires further studies (ESM).

Important considerations include the following:

- The requirements for vitamin C, vitamin D, and thiamine are likely higher in severe illness than in health (ESM).
- The beneficial effect on clinical outcomes will be greater in depleted subjects.
- Determination of thiamine and vitamin C deficiency is not possible without major delay and may be invalidated by improper sampling.
- A better understanding of the role of micronutrients in critical illness may be achievable by means of novel methods including genomics and metabolomics.
- The time is ripe for pragmatic randomized trials in different high-risk populations exhibiting overwhelming oxidative stress using different treatment regimes.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-018-5107-y) contains supplementary material, which is available to authorized users.

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References

1. Leite HP, de Lima LF (2016) Metabolic resuscitation in sepsis: a necessary step beyond the hemodynamic? J Thorac Dis 8:E552–E557
2. Mallat J, Lemyze M, Thevenin D (2016) Do not forget to give thiamine to your septic shock patient! J Thorac Dis 8:1062–1066
3. Luger M, Hiesmayr M, Koppel P, Sima B, Ranz I, Weiss C, Konig J, Luger E, Kruschitz R, Ludvik B, Schindler K (2015) Influence of intravenous thiamine supplementation on blood lactate concentration prior to cardiac surgery: a double-blinded, randomised controlled pilot study. Eur J Anaesthesiol 32:543–548
4. Donnino MW, Andersen LW, Chase M, Berg KM, Tidswell M, Giberson T, Wolfe R, Moskowitz A, Smithline H, Ngo L, Cocchi MN, Center for Resuscitation Science Research Group (2016) Randomized, double-blind, placebo-controlled trial of thiamine as a metabolic resuscitator in septic shock: a pilot study. Crit Care Med 44:360–367
5. Moskowitz A, Andersen LW, Cocchi MN, Karlsson M, Patel PV, Donnino MW (2017) Thiamine as a renal protective agent in septic shock. a secondary analysis of a randomized, double-blind. Placebo-controlled Trial. Ann Am Thorac Soc 14:737–741

6. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J (2017) Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before–after study. Chest 151:1229–1238
7. Padayatty SJ, Levine M (2016) Vitamin C: the known and the unknown and Goldilocks. Oral Dis 22:463–493
8. Oudemans-van Straaten HM, Spoelstra-de Man AM, de Waard MC (2014) Vitamin C revisited. Crit Care 18:460
9. Fowler AA, Syed AA 3rd, Knowlson S, Sculthorpe R, Farthing D, DeWilde C, Farthing CA, Larus TL, Martin E, Brophy DF, Gupta S, Nursing Medical Respiratory Intensive Care Unit, Fisher BJ, Natarajan R (2014) Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. J Transl Med 12:32
10. Zabet MH, Mohammadi M, Ramezani M, Khalili H (2016) Effect of high-dose Ascorbic acid on vasopressor's requirement in septic shock. J Res Pharm Pract 5:94–100
11. Holick MF (2007) Vitamin D deficiency. N Engl J Med 357:266–281
12. Putzu A, Belletti A, Cassina T, Clivio S, Monti G, Zangrillo A, Landoni G (2017) Vitamin D and outcomes in adult critically ill patients. A systematic review and meta-analysis of randomized trials. J Crit Care 38:109–114
13. Lasky-Su J, Dahlin A, Litonjua AA, Rogers AJ, McGeachie MJ, Baron RM, Gazourian L, Barragan-Bradford D, Fredenburgh LE, Choi AMK, Mogensen KM, Quraishi SA, Amrein K, Christopher KB (2017) Metabolome alterations in severe critical illness and vitamin D status. Crit Care 21:193
14. Amrein K, Martucci G, McNally JD (2017) When not to use meta-analysis: analysing the meta-analyses on vitamin D in critical care. Clin Nutr 36(6):1729–1730
15. Amrein K, Schnedl C, Holl A, Riedl R, Christopher KB, Pachler C, Urbanic Purkart T, Waltensdorfer A, Munch A, Warnkross H, Stojakovic T, Bisping E, Toller W, Smolle KH, Berghold A, Pieber TR, Dobnig H (2014) Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial. JAMA 312:1520–1530