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REVIEW

Vitamin therapy in sepsis

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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 B_1), 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, B_2, B_6, B_{12}, and E.

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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 B_1), 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, B_2, B_6, B_{12}, 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

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

Study/design	Patient, *n* (intervention/control)	Protocol	Important clinical outcomes
Fowler et al. (2014);[32] RCT	Severe sepsis, $n = 24$ (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, $n = 28$ (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, $p = 0.009$ Decreased vasopressor requirement in the treatment arm
Fowler et al.;[5] RCT	Sepsis and ARDS, $n = 167$ (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, $p = 0.03$; 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), $n = 37$ (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, $n = 75$ (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), $n = 785$ (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 ($p = 0.006$); 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 (BH_4) deactivation and dephosphorylation of occludin, a key component in tight junctions.[13] Vitamin C also inhibits the oxidation of BH_4 and recovers it from its oxidized state. BH_4 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 adrenocorticotropic 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, *n* (intervention/control)	Protocol	Important clinical outcomes
Nathens et al. (2002);[33] RCT	Critically ill surgical patients, $n = 595$ (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-1β, 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; $n = 94$ (47/47	HAT therapy (HCT 50 mg q6 h × 7 d; VitC 1.5 g IV q6 h × 4 days or until ICU discharge, thiamine 200 mg q12 × 4 d) vs. control	Mortality reduction; 8.5% mortality in treatment arm vs. 40.4% in control arm, $p < 0.001$; median 72 h PCT, SOFA scores, vasopressor requirements decreased in the treatment arm
Fujii et al. (2020) VITAMINS trial;[36] RCT	Septic shock, $n = 211$ (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, $n = 205$ (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; $n = 137$ (68/69)	HAT therapy (identical to Marik) vs. placebo	Vasopressor time (resolution of shock) reduced in HAT arm (27 ± 22 vs. 53 ± 38 h, $p < 0.001$); 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; $n = 80$ (40/40)	HAT therapy (identical to Marik) vs. placebo	Terminated early (underpowered). No mortality benefit. Improvement of 72-h change in SOFA score ($p = 0.02$). Treatment group > incidents of hypernatremia ($p = 0.005$). In prespecified subgroup analysis, patients in the treatment subgroup diagnosed with sepsis within 48 h showed lower mortality than the control subgroup ($p = 0.02$)
Wald et al. (2020);[5] retrospective, propensity-scored matched analysis	Septic shock requiring vasopressors; $n = 557$ (47 HAT arm/181 hydrocortisone arm/333 control arm)	HAT therapy arm vs. hydrocortisone arm vs. control arm (standard care); HCT 50 mg/m2/day divided every 6 hours VitC 30 mg/kg/dose q6 h × 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%, $p = 0.03$) and 90 days (14 vs. 35%, $p = 0.02$). HAT therapy vs. matched hydrocortisone only patients (9% vs. 28%, $p = 0.03$) and 90 days (14 vs. 33%, $p = 0.04$)
Sevransky et al. (2021) VICTAS trial;[38] RCT	Septic shock, $n = 501$ (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, *n* (intervention/control)	Protocol	Important clinical outcomes
Holmberg et al. 2018;[54] retrospective	Patients with alcohol-use disorders and septic shock, $n = 53$ (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, $p = 0.02$
Donnino et al. 2016;[3] RCT	Septic shock and elevated lactate, $n = 92$ (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 ($p = 0.047$)
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 B_1)

Thiamine, or vitamin B_1, 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 Kreb 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, *n* (intervention/control)	Intervention/protocol	Important clinical outcomes
Han et al. (2016),[92] RCT	Mechanically ventilated adult ICU patients, $n = 31$ (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; $p = 0.03$)
Amrein et al. (2014) VITdAL trial,[93] RCT	Medical/surgical ICU critically ill adult white patients with vitamin D deficiency (≤20 ng/mL), $n = 492$ (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, $n = 67$ (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 (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 intramuscularly[64] 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 B_2

Vitamin B_2, also known as riboflavin, is an essential micronutrient present in eggs, dairy, and green plants, and has key functions in cellular respiration. Vitamin B_2 has both anti-inflammatory and antioxidant properties, but most of the existing evidence is derived from preclinical studies in animal models.[109] Vitamin B_2 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 B_2 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 B_2 supplementation during sepsis and further research is warranted.

Vitamin B_6

Vitamin B_6 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 B_6 has roles in hundreds of enzymatic reactions in multiple metabolic pathways.[113] In preclinical studies, vitamin B_6 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 B_6 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 B_6 as an antioxidant or as a treatment for neuroinflammation in sepsis and further research is warranted.

Vitamin B_{12}

Vitamin B_{12}, 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 B_{12} 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 B_{12} 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 B_{12} have not been tested in prospective clinical trials. Some experts have called for broader testing of vitamin B_{12} in sepsis, arguing that large parenteral doses have historically been well tolerated when used for cyanide poisoning.[118,120] However, vitamin B_{12} 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 B_{12} as an acute-phase reactant, it seems counterintuitive to administer additional vitamin B_{12} given these findings.[116] There is currently a single-center randomized control trial of vitamin B_{12} 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, B_2, B_6, 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.

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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

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