

REVIEW



Vitamin therapy in sepsis

 Eric L. Wald¹✉, Colleen M. Badke¹, Lauren K. Hintz², Michael Spewak³ and L. Nelson Sanchez-Pinto¹✉

© The Author(s), under exclusive licence to the International Pediatric Research Foundation, Inc 2021

ABSTRACT: Vitamins are essential micronutrients with key roles in many biological pathways relevant to sepsis. Some of these relevant biological mechanisms include antioxidant and anti-inflammatory effects, protein and hormone synthesis, energy generation, and regulation of gene transcription. Moreover, relative vitamin deficiencies in plasma are common during sepsis and vitamin therapy has been associated with improved outcomes in some adult and pediatric studies. High-dose intravenous vitamin C has been the vitamin therapy most extensively studied in adult patients with sepsis and septic shock. This includes three randomized control trials (RCTs) as monotherapy with a total of 219 patients showing significant reduction in organ dysfunction and lower mortality when compared to placebo, and five RCTs as a combination therapy with thiamine and hydrocortisone with a total of 1134 patients showing no difference in clinical outcomes. Likewise, the evidence for the role of other vitamins in sepsis remains mixed. In this narrative review, we present the preclinical, clinical, and safety evidence of the most studied vitamins in sepsis, including vitamin C, thiamine (i.e., vitamin B₁), and vitamin D. We also present the relevant evidence of the other vitamins that have been studied in sepsis and critical illness in both children and adults, including vitamins A, B₂, B₆, B₁₂, and E.

Pediatric Research (2022) 91:328–336; <https://doi.org/10.1038/s41390-021-01673-6>

IMPACT:

- Vitamins are key effectors in many biological processes relevant to sepsis.
- We present the preclinical, clinical, and safety evidence of the most studied vitamins in pediatric sepsis.
- Designing response-adaptive platform trials may help fill in knowledge gaps regarding vitamin use for critical illness and association with clinical outcomes.

INTRODUCTION

Sepsis is associated with a significant degree of morbidity and mortality in children worldwide, and new therapies are needed.¹ Vitamins are essential micronutrients, with key roles in many biological pathways relevant to sepsis, including those leading to anti-inflammatory and antioxidant effects.^{2,3} Furthermore, relative vitamin deficiencies in plasma are common during sepsis, and vitamin therapy has been associated with improved outcomes in some observational and randomized control trials of both adult and pediatric patients with sepsis.^{4–7} However, as a whole, the evidence for the role of vitamins in sepsis remains mixed.

In this narrative review, we present the preclinical, clinical, and safety evidence of the most studied vitamins in sepsis, including vitamin C, thiamine (i.e., vitamin B₁), and vitamin D. We also present the relevant evidence of the other vitamins that have been studied in sepsis and critical illness in both children and adults, including vitamins A, B₂, B₆, B₁₂, and E.

VITAMIN C

Vitamin C, also known as ascorbic acid, is a water-soluble essential micronutrient commonly found in plants, especially fruits.⁸ When absorbed, it dissociates at physiological pH to form ascorbate, the

redox state of the vitamin most commonly found in cells. In addition to being a potent antioxidant, vitamin C is a cofactor for enzymes involved in protein and hormone synthesis, metabolic pathways for energy generation, and regulation of gene transcription.⁸ The recommended daily dosage of vitamin C in humans depending on age, gender, and pregnancy state ranges from 15 to 120 mg, far below the parenteral doses used as treatment during sepsis.⁸

Critically ill patients with sepsis are known to have low plasma concentrations of vitamin C, and this depletion has a dose-dependent association with increased organ dysfunction and mortality.⁹ This association with outcomes may be explained by its pleiotropic effects in sepsis-relevant biologic pathways, including (i) acting as an enzymatic cofactor in the production of catecholamines, cortisol, and vasopressin,^{10,11} (ii) scavenging reactive oxygen species (ROS);^{10,11} (iii) preserving capillary blood flow and arteriolar responsiveness to vasoactive medications through effects on redox-sensitive pathways;^{11–13} (iv) protecting against the loss of endothelial function and enhancing lung epithelial barrier function via nitric oxide-dependent pathways;^{12,14,15} (v) regulating the clearance of alveolar fluid by inducing the expression of several protein channels such as aquaporin 5, cystic fibrosis transmembrane conductance

¹Division of Critical Care, Ann & Robert H. Lurie Children's Hospital of Chicago and Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, USA. ²McGaw Medical Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA. ³Division of Hospital Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago and Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, USA. ✉email: ewald@luriechildrens.org; lsanchezpinto@luriechildrens.org

Table 1. Studies in critical illness using vitamin C as monotherapy.

Study/design	Patient, <i>n</i> (intervention/control)	Protocol	Important clinical outcomes
Fowler et al. (2014); ³² RCT	Severe sepsis, <i>n</i> = 24 (8 in high-dose arm; 8 in low-dose arm; 8 controls)	VitC 50 mg (low dose) or VitC 200 mg (high dose)/kg/24 h IV × 96 h vs. placebo	Treatment group experienced significant reductions in SOFA scores, CRP, and PCT compared to the control group
Zabet et al. (2019); ³³ RCT	Surgical patients with septic shock requiring vasopressors, <i>n</i> = 28 (14/14)	VitC 25 mg/kg IV q6 h × 72 h vs. placebo	Mortality reduction; 14.3% mortality in treatment arm vs. 64.3% in placebo, <i>p</i> = 0.009 Decreased vasopressor requirement in the treatment arm
Fowler et al.; ⁵ RCT	Sepsis and ARDS, <i>n</i> = 167 (84/83)	VitC 50 mg/kg IV q6 h × 96 h vs. placebo	Mortality reduction; 29.8% mortality in treatment arm vs. 46.3% in placebo, <i>p</i> = 0.03; reduction in mSOFA scores at 96 h in post hoc analysis ³⁴
Tanaka et al. (2000); ¹³² prospective, randomized	Severely burned patients (burn >30% BSA), <i>n</i> = 37 (19/18)	VitC 66 mg/kg/h IV in LR × 24 h vs. placebo	Decreased fluid requirements, edema, and weight gain in the treatment arm
Ahn et al. (2019); ¹³³ retrospective	Severe sepsis or septic shock requiring mechanical ventilation, <i>n</i> = 75 (35/40)	VitC 2 g IV q8 h until discharge from ICU vs. control	No difference in change in SOFA scores, mortality, or median time to shock reversal
Nakajima et al. (2019); ¹³⁴ retrospective	Severe burn patients (burn index ≥15), <i>n</i> = 785 (157/628)	VitC ≥10 g and <24 g IV or VitC ≥24 g IV	Mortality reduction; 45.9% mortality in ≥10 g treatment arm vs. 58.0% in the control arm (<i>p</i> = 0.006); No difference in ≥24 g arm

VitC vitamin C, LR lactated ringers, PCT procalcitonin, RCT randomized control trial, ICU intensive care unit, [m]SOFA [modified] Sequential Organ Failure Assessment, BSA body surface area, CRP C-reactive protein.

regulator, epithelial sodium channel, and Na-K-ATPase;¹⁶ and (vi) enhancing neutrophil and lymphocyte function while down-regulating pro-inflammatory pathways.^{17,18}

Vitamin C has been studied in sepsis and critical illness for many decades, but it has usually been administered enterally and is generally not proven efficacious.¹⁹ This may be due to limits in absorption, as the intestinal sodium-dependent vitamin C transporter reaches maximal saturation at ~500–1000 mg. Parenteral administration of vitamin C has been shown to raise plasma and cellular levels of the vitamin >70-fold when compared with oral dosing and may protect or restore many of the pathologic changes that occur during sepsis.²⁰ Antioxidant capacity is maximal at a plasma vitamin C level >1000 μmol/L, which is more than ten times normal and can be achieved only with intravenous (IV) administration.²⁰ Furthermore, many of the potentially therapeutic features of vitamin C—such as immune modulation, microcirculatory support, and neuroprotection—are dose-dependent.²¹

Preclinical studies

Effects on vasopressor synthesis and response. Vitamin C is required for two steps along the catecholamine biosynthetic pathway and thus is vital for endogenous catecholamine production.²² It also serves as the cofactor for the enzyme peptidoglycine alpha-monooxygenase, which is required in the synthesis of vasopressin.²³ These properties may protect against catecholamine-resistant shock and vasoplegia and help avoid high concentrations of vasoactive infusions, which can lead to myocardial dysfunction and worsening shock. Studies have shown that vitamin C modulates adrenergic receptor activity in vitro, increasing the potency and duration of beta-agonist effect via receptor-mediated mechanisms in vivo.^{24,25}

Immunogenic properties. Vitamin C has shown in vitro bacteriostatic activity and assistance of oxidative killing of bacteria by leukocytes.²⁶ In animal models, it attenuates lipopolysaccharide-mediated lung injury in sepsis, enhances lymphocytic proliferation, improves chemotaxis, and reduces pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β via inhibition of nuclear factor-kappa B.^{11,17,24}

Microvascular support. Vitamin C inhibits both the activation of nicotinamide adenine dinucleotide phosphate oxidase and

inducible nitric oxide synthase (iNOS) and iNOS expression.¹³ This inhibition reduces ROS, including superoxide and peroxynitrite, which can injure the endothelial barrier by tetrahydrobiopterin (BH₄) deactivation and dephosphorylation of occludin, a key component in tight junctions.¹³ Vitamin C also inhibits the oxidation of BH₄ and recovers it from its oxidized state. BH₄ is the cofactor of endothelial NOS, which is instrumental in maintaining the endothelium's antithrombotic and antiatherogenic properties, preventing increased blood coagulability and microthrombus formation.^{12,14} Finally, vitamin C inhibits the expression of TNF-induced intracellular adhesion molecule, which generates leukocyte stickiness and thrombi in the microvasculature.¹⁴

Synergy with the adrenal axis and corticosteroids. During the stress response, the adrenocorticotrophic hormone stimulates the local release of vitamin C from the adrenal glands.²⁷ Corticosteroids can enhance cellular uptake of vitamin C via increased expression of the sodium-vitamin C transporter 2, which is normally suppressed by pro-inflammatory cytokines.^{28–30} Similarly, vitamin C may restore glucocorticoid receptor function by recovering glucocorticoid receptor binding via reduction of the cysteine thiol group.^{28,29,31} Synergy between vitamin C and hydrocortisone has been demonstrated in in vitro studies using human lung vascular endothelial cells where the combination of the two therapies resulted in the recovery of vascular endothelial integrity in response to lipopolysaccharide, whereas each therapy in isolation failed to achieve this effect.¹⁵

Clinical studies

Vitamin C as monotherapy. Most clinical trials of high-dose IV vitamin C as a single agent in critically ill adults with sepsis have shown benefits. IV vitamin C therapy had a dose-dependent effect on reducing organ dysfunction and lowering markers of inflammation and endothelial injury in a 2014 phase I clinical trial of 24 adults with sepsis.³² In 2016, a randomized controlled trial (RCT) of IV vitamin C in 28 adult surgical patients with sepsis found that treated patients had an earlier reversal of shock, reduced requirement for vasopressors, and improved survival.³³

In 2019, Fowler et al. conducted the Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure

Table 2. Studies in critical illness using vitamin C in combination therapy

Study/design	Patient, <i>n</i> (intervention/control)	Protocol	Important clinical outcomes
Nathens et al. (2002); ³³ RCT	Critically ill surgical patients, <i>n</i> = 595 (301/294)	VitC and alpha-tocopherol vs. placebo; VitC 1000 mg q8 h until discharge from ICU or 28 days (whichever was shorter)	Decreased multiple organ failure, reduction of TNF- α , IL-1 β , IL-6; decreased ICU and hospital stay, and increased ventilator-free days in the treatment arm
Marik et al. (2017); ²⁷ before–after retrospective	Severe sepsis or septic shock and PCT >2 ng/mL; <i>n</i> = 94 (47/47)	HAT therapy (HCT 50 mg q6 h \times 7 d; VitC 1.5 g IV q6 h \times 4 days or until ICU discharge, thiamine 200 mg q12 \times 4 d) vs. control	Mortality reduction; 8.5% mortality in treatment arm vs. 40.4% in control arm, <i>p</i> < 0.001; median 72 h PCT, SOFA scores, vasopressor requirements decreased in the treatment arm
Fujii et al. (2020) VITAMINS trial; ³⁶ RCT	Septic shock, <i>n</i> = 211 (107/104)	HAT therapy (identical to Marik) vs. hydrocortisone alone	No difference in 28- or 90-day mortality or vasopressor-free days
Moskowitz et al. (2020) ACTS trial; ³⁷ RCT	Septic shock, <i>n</i> = 205 (103/102)	HAT therapy vs. placebo; HCT 50 mg, VitC 1.5 g IV, thiamine 100 mg q6 4 d	No difference in SOFA score over 72 h, the incidence of kidney failure, 30-day mortality
Iglesias et al. (2020) ORANGES trial; ⁴⁰ RCT	Sepsis and septic shock; <i>n</i> = 137 (68/69)	HAT therapy (identical to Marik) vs. placebo	Vasopressor time (resolution of shock) reduced in HAT arm (27 \pm 22 vs. 53 \pm 38 h, <i>p</i> < 0.001); no significant differences ICU and hospital mortality, ICU and hospital LOS, ventilator-free days, and PCT
Chang et al. (2020) HYVCTTSSS trial; ³⁹ RCT	Sepsis and septic shock; <i>n</i> = 80 (40/40)	HAT therapy (identical to Marik) vs. placebo	Terminated early (underpowered). No mortality benefit. Improvement of 72-h change in SOFA score (<i>p</i> = 0.02). Treatment group > incidents of hyponatremia (<i>p</i> = 0.005). In prespecified subgroup analysis, patients in the treatment subgroup diagnosed with sepsis within 48 h showed lower mortality than the control subgroup (<i>p</i> = 0.02)
Wald et al. (2020); ⁵ retrospective, propensity-scored matched analysis	Septic shock requiring vasopressors; <i>n</i> = 557 (47 HAT arm/181 hydrocortisone arm/333 control arm)	HAT therapy arm vs. hydrocortisone arm vs. control arm (standard care); HCT 50 mg/m ² /day divided every 6 hours VitC 30 mg/kg/dose q6 h \times 4 d up to 1500 mg/dose, thiamine 4 mg/kg/day divided BID	Mortality reduction, HAT therapy vs. matched untreated controls at 30 days (9 vs. 28%, <i>p</i> = 0.03) and 90 days (14 vs. 35%, <i>p</i> = 0.02). HAT therapy vs. matched hydrocortisone only patients (9% vs. 28%, <i>p</i> = 0.03) and 90 days (14 vs. 33%, <i>p</i> = 0.04)
Sevransky et al. (2021) VICTAS trial; ³⁸ RCT	Septic shock, <i>n</i> = 501 (252/249)	HAT therapy vs. placebo; HCT 50 mg, VitC 1.5 g IV, thiamine 100 mg q6 4 d	No increase in ventilator- and vasopressor-free days within 30 days. However, the trial was terminated early and may have been underpowered to detect a clinically important difference

HAT hydrocortisone, ascorbic acid, thiamine therapy, HCT hydrocortisone, VitC vitamin C, LR lactated ringers, PCT procalcitonin, RCT, randomized control trial, ICU intensive care unit, [m]SOFA [modified] Sequential Organ Failure Assessment, BSA body surface area, CRP C-reactive protein.

(CITRIS-ALI) trial. CITRIS-ALI was a multicenter, randomized, double-blinded trial of high-dose IV vitamin C in adult patients with sepsis and acute respiratory distress syndrome (ARDS), which showed that treated patients had lower 28-day mortality and more intensive care unit (ICU)- and hospital-free days.⁵ These were secondary outcomes, and the trial did not find significant differences in the primary endpoints: change in the Sequential Organ Failure Assessment (SOFA) scores or biomarkers at 96 h. However, failure to include patients who died in the first 96 h in the primary endpoint analysis led to potential survivorship bias. Subsequently, a secondary analysis, which included patients who died early, demonstrated a reduction in the SOFA score at 96 h (Table 1).³⁴

Vitamin C in combination therapy. Results of studies using vitamin C in combination therapy have been mixed. In a prospective, randomized trial of antioxidant therapy, patients at risk for sepsis following major surgery or trauma, who were

treated with a combination of vitamin C and vitamin E, had an associated decreased incidence of organ failure and a shorter length of ICU stay.³⁵ Similar results were found in a Brazilian study, in which patients who were randomized to an enteral diet enriched with eicosapentaenoic acid, gamma-linoleic acid, vitamin C, and vitamin E demonstrated lower mortality, less organ dysfunction, and more ventilator- and ICU-free days than patients given a control enteral diet.³⁶

High-dose vitamin C has also been studied in combination with hydrocortisone and thiamine as adjuvant therapy in sepsis. This combination therapy has been termed “HAT” therapy, an acronym for hydrocortisone, ascorbic acid, and thiamine. In 2017, a retrospective before–after study of 94 adult patients with severe sepsis and septic shock compared patients who received HAT therapy with historic controls and found a decrease in organ dysfunction and mortality associated with the treatment.²⁹ Our group at Lurie Children’s Hospital published a single-center retrospective, propensity-scored matched analysis of 129 children

Table 3. Studies of thiamine in critical illness.

Study/design	Patient, <i>n</i> (intervention/control)	Protocol	Important clinical outcomes
Holmberg et al. 2018; ⁵⁴ retrospective	Patients with alcohol-use disorders and septic shock, <i>n</i> = 53 (34/19)	Thiamine therapy 100 mg IV (nonuniform dosing/duration) vs. control	Mortality benefit in patients receiving thiamine, 15/34 (44%) died, compared to 15/19 (79%) of those not receiving thiamine, <i>p</i> = 0.02
Donnino et al. 2016; ³ RCT	Septic shock and elevated lactate, <i>n</i> = 92 (45/47)	Thiamine 200 mg IV BID × 7 days vs. control	No difference in the primary outcome of lactate levels at 24 h or secondary outcomes, including time to shock reversal, the severity of illness and mortality. Decrease in mortality over time in those receiving thiamine in the pre-defined thiamine-deficient subgroup (<i>p</i> = 0.047)
Moskowitz et al. 2017; ⁵⁹ secondary analysis from RCT	70 patients analyzed	Thiamine vs. control; 200 mg IV BID × 7 days	Lower serum creatinine levels and a lower rate of progression to RRT than patients randomized to placebo

RCT randomized controlled trial, BID twice daily, RRT renal replacement therapy.

with septic shock comparing patients who received HAT therapy to those receiving hydrocortisone only and those who received no adjuvant therapies.⁶ We reported a decreased mortality associated with HAT therapy, particularly early in the course and in patients with severe hypoxemia, although we did not find a difference in length of stay or use of vasopressors.⁶ Using a similar retrospective design with propensity matching, investigators found improved ICU mortality for adult patients treated with HAT therapy.³⁷ In contrast to these findings in observational studies, multiple RCTs of HAT therapy in adults with septic shock have failed to show clinical benefits, with treated patients experiencing no difference in vasopressor needs, ventilator days, or other clinical outcomes compared to controls^{38–42} (Table 2).

Safety

Potential side effects from the administration of high IV doses of vitamin C include pro-oxidant effects, excess iron absorption, and interference with blood glucose measurements. There is also a risk that high-dose vitamin C can cause oxalate crystal deposition in the tissues and kidney.^{43,44} Although controlled trials with short-term use of high-dose vitamin C have not demonstrated this complication.^{5,32,38} Thiamine pyrophosphate is a coenzyme necessary for the breakdown of glyoxylate to carbon dioxide instead of oxalate and has been commonly used in combination therapy in sepsis for this reason. A recent RCT of adults with sepsis was terminated early for a higher incidence of severe hypernatremia with HAT therapy,⁴¹ although this has not been seen in other studies. Animal and human studies have determined that high-dose IV vitamin C use is generally safe and has low or no toxicity.^{5,6,29,32,35,38} High-dose vitamin C is contraindicated in patients with a history of oxalate nephrolithiasis, glucose-6-phosphate dehydrogenase deficiency and paroxysmal nocturnal hemoglobinuria, as its administration may result in hemolysis.^{11,45}

THIAMINE (VITAMIN B₁)

Thiamine, or vitamin B₁, is a water-soluble vitamin involved in cellular respiration, which has several mechanisms of action that may be relevant to sepsis and critical illness.⁴⁶ Its predominantly active form, thiamine pyrophosphate (TPP), enters mitochondria via a TPP/thiamine antiporter and enters the Krebs cycle as a cofactor for pyruvate dehydrogenase, which converts pyruvate to acetyl-coenzyme A, and acts as a critical component in α-ketoglutarate dehydrogenase and branched-chain ketoacid dehydrogenase complexes.^{46–48} Inhibition of any of these steps leads to increased lactate and decreased adenosine triphosphate production in the electron transport chain. Likewise, as TPP is a cofactor for transketolase and the pentose phosphate pathway, its deficiency increases oxidative stress via the impairment of

glutathione and other redox mechanisms. In addition, thiamine has other direct antioxidant effects and may influence the overall inflammatory response.^{47,49}

Thiamine levels are depleted during sepsis via rapid usage of thiamine stores, inadequate intake, and altered absorption. Increased energy demands, increased production of ROS, and direct mitochondrial injury are sequelae of sepsis and may be compounded by thiamine depletion.^{46,50–58} Several studies have demonstrated severe thiamine deficiency in patients with sepsis. Donnino et al. found that 20% of adult patients with shock were thiamine-deficient upon admission or became so within 72 h and reported that lactic acidosis decreased as thiamine levels rose.⁵⁸ Similarly, in a study of Brazilian children admitted to the ICU, Lima et al. found absolute thiamine deficiency in nearly 30% of patients, a durable finding across age groups, sex, diagnoses (including sepsis and septic shock), and nutritional status.⁵⁵ In addition, that study found that children with an elevated C-reactive protein had a significantly higher likelihood of thiamine deficiency, suggesting a link between severe inflammation and thiamine levels.⁵⁵

Preclinical studies

In a murine model of cardiac arrest, mice treated with thiamine demonstrated improved neurological function, increased 10-day survival, and markedly improved histological brain injury compared to controls.⁵⁹ Treated mice also showed improved oxygen consumption in the mitochondria. Similarly, in a canine model of septic shock, thiamine improved oxygen consumption, blood pressure, and clearance of lactate, regardless of underlying thiamine level at baseline.⁶⁰

Clinical studies

Thiamine as monotherapy. In 2016, Donnino et al. conducted a multicenter randomized, double-blind placebo-controlled study of thiamine 200 mg IV administered twice daily for 7 days in adults admitted to the ICU with sepsis, elevated lactate, and fluid-refractory shock necessitating vasopressor administration.⁴ Lactate clearance was improved in the group treated with thiamine at 24 h, and in the 35% of patients with baseline thiamine deficiency, mortality was significantly lower. There was no difference, however, in overall mortality, the severity of illness scores, ICU, or hospital length of stay.⁴ Moskowitz et al. proposed a separate mechanism by which thiamine might lead to more enduring clinical benefits. Their group performed a post hoc analysis of the Donnino trial and found a significantly lower need for renal replacement therapy (RRT) in the thiamine-treated group compared to placebo.^{4,61} As in the original trial, no differences in overall mortality were noted, but mortality was higher for patients placed on RRT compared to patients who did not require RRT. In an observational study of adults with septic shock and alcohol-use

Table 4. Studies of vitamin D therapy in critical illness.

Study/design	Patient, <i>n</i> (intervention/control)	Intervention/protocol	Important clinical outcomes
Han et al. (2016), ⁹² RCT	Mechanically ventilated adult ICU patients, <i>n</i> = 31 (16/15)	Vitamin D ₃ 50,000 vs. 100,000 IU enterally vs. placebo	Increased plasma 25(OH)D concentrations; a significant decrease in hospital LOS in the 250,000 and the 500,000 IU vitamin D ₃ group, compared to the placebo group (25 ± 14 and 18 ± 11 days compared to 36 ± 19 days; <i>p</i> = 0.03)
Amrein et al. (2014) VITdAL trial, ⁹³ RCT	Medical/surgical ICU critically ill adult white patients with vitamin D deficiency (≤20 ng/mL), <i>n</i> = 492 (249/243)	Vitamin D ₃ 540,000 IU enterally × 1, followed by 90,000 IU monthly for 5 months vs. placebo.	No reduction in hospital length of stay, hospital mortality, or 6-month mortality
Leaf et al. (2014), ⁹¹ RCT	Adults with severe sepsis, septic shock, <i>n</i> = 67 (36/31)	2 µg 1,25-dihydroxyvitamin D (calcitriol) × single dose vs. placebo	No difference in plasma cathelicidin protein levels, inflammatory cytokines or markers of kidney injury
Lan et al. (2020), ⁹⁵ meta-analysis	9 RCTs, 1867 patients	Varying protocols with different routes of administration	No difference in 28-day mortality between the vitamin D supplementation and placebo groups (20.4 vs. 21.7%, OR, 0.73; 95% CI, 0.46–1.15; <i>I</i> (2) = 51%); no difference in hospital LOS, ICU LOS, or duration of mechanical ventilation

disorders, investigators found a significant reduction in mortality in patients receiving thiamine.⁵⁶ Finally, in a small retrospective cohort study of six children with septic shock and hyperlactatemia, who received variable regimens of thiamine, there was no difference in mortality nor lactate clearance when compared to nine matched controls (Table 3).⁶²

Thiamine in combination therapy. Thiamine in combination therapy has largely been studied in the context of HAT therapy, which has already been discussed in the section “Vitamin C in combination therapy.”

Safety

Thiamine has a good safety profile in both adults and children with no significant long-term complications; in the short term, it has a risk of anaphylaxis similar to penicillin and contrast media.^{46,63} In reports of small groups of infants (from *n* = 1 to 23) receiving doses from 50 mg intramuscularly⁶⁴ to 100 mg IV,^{65,66} there have been no adverse events noted.

VITAMIN D

Vitamin D is a prohormone obtained through exposure to sunlight and diet. Many tissues convert the primary circulating form, 25-hydroxyvitamin D, to the active form, 1,25-hydroxyvitamin D, which has key roles in calcium and phosphate metabolism.⁶⁷ In addition, the vitamin D receptor is expressed throughout the body, including on B and T lymphocytes and antigen-presenting cells.⁶⁸ The receptor is upregulated during infection, modulating the innate and adaptive immune systems, with downstream effects including dendritic cell maturation, macrophage differentiation, and reduced cytokine release.⁶⁸ In sepsis, vitamin D upregulates expression of vitamin D-binding protein (DBP) and the anti-microbial peptide cathelicidin,⁶⁹ which is bactericidal, deactivates toxins, suppresses inflammation, and prevents endothelial cell apoptosis.^{70,71} In addition, vitamin D is associated with the structural integrity of tight junctions and mucosal barrier homeostasis.^{72,73} Vitamin D deficiency is defined as a 25-hydroxyvitamin D concentration <50 nmol/L, with severe deficiency developing at 25–30 nmol/L.⁷⁴ Potential mechanisms for deficiency in critical illness include hemodilution, decreased renal activation, decreased hepatic protein synthesis of DBP, increased vascular permeability, and renal wasting.^{75,76} It is unclear whether vitamin D deficiency is truly associated with poor outcomes in

critical illness, is simply a biomarker of acuity, or is it indicative of other metabolic derangements.^{3,77}

Preclinical studies

Several preclinical studies have suggested some of the potential benefits of vitamin D therapy in sepsis-relevant pathways. Vitamin D supplementation in a rat model of disseminated intravascular coagulation was associated with improved coagulation parameters.^{78,79} In a mouse model of endotoxemia, vitamin D supplementation was associated with improved survival related to the regulation of thromboxane A2 and free radicals.⁸⁰ Finally, in an endothelial cell model of endotoxemia, pretreatment with vitamin D inhibited endothelial cell activation by blocking the transcription factor nuclear factor-kappa B.⁸¹

Clinical studies

Observational clinical studies have demonstrated that vitamin D deficiency is common in critically ill children, with a prevalence ranging from 35 to 85%.^{82–85} While levels are lower in adult non-survivors compared to survivors,^{77,86,87} observational outcome studies in children are conflicting, with some describing increased severity of illness with vitamin D deficiency,⁸⁴ while others showing no difference in the severity of illness or mortality.^{82,83,88} Reviews and meta-analyses in children also demonstrate conflicting results. One meta-analysis found that vitamin D deficiency was associated with higher rates of sepsis, severity of illness, and length of stay.⁸⁹ In contrast, other studies of pediatric sepsis and vitamin D deficiency showed weak or no association with ventilator days or mortality.^{7,90} In addition, vitamin D levels in pediatric sepsis are not consistently correlated with levels of DBP or cathelicidin;^{91–93} therefore, the potential mechanisms for improved outcomes with vitamin D supplementation remain incompletely defined.

The results of randomized clinical trials of vitamin D supplementation in sepsis are inconsistent. In some studies of critically ill adults, supplementation is associated with improved functional outcomes, decreased length of stay, and reduced mortality.^{94–96} However, a recent meta-analysis in adults showed no association with length of stay, duration of mechanical ventilation, or mortality.⁹⁷ In contrast, an RCT of 109 children with sepsis demonstrated that a single dose of vitamin D reduced inflammatory markers, reduced cardiovascular organ failure scores, and decreased progression to septic shock.⁹⁸ Factors such as variability in study design, small sample size, and heterogeneous

populations have made it difficult to ascertain the effect of vitamin D supplementation on outcomes in critical illness and whether vitamin D deficiency is a modifiable risk factor (Table 4).^{89,97,99}

Safety

Vitamin D toxicity is rare, although hypercalcemia, hyperphosphatemia, and dehydration have been reported.¹⁰⁰ Patients with granulomatous disorders and Williams syndrome are at higher risk for adverse events due to their predisposition to hypercalcemia.¹⁰⁰ Currently, a multicenter phase II trial in critically ill children is investigating whether a dosing protocol can rapidly normalize vitamin D levels, with secondary outcomes including safety.¹⁰¹

OTHER VITAMINS

Vitamin A

Vitamin A, also known as retinol, is ingested as preformed vitamin A from animal sources (especially dairy, fish, and meat) and provitamin precursors (especially beta-carotene from plants and fruits), metabolized in the small intestine, and stored in the liver.¹⁰² It plays key roles in retinal function as well as mitochondrial oxidative phosphorylation.¹⁰³ Vitamin A also supports innate and adaptive immunity and has been shown to inhibit pro-inflammatory cytokine production.¹⁰² Metabolism of vitamin A may be altered in critically ill patients, and increased renal clearance is observed during acute infection.¹⁰⁴ In a study of adults with ARDS, retinol levels were lower than in healthy controls, and vitamin A supplementation using recommended daily allowances did not resolve the deficiency.¹⁰⁵ In a study of critically ill patients, vitamin A levels were inversely correlated with C-reactive protein.² In another study of critically ill adults with sepsis and septic shock, retinol and beta-carotene levels were inversely correlated with oxidation, but no correlation was found with outcomes.^{106,107} In a study of micronutrient levels in critically ill children, lower beta-carotene levels were associated with higher organ dysfunction and oxidation.¹⁰⁸

Overall, there is limited research on vitamin A supplementation in the form of retinol or beta-carotene during critical illness. Further research is needed to determine whether vitamin A therapy can help mitigate organ dysfunction during sepsis.

Vitamin B₂

Vitamin B₂, also known as riboflavin, is an essential micronutrient present in eggs, dairy, and green plants, and has key functions in cellular respiration. Vitamin B₂ has both anti-inflammatory and antioxidant properties, but most of the existing evidence is derived from preclinical studies in animal models.¹⁰⁹ Vitamin B₂ has been shown in mice to reduce pro-inflammatory cytokines and NO, both of which are implicated in sepsis pathobiology.¹¹⁰ IV infusion of highly purified vitamin B₂ was associated with reduced lethality in a murine model of sepsis following *Escherichia coli* and *Staphylococcus aureus* infection.¹¹¹ It is possible that the mechanism responsible for these findings is the induction of heat-shock protein 25 expression and attenuation of the inflammasome.^{109,112}

There is currently no clinical evidence of the effects of vitamin B₂ supplementation during sepsis and further research is warranted.

Vitamin B₆

Vitamin B₆ is an essential micronutrient present in non-citrus fruits, starchy vegetables, meats, and fortified cereals and oftentimes given in the form of pyridoxine for supplementation. Vitamin B₆ has roles in hundreds of enzymatic reactions in multiple metabolic pathways.¹¹³ In preclinical studies, vitamin B₆ has been shown to exert anti-inflammatory and antioxidative effects in a polymicrobial sepsis model in rats.¹¹⁴ In other animal models of sepsis, vitamin B₆ has also been shown to reduce neurotoxic metabolites and neuroinflammation through effects in the kynurenine pathway.^{113,115}

There is currently no clinical evidence of the use of vitamin B₆ as an antioxidant or as a treatment for neuroinflammation in sepsis and further research is warranted.

Vitamin B₁₂

Vitamin B₁₂, also known as cobalamin, is an essential micronutrient present in animal protein.¹¹⁶ It is one of the largest and most complex vitamins, playing a crucial role in human cell metabolism, and is necessary for central nervous system and bone marrow function.¹¹⁶ Vitamin B₁₂ has anti-inflammatory and antioxidant properties and plays a number of key roles that are relevant to sepsis.^{116–119} These key effects include (i) selective inhibition of iNOS and reduction of NO, (ii) decreased production of ROS through glutathione-sparing effects, (iii) increased synthesis of acetylcholine and enhancement of the cholinergic anti-inflammatory pathway, (iv) stimulation of oxidative phosphorylation, (v) enhancement of bacteriostasis, and (vi) control of nuclear factor-kappa B activation.^{118,120} In addition, vitamin B₁₂ exerts anti-vasoplegic effects through the binding of hydrogen sulfide (an endogenous vasodilator) and is associated with decreased vasopressor requirements in multiple case reports.¹²¹

However, despite the existing evidence and its theoretical advantages, the benefits of vitamin B₁₂ have not been tested in prospective clinical trials. Some experts have called for broader testing of vitamin B₁₂ in sepsis, arguing that large parenteral doses have historically been well tolerated when used for cyanide poisoning.^{118,120} However, vitamin B₁₂ levels have been positively correlated with increased inflammatory markers, higher organ dysfunction scores, and increased mortality in observational studies.^{2,116} While this may point at a possible role of vitamin B₁₂ as an acute-phase reactant, it seems counterintuitive to administer additional vitamin B₁₂ given these findings.¹¹⁶ There is currently a single-center randomized control trial of vitamin B₁₂ in adult patients with septic shock registered in ClinicalTrials.gov (NCT03783091), but no results have been reported.

Vitamin E

Vitamin E is a fat-soluble antioxidant most commonly consumed in the form of tocopherols, which can be found in vegetable oils. Vitamin E has important biological roles including scavenging of ROS, suppression of nuclear factor-kappa B, and reduction of pro-inflammatory cytokines.^{122,123} In preclinical animal models of sepsis, vitamin E has also been shown to modulate the function of macrophages and be inversely correlated with oxidative stress.^{124,125}

Several clinical observational studies in critically ill patients have associated lower levels of vitamin E with sepsis, septic shock, and ARDS in both adults and children.^{105–108} Vitamin E levels have also been inversely correlated with C-reactive protein in critically ill patients.² However, vitamin E supplementation has not been shown to consistently elevate vitamin E levels in patients with acute lung injury.¹²⁶ The only trial of vitamin E in combination therapy was discussed in the section "Vitamin C in combination therapy."³⁶ This remains the only clinical trial evaluating this particular dietary intervention and vitamin E's specific contribution to the findings remains unclear. However, given that vitamin E has both preclinical and clinical studies supporting its possible benefits, further prospective clinical trials to evaluate its effects in patients with sepsis are warranted.

DISCUSSION

In this narrative review, we present the pertinent preclinical and clinical evidence of vitamin use in sepsis and critical illness. Vitamins are key cofactors and effectors in many biological processes relevant to sepsis, including major antioxidant and anti-inflammatory pathways.² The biological plausibility and the supporting clinical evidence for some of the major vitamins, such

as vitamin C, thiamine, and vitamin D, make a compelling case for their use in sepsis, but thus far, vitamin supplementation has had mixed results in large, multicenter RCTs and in observational studies. Other vitamins, such as vitamin A, B₂, B₆, and E, warrant further study in sepsis. In addition, a significant limitation is that most of the current evidence originates from adult studies and data in children is less robust.

Several factors should be considered as clinicians evaluate the literature and researchers design future studies of vitamins in sepsis. While low vitamin levels have been reported in both adults and children with critical illness, the levels themselves have not always been independently associated with outcomes.^{107,108} Thus, whether certain vitamin deficiencies during sepsis contribute to organ dysfunction or whether they are merely proxies for critical illness remains unknown. Assuming vitamin deficiencies in sepsis is undesirable, it is also unclear whether simple correction of the deficiency or supplementation to achieve supraphysiologic levels is the right approach.² The lack of evidence regarding the optimal dosing strategy in different age groups for most vitamin therapies further confounds the issue. In addition, vitamin supplementation in sepsis has often been studied in combination therapy, which makes it impossible to discern which vitamin is having an effect, if any. Finally, sepsis is a heterogeneous disease consisting of different phenotypes and it is unlikely that a single drug will benefit all patients.^{127–129} For example, while many patients may be negatively impacted by excessive oxidative stress, this may be particularly critical in patients with sepsis-associated ARDS, as they are exposed to both endogenous production of ROS and high levels of inspired oxygen. Perhaps, this is why studies like the CITRIS-ALI trial of adults with sepsis-associated ARDS showed that vitamin C, a potent antioxidant, had a mortality benefit, while other “all-comer” sepsis RCTs have had negative results.⁵ Future research of vitamins in pediatric sepsis should acknowledge and address some of these important knowledge gaps, namely, whether the actual levels of vitamins prior to therapy are relevant, whether replacement therapy or pharmacotherapy is needed and what doses are required to achieve the desired targets in different age groups, and whether specific vitamins have a role in different sepsis phenotypes.

We propose that designing response-adaptive platform trials will help address these issues. With a response-adaptive design, multiple dosing strategies can be tested and analyzed based on pre-defined phenotypes, with the randomization ratio adjusted over time to increase the probability that participants with certain phenotypes of sepsis who enroll later receive the treatment regimen that is more likely to be optimal.¹³⁰ With the platform design, multiple vitamins and combinations of vitamins can be tested over time and ineffective intervention arms can be removed sooner than in traditional trial designs, improving efficiency.¹³¹

The role of vitamins, micronutrients, and other metabolic therapies in sepsis warrant further research. We hope this review will provide a better understanding of the role these important metabolic mediators play in sepsis pathobiology and assist in the design of clinical studies and the development of successful therapeutic regimens for the patients that need it most.

REFERENCES

- Tan, B. et al. Global case-fatality rates in pediatric severe sepsis and septic shock: a systematic review and meta-analysis. *JAMA Pediatr.* **173**, 352–362 (2019).
- Corcoran, T., O'Neill, M., Webb, S. & Ho, K. Prevalence of vitamin deficiencies on admission: relationship to hospital mortality in critically ill patients. *Anaesth. Intens. Care* **37**, 254–260 (2009).
- Gerasimidis, K. et al. Assessment and interpretation of vitamin and trace element status in sick children: a position paper from the European Society for Paediatric Gastroenterology Hepatology, and Nutrition Committee on Nutrition. *J. Pediatr. Gastroenterol. Nutr.* **70**, 873–881 (2020).
- Donnino, M. W. et al. Randomized, double-blind, placebo-controlled trial of thiamine as a metabolic resuscitator in septic shock: a pilot Study. *Crit. Care Med.* **44**, 360–367 (2016).
- Fowler, A. A. 3rd 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* **322**, 1261–1270 (2019).
- Wald, E. L. et al. Hydrocortisone-ascorbic acid-thiamine use associated with lower mortality in pediatric septic shock. *Am. J. Respir. Crit. Care Med.* **201**, 863–867 (2020).
- Wang, Y., Shi, C., Yang, Z., Chen, F. & Gao, L. Vitamin D deficiency and clinical outcomes related to septic shock in children with critical illness: a systematic review. *Eur. J. Clin. Nutr.* **73**, 1095–1101 (2019).
- Linster, C. L. & Van Schaftingen, E. Vitamin C. Biosynthesis, recycling and degradation in mammals. *FEBS J.* **274**, 1–22 (2007).
- Borrelli, E. et al. Plasma concentrations of cytokines, their soluble receptors, and antioxidant vitamins can predict the development of multiple organ failure in patients at risk. *Crit. Care Med.* **24**, 392–397 (1996).
- Carr, A. C., Shaw, G. M., Fowler, A. A. & Natarajan, R. Ascorbate-dependent vasopressor synthesis: a rationale for vitamin C administration in severe sepsis and septic shock? *Crit. Care* **19**, 418 (2015).
- Wilson, J. X. Evaluation of vitamin C for adjuvant sepsis therapy. *Antioxid. Redox Signal.* **19**, 2129–2140 (2013).
- Wilson, J. X. Mechanism of action of vitamin C in sepsis: ascorbate modulates redox signaling in endothelium. *BioFactors* **35**, 5–13 (2009).
- Oudemans-van Straaten, H. M., Spoelstra-de Man, A. M. & de Waard, M. C. Vitamin C revisited. *Crit. Care* **18**, 460 (2014).
- May, J. M. & Harrison, F. E. Role of vitamin C in the function of the vascular endothelium. *Antioxid. Redox Signal.* **19**, 2068–2083 (2013).
- Barabutis, N., Khangoora, V., Marik, P. E. & Catravas, J. D. Hydrocortisone and ascorbic acid synergistically prevent and repair lipopolysaccharide-induced pulmonary endothelial barrier dysfunction. *Chest* **152**, 954–962 (2017).
- Fisher, B. J. et al. Mechanisms of attenuation of abdominal sepsis induced acute lung injury by ascorbic acid. *Am. J. Physiol. Lung Cell Mol. Physiol.* **303**, L20–32 (2012).
- Carr, A.C. & Maggini, S. Vitamin C and Immune Function. *Nutrients*. **9**; 1211 (2017).
- Spoelstra-de Man, A. M. E., Elbers, P. W. G. & Oudemans-van Straaten, H. M. Making sense of early high-dose intravenous vitamin C in ischemia/reperfusion injury. *Crit. Care* **22**, 70 (2018).
- Heyland, D. et al. A randomized trial of glutamine and antioxidants in critically ill patients. *N. Engl. J. Med.* **368**, 1489–1497 (2013).
- Padayatty, S. J. et al. Vitamin C pharmacokinetics: implications for oral and intravenous use. *Ann. Intern. Med.* **140**, 533–537 (2004).
- Huang, J. et al. Dehydroascorbic acid, a blood-brain barrier transportable form of vitamin C, mediates potent cerebroprotection in experimental stroke. *Proc. Natl. Acad. Sci. USA* **98**, 11720–11724 (2001).
- Levine, M. Ascorbic acid specifically enhances dopamine beta-monooxygenase activity in resting and stimulated chromaffin cells. *J. Biol. Chem.* **261**, 7347–7356 (1986).
- Prigge, S. T., Mains, R. E., Eipper, B. A. & Amzel, L. M. New insights into copper monooxygenases and peptide amidation: structure, mechanism and function. *Cell Mol. Life Sci.* **57**, 1236–1259 (2000).
- Teng, J., Pourmand, A. & Mazer-Amirshahi, M. Vitamin C: The next step in sepsis management? *J. Crit. Care* **43**, 230–234 (2018).
- Dillon, P. F., Root-Bernstein, R., Robinson, N. E., Abraham, W. M. & Berney, C. Receptor-mediated enhancement of beta adrenergic drug activity by ascorbate in vitro and in vivo. *PLoS ONE* **5**, e15130 (2010).
- Kallio, J., Jaakkola, M., Maki, M., Kilpelainen, P. & Virtanen, V. Vitamin C inhibits *Staphylococcus aureus* growth and enhances the inhibitory effect of quercetin on growth of *Escherichia coli* in vitro. *Planta Med.* **78**, 1824–1830 (2012).
- Padayatty, S. J. et al. Human adrenal glands secrete vitamin C in response to adrenocorticotropic hormone. *Am. J. Clin. Nutr.* **86**, 145–149 (2007).
- Kuhn, S. O., Meissner, K., Mayes, L. M. & Bartels, K. Vitamin C in sepsis. *Curr. Opin. Anaesthesiol.* **31**, 55–60 (2018).
- Marik, P. E., Khangoora, V., Rivera, R., Hooper, M. H. & Catravas, J. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. *Chest* **151**, 1229–1238 (2017).
- Fujita, I., Hirano, J., Itoh, N., Nakanishi, T. & Tanaka, K. Dexamethasone induces sodium-dependant vitamin C transporter in a mouse osteoblastic cell line MC3T3-E1. *Br. J. Nutr.* **86**, 145–149 (2001).
- Okamoto, K., Tanaka, H., Makino, Y. & Makino, I. Restoration of the glucocorticoid receptor function by the phosphodiester compound of vitamins C and E, EPC-K1 (L-ascorbic acid 2-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-

- 2H-1-benzopyran-6-yl hydrogen phosphate] potassium salt), via a redox-dependent mechanism. *Biochem. Pharmacol.* **56**, 79–86 (1998).
32. Fowler, A. A. 3rd et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. *J. Transl. Med.* **12**, 32 (2014).
 33. Zabet, M. H., Mohammadi, M., Ramezani, M. & Khalili, H. Effect of high-dose Ascorbic acid on vasopressor's requirement in septic shock. *J. Res. Pharm. Pract.* **5**, 94–100 (2016).
 34. de Grooth, H. J., Elbers, P. W. G. & Vincent, J. L. Vitamin C for sepsis and acute respiratory failure. *JAMA* **323**, 792 (2020).
 35. Nathens, A. B. et al. Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. *Ann. Surg.* **236**, 814–822 (2002).
 36. Pontes-Arruda, A., Aragao, A. M. & Albuquerque, J. D. Effects of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in mechanically ventilated patients with severe sepsis and septic shock. *Crit. Care Med.* **34**, 2325–2333 (2006).
 37. Sadaka, F. et al. Ascorbic acid, thiamine, and steroids in septic shock: propensity matched analysis. *J. Intens. Care Med.* **35**, 1302–1306 (2020).
 38. Fujii, T. et al. Effect of vitamin C, hydrocortisone, and thiamine vs hydrocortisone alone on time active and free of vasopressor support among patients with septic shock: the Vitamins Randomized Clinical Trial. *JAMA* **323**, 423–431 (2020).
 39. Moskowitz, A. et al. Effect of ascorbic acid, corticosteroids, and thiamine on organ injury in septic shock: the ACTS Randomized Clinical Trial. *JAMA* **324**, 642–650 (2020).
 40. Sevransky, J. E. et al. Effect of vitamin C, thiamine, and hydrocortisone on ventilator- and vasopressor-free days in patients with sepsis: the VICTAS Randomized Clinical Trial. *JAMA* **325**, 742–750 (2021).
 41. Chang, P. et al. Combined treatment with hydrocortisone, vitamin C, and thiamine for sepsis and septic shock: a Randomized Controlled Trial. *Chest* **158**, 174–182 (2020).
 42. Iglesias, J. et al. Outcomes of metabolic resuscitation using ascorbic acid, thiamine, and glucocorticoids in the early treatment of sepsis: the ORANGES Trial. *Chest* **158**, 164–173 (2020).
 43. Massey, L. K., Liebman, M. & Kynast-Gales, S. A. Ascorbate increases human oxaluria and kidney stone risk. *J. Nutr.* **135**, 1673–1677 (2005).
 44. Wandzilak, T. R., D'Andre, S. D., Davis, P. A. & Williams, H. E. Effect of high dose vitamin C on urinary oxalate levels. *J. Urol.* **151**, 834–837 (1994).
 45. Padayatty, S. J. et al. Vitamin C: intravenous use by complementary and alternative medicine practitioners and adverse effects. *PLoS ONE* **5**, e11414 (2010).
 46. Leite, H. P. & de Lima, L. F. P. in *Diet and Nutrition in Critical Care* (eds Rajendram, R., Preedy, V. R. & Patel, V.) Ch. 6, 959–972 (Springer, 2015).
 47. Depeint, F., Bruce, W. R., Shangari, N., Mehta, R. & O'Brien, P. J. Mitochondrial function and toxicity: role of the B vitamin family on mitochondrial energy metabolism. *Chem. Biol. Interact.* **163**, 94–112 (2006).
 48. Shah, S. & Wald, E. Type B lactic acidosis secondary to thiamine deficiency in a child with malignancy. *Pediatrics* **135**, e221–224 (2015).
 49. de Andrade, J. A. A. et al. The effect of thiamine deficiency on inflammation, oxidative stress and cellular migration in an experimental model of sepsis. *J. Inflamm.* **11**, 11 (2014).
 50. Collie, J. T. B. et al. Vitamin B1 in critically ill patients: needs and challenges. *Clin. Chem. Lab. Med.* **55**, 1652–1668 (2017).
 51. Sassoon, C. S., Zhu, E., Fang, L., Subramanian, V. S. & Said, H. M. Inhibition of intestinal thiamin transport in rat model of sepsis. *Crit. Care Med.* **44**, e875–881 (2016).
 52. Dean, R. K., Subedi, R., Gill, D. & Nat, A. Consideration of alternative causes of lactic acidosis: thiamine deficiency in malignancy. *Am. J. Emerg. Med.* **35**, 1214 e1215–1214 e1216 (2017).
 53. Attaluri, P., Castillo, A., Edriss, H. & Nugent, K. Thiamine deficiency: an important consideration in critically ill patients. *Am. J. Med. Sci.* **356**, 382–390 (2018).
 54. Amrein, K., Oudemans-van Straaten, H. M. & Berger, M. M. Vitamin therapy in critically ill patients: focus on thiamine, vitamin C, and vitamin D. *Intens. Care Med.* **44**, 1940–1944 (2018).
 55. Lima, L. F., Leite, H. P. & Taddei, J. A. Low blood thiamine concentrations in children upon admission to the intensive care unit: risk factors and prognostic significance. *Am. J. Clin. Nutr.* **93**, 57–61 (2011).
 56. Holmberg, M. J. et al. Thiamine in septic shock patients with alcohol use disorders: an observational pilot study. *J. Crit. Care* **43**, 61–64 (2018).
 57. Leite, H. P., de Lima, L. F. P., Taddei, J. & Paes, A. T. Effect of blood thiamine concentrations on mortality: influence of nutritional status. *Nutrition* **48**, 105–110 (2018).
 58. Donnino, M. W. et al. Thiamine deficiency in critically ill patients with sepsis. *J. Crit. Care* **25**, 576–581 (2010).
 59. Ikeda, K. et al. Thiamine as a neuroprotective agent after cardiac arrest. *Resuscitation* **105**, 138–144 (2016).
 60. Lindenbaum, G. A., Larrieu, A. J., Carroll, S. F. & Kapusnick, R. A. Effect of cocarboxylase in dogs subjected to experimental septic shock. *Crit. Care Med.* **17**, 1036–1040 (1989).
 61. Moskowitz, A. et al. 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 (2017).
 62. Weiss, S. L. et al. Matched retrospective cohort study of thiamine to treat persistent hyperlactatemia in pediatric septic shock. *Pediatr. Crit. Care Med.* **20**, e452–e456 (2019).
 63. Wrenn, K. D. & Slovis, C. M. Is intravenous thiamine safe? *Am. J. Emerg. Med.* **10**, 165 (1992).
 64. Ozdemir, H. et al. Severe lactic acidosis in an extremely low birth weight infant due to thiamine deficiency. *J. Pediatr. Endocrinol. Metab.* **31**, 693–695 (2018).
 65. Qureshi, U. A. et al. Thiamine responsive acute life threatening metabolic acidosis in exclusively breast-fed infants. *Nutrition* **32**, 213–216 (2016).
 66. Perez-Duenas, B. et al. Reversible lactic acidosis in a newborn with thiamine transporter-2 deficiency. *Pediatrics* **131**, e1670–1675 (2013).
 67. Holick, M. F. Vitamin D deficiency. *N. Engl. J. Med.* **357**, 266–281 (2007).
 68. Hewison, M. Vitamin D and the immune system: new perspectives on an old theme. *Rheum. Dis. Clin. N. Am.* **38**, 125–139 (2012).
 69. Liu, P. T. et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* **311**, 1770–1773 (2006).
 70. Hu, Z. et al. Antimicrobial cathelicidin peptide LL-37 inhibits the LPS/ATP-induced pyroptosis of macrophages by dual mechanism. *PLoS ONE* **9**, e85765 (2014).
 71. Suzuki, K. et al. Human anti-microbial cathelicidin peptide LL-37 suppresses the LPS-induced apoptosis of endothelial cells. *Int. Immunol.* **23**, 185–193 (2011).
 72. Zhao, H. et al. Protective role of 1,25(OH)₂ vitamin D₃ in the mucosal injury and epithelial barrier disruption in DSS-induced acute colitis in mice. *BMC Gastroenterol.* **12**, 57 (2012).
 73. Kong, J. et al. VDR attenuates acute lung injury by blocking Ang-2-Tie-2 pathway and renin-angiotensin system. *Mol. Endocrinol.* **27**, 2116–2125 (2013).
 74. McNally, J. D. et al. Vitamin D deficiency in critically ill children: a systematic review and meta-analysis. *Crit. Care* **21**, 287 (2017).
 75. Quraishi, S. A. & Camargo, C. A. Jr. Vitamin D in acute stress and critical illness. *Curr. Opin. Clin. Nutr. Metab. Care* **15**, 625–634 (2012).
 76. Czarnik, T. et al. Vitamin D kinetics in the acute phase of critical illness: A prospective observational study. *J. Crit. Care* **43**, 294–299 (2018).
 77. Li, C. H. et al. Mechanistic study of the cause of decreased blood 1,25-dihydroxyvitamin D in sepsis. *BMC Infect. Dis.* **19**, 1020 (2019).
 78. Asakura, H. et al. Beneficial effect of the active form of vitamin D₃ against LPS-induced DIC but not against tissue-factor-induced DIC in rat models. *Thromb. Haemost.* **85**, 287–290 (2001).
 79. Moller, S., Laigaard, F., Olgaard, K. & Hemmingsen, C. Effect of 1,25-dihydroxyvitamin D₃ in experimental sepsis. *Int. J. Med. Sci.* **4**, 190–195 (2007).
 80. Horiuchi, H., Nagata, I. & Komoriya, K. Protective effect of vitamin D₃ analogues on endotoxin shock in mice. *Agents Actions* **33**, 343–348 (1991).
 81. Equils, O. et al. 1,25-Dihydroxyvitamin D inhibits lipopolysaccharide-induced immune activation in human endothelial cells. *Clin. Exp. Immunol.* **143**, 58–64 (2006).
 82. Shah, S. K., Kabra, S. K., Gupta, N., Pai, G. & Lodha, R. Vitamin D deficiency and parathyroid response in critically-ill children: association with illness severity and clinical outcomes. *Indian Pediatr.* **53**, 479–484 (2016).
 83. Rippel, C., South, M., Butt, W. W. & Shekerdemian, L. S. Vitamin D status in critically ill children. *Intens. Care Med.* **38**, 2055–2062 (2012).
 84. Madden, K. et al. Vitamin D deficiency in critically ill children. *Pediatrics* **130**, 421–428 (2012).
 85. Xiao, D. et al. Association between vitamin D status and sepsis in children: a meta-analysis of observational studies. *Clin. Nutr.* **39**, 1735–1741 (2020).
 86. de Haan, K., Groeneveld, A. B., de Geus, H. R., Egal, M. & Struijs, A. Vitamin D deficiency as a risk factor for infection, sepsis and mortality in the critically ill: systematic review and meta-analysis. *Crit. Care* **18**, 660 (2014).
 87. Zhang, Y. P., Wan, Y. D., Sun, T. W., Kan, Q. C. & Wang, L. X. Association between vitamin D deficiency and mortality in critically ill adult patients: a meta-analysis of cohort studies. *Crit. Care* **18**, 684 (2014).
 88. Ponnarmeni, S. et al. Vitamin D deficiency in critically ill children with sepsis. *Paediatr. Int. Child Health* **36**, 15–21 (2016).
 89. He, M., Cao, T., Wang, J., Wang, C., Wang, Z., Abdelrahim, M.E.A. Vitamin D deficiency relation to sepsis, paediatric risk of mortality III score, need for ventilation support, length of hospital stay, and duration of mechanical ventilation in critically ill children: A meta-analysis. *Int. J. Clin. Pract.* **75**, e13908 (2021).
 90. Yu, W., Ying, Q., Zhu, W., Huang, L. & Hou, Q. Vitamin D status was associated with sepsis in critically ill children: A PRISMA compliant systematic review and meta-analysis. *Medicine* **100**, e23827 (2021).

91. Watkins, R. R., Yamshchikov, A. V., Lemonovich, T. L. & Salata, R. A. The role of vitamin D deficiency in sepsis and potential therapeutic implications. *J. Infect.* **63**, 321–326 (2011).
92. Mathias, E., Tangpricha, V., Sarnaik, A., Farooqi, A. & Sethuraman, U. Association of vitamin D with cathelicidin and vitamin D binding protein in pediatric sepsis. *J. Clin. Transl. Endocrinol.* **10**, 36–38 (2017).
93. Leaf, D. E., Raed, A., Donnino, M. W., Ginde, A. A. & Waikar, S. S. Randomized controlled trial of calcitriol in severe sepsis. *Am. J. Respir. Crit. Care Med.* **190**, 533–541 (2014).
94. Han, J. E. et al. High dose vitamin D administration in ventilated intensive care unit patients: a Pilot Double Blind Randomized Controlled Trial. *J. Clin. Transl. Endocrinol.* **4**, 59–65 (2016).
95. Amrein, K. et al. 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 (2014).
96. Weng, H., Li, J. G., Mao, Z. & Zeng, X. T. Randomised trials of vitamin D3 for critically ill patients in adults: systematic review and meta-analysis with trial sequential analysis. *Intens. Care Med.* **43**, 277–278 (2017).
97. Lan, S. H. et al. Vitamin D supplementation and the outcomes of critically ill adult patients: a systematic review and meta-analysis of randomized controlled trials. *Sci. Rep.* **10**, 14261 (2020).
98. Wang, Y., Yang, Z., Gao, L., Cao, Z. & Wang, Q. Effects of a single dose of vitamin D in septic children: a randomized, double-blinded, controlled trial. *J. Intern. Med. Res.* **48**, 300060520926890 (2020).
99. Kearns, M. D., Alvarez, J. A., Seidel, N. & Tangpricha, V. Impact of vitamin D on infectious disease. *Am. J. Med. Sci.* **349**, 245–262 (2015).
100. Vogiatzi, M. G., Jacobson-Dickman, E. & DeBoer, M. D. Drugs & Therapeutics Committee of The Pediatric Endocrine, S. Vitamin D supplementation and risk of toxicity in pediatrics: a review of current literature. *J. Clin. Endocrinol. Metab.* **99**, 1132–1141 (2014).
101. McNally, D. et al. Study protocol for a phase II dose evaluation randomized controlled trial of cholecalciferol in critically ill children with vitamin D deficiency (VITdAL-PICU study). *Pilot Feasibility Stud.* **3**, 70 (2017).
102. Tanumihardjo, S. A. et al. Biomarkers of Nutrition for Development (BOND)—vitamin A review. *J. Nutr.* **146**, 18165–18485 (2016).
103. Berdanier, C. D., Everts, H. B., Hermoyian, C. & Mathews, C. E. Role of vitamin A in mitochondrial gene expression. *Diabetes Res. Clin. Pract.* **54**, S11–S27 (2001).
104. Stephensen, C. B. et al. Vitamin A is excreted in the urine during acute infection. *Am. J. Clin. Nutr.* **60**, 388–392 (1994).
105. Metnitz, P. et al. Antioxidant status in patients with acute respiratory distress syndrome. *Intens. Care Med.* **25**, 180–185 (1999).
106. Doise, J. M. et al. Plasma antioxidant status in septic critically ill patients: a decrease over time. *Fundam. Clin. Pharmacol.* **22**, 203–209 (2008).
107. Goode, H. F., Cowley, H. C., Walker, B. E., Howdle, P. D. & Webster, N. R. Decreased antioxidant status and increased lipid peroxidation in patients with septic shock and secondary organ dysfunction. *Crit. Care Med.* **23**, 646–651 (1995).
108. Valla, F. V. et al. Multiple micronutrient plasma level changes are related to oxidative stress intensity in critically ill children. *Pediatr. Crit. Care Med.* **19**, e455–e463 (2018).
109. Ahn, H. & Lee, G. S. Riboflavin, vitamin B2, attenuates NLRP3, NLRC4, AIM2, and non-canonical inflammasomes by the inhibition of caspase-1 activity. *Sci. Rep.* **10**, 19091 (2020).
110. Toyosawa, T., Suzuki, M., Kodama, K. & Araki, S. Highly purified vitamin B2 presents a promising therapeutic strategy for sepsis and septic shock. *Infect. Immun.* **72**, 1820–1823 (2004).
111. Toyosawa, T., Suzuki, M., Kodama, K. & Araki, S. Effects of intravenous infusion of highly purified vitamin B2 on lipopolysaccharide-induced shock and bacterial infection in mice. *Eur. J. Pharmacol.* **492**, 273–280 (2004).
112. Shih, C. K. et al. Riboflavin protects mice against liposaccharide-induced shock through expression of heat shock protein 25. *Food Chem. Toxicol.* **48**, 1913–1918 (2010).
113. Barichello, T. et al. Vitamin B6 prevents cognitive impairment in experimental pneumococcal meningitis. *Exp. Biol. Med.* **239**, 1360–1365 (2014).
114. Giustina, A. D. et al. Vitamin B6 reduces oxidative stress in lungs and liver in experimental sepsis. *An. Acad. Bras. Ciênc.* **91**, e20190434 (2019).
115. Danielski, L. G. et al. Vitamin B6 reduces neurochemical and long-term cognitive alterations after polymicrobial sepsis: involvement of the kynurenine pathway modulation. *Mol. Neurobiol.* **55**, 5255–5268 (2018).
116. Romain, M., Sviri, S., Linton, D., Stav, I. & van Heerden, P. V. The role of vitamin B12 in the critically ill—a review. *Anaesth. Intens. Care* **44**, 447–452 (2016).
117. Birch, C. S., Brasch, N. E., McCaddon, A. & Williams, J. H. H. A novel role for vitamin B12: cobalamins are intracellular antioxidants in vitro. *Free Radic. Biol. Med.* **47**, 184–188 (2009).
118. Manzanera, W. & Hardy, G. Vitamin B12: the forgotten micronutrient for critical care. *Curr. Opin. Clin. Nutr. Metab. Care* **13**, 662–668 (2010).
119. Weinberg, J. B. et al. Inhibition of nitric oxide synthase by cobalamins and cobinamides. *Free Radic. Biol. Med.* **46**, 1626–1632 (2009).
120. Wheatley, C. A scarlet pimpernel for the resolution of inflammation? The role of supra-therapeutic doses of cobalamin, in the treatment of systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic or traumatic shock. *Med. Hypotheses* **67**, 124–142 (2006).
121. Chudow, M. & Adams, B. ABC's of vitamin supplementation in critical illness. *J. Pharm. Pract.* 897190020958234 (2020).
122. Jiang, Q. Natural forms of vitamin E: metabolism, antioxidant, and anti-inflammatory activities and their role in disease prevention and therapy. *Free Radic. Biol. Med.* **72**, 76–90 (2014).
123. Minter, B. E., Lowes, D. A., Webster, N. R. & Galley, H. F. Differential effects of MitoVitE, alpha-tocopherol and trolox on oxidative stress, mitochondrial function and inflammatory signalling pathways in endothelial cells cultured under conditions mimicking sepsis. *Antioxidants* **9**, 195 (2020).
124. Basu, S. & Eriksson, M. Vitamin E in relation to lipid peroxidation in experimental septic shock. *Prostaglandins Leukot. Essent. Fatty Acids* **62**, 195–199 (2000).
125. Bulger, E. M. et al. Enteral vitamin E supplementation inhibits the cytokine response to endotoxin. *Arch. Surg.* **132**, 1337–1341 (1997).
126. Seeger, W., Ziegler, A. & Wolf, H. Serum alpha-tocopherol levels after high-dose enteral vitamin E administration in patients with acute respiratory failure. *Intens. Care Med.* **13**, 395–400 (1987).
127. Carcillo, J. A. et al. A Multicenter network assessment of three inflammation phenotypes in pediatric sepsis-induced multiple organ failure. *Pediatr. Crit. Care Med.* **20**, 1137–1146 (2019).
128. Seymour, C. W. et al. Derivation, validation, and potential treatment implications of novel clinical phenotypes for sepsis. *JAMA* **321**, 2003–2017 (2019).
129. Wong, H. R. et al. Combining prognostic and predictive enrichment strategies to identify children with septic shock responsive to corticosteroids. *Crit. Care Med.* **44**, e1000–1003 (2016).
130. Meurer, W. J., Lewis, R. J. & Berry, D. A. Adaptive clinical trials: a partial remedy for the therapeutic misconception? *JAMA* **307**, 2377–2378 (2012).
131. Seymour, C. W. et al. Precision medicine for all? Challenges and opportunities for a precision medicine approach to critical illness. *Crit. Care* **21**, 257 (2017).
132. Tanaka, H. et al. Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration: a randomized, prospective study. *Arch. Surg.* **135**, 326–331 (2000).
133. Ahn, J. H. et al. Vitamin C alone does not improve treatment outcomes in mechanically ventilated patients with severe sepsis or septic shock: a retrospective cohort study. *J. Thorac. Dis.* **11**, 1562–70 (2019).
134. Nakajima, M. et al. Effect of high-dose vitamin C therapy on severe burn patients: a nationwide cohort study. *Crit. Care* **23**, 407 (2019).

AUTHOR CONTRIBUTIONS

E.L.W. and L.N.S.-P. conceived and designed the review and supervised all aspects of the work. E.L.W. and L.K.H. were responsible for the vitamin C section; C.M.B. was responsible for the vitamin A and D sections; M.S. was responsible for the vitamin B1 section; and L.N.S.-P. was responsible for the vitamin B2, B9, B12, and E sections. E.L.W. and L.N.S.-P. were responsible for the first draft of the document and for editing the manuscript. No internal or external financial support was provided.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to E.L.W. or L.N.S.-P.

Reprints and permission information is available at <http://www.nature.com/reprints>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.