Review Article

# Thiamine (vitamin B1) in septic shock: a targeted therapy

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**Abstract:** Thiamine (vitamin B1) is a water-soluble vitamin essential for human health. Thiamine deficiency is causal and/or contributory in a number of debilitating diseases including beri-beri, the Wernicke-Korsakoff syndrome, optic neuropathy, and others. While thiamine deficiency is relatively rare in developed nations as a result of dietary supplementation, thiamine deficiency is more common in nutritionally compromised populations. Thiamine pyrophosphate, a thiamine derivative, is essential to the citric acid cycle and thiamine deficiency can result in impaired aerobic respiration and cellular energy production. Thiamine also plays an important role in the pentose phosphate pathway and other key metabolic processes. Although thiamine deficiency is a known cause of lactic acidosis, it has been recently evaluated as a potential contributor to refractory lactic acidosis and organ injury in septic shock and other shock states. In this article, we review the epidemiology of thiamine deficiency in septic shock and the existing evidence base supporting thiamine supplementation. We conclude that specific sepsis phenotypes may stand to benefit the most from thiamine supplementation, and efforts might be made to identify and supplement these patients early in their hospital course.

**Keywords:** Thiamine; vitamin B1; sepsis; septic shock; alcoholism

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## Introduction

Thiamine (vitamin B1) is an essential micronutrient whose phosphate derivatives play critical roles in a number of cellular processes. Of particular relevance to the critically ill population, thiamine pyrophosphate (TPP, a thiamine derivative) is a necessary cofactor for important metabolic enzymes including pyruvate dehydrogenase and transketolase. Pyruvate dehydrogenase (PDH) is a key player in aerobic respiration, without which mitochondrial aerobic respiration cannot occur and cellular energy production shifts to an anaerobic mechanism. Transketolase is an enzyme in the pentose phosphate pathway which, among other crucial functions, allows for the generation of important cellular antioxidants. Both pyruvate dehydrogenase and transketolase activity are substantially reduced in thiamine deficient states, which can result in bioenergetic failure, excess reactive oxygen species, and potentially cell death via apoptosis (1-5).

Thiamine deficiency is a well-documented cause of a number of debilitating diseases. Beri-beri (meaning 'weak-weak' in Sinhalese) is a classically described disorder related to thiamine deficiency that can take many forms including wet, dry, and gastrointestinal beri-beri. Gastrointestinal beri-beri, while more recently described, bears striking similarities to intestinal ischemia with pain and refractory serum lactate elevation (6). Thiamine deficiency is also the cause of the Wernicke-Korsakoff syndrome, a potentially devastating neurologic condition characterized by ocular abnormalities, mental status changes, and/or gait instability

and often progressing to confabulation, amnesia, and cognitive deficits. Given a short half-life and limited stores in the human body, individuals with poor nutritional intake, absorption abnormalities (i.e., gastric bypass), and/or those in highly catabolic states are particularly susceptible to the development of thiamine deficiency. While the occurrence of the above classically recognized syndromes of thiamine deficiency are relatively rare [although certainly more common in certain 'at risk' populations (7)], the contribution of thiamine deficiency to morbidity and mortality in critical illness may be substantially underestimated (8).

## The epidemiology of thiamine deficiency in critical illness

The recommended daily allowance of thiamine in adults is 1.1–1.2 mg/day (9). The half-life of thiamine in the human body is short, however, and body stores are lower than those for many other mammals. As such, thiamine deficiency can occur rather quickly, over the course of weeks if dietary intake is not maintained (9). In addition, high catabolic states in which metabolic processes are upregulated can result in more rapid depletion of thiamine and result in deficiency. While thiamine deficiency is rare in developed nations, certain medical conditions (e.g., alcoholism, diabetes mellitus, gastric/intestinal resection) predispose individuals to thiamine deficiency and certain medical interventions (e.g., furosemide, hemofiltration) can result in increased thiamine loss (7,10,11). In areas of the developing world, outbreaks of thiamine deficiency are known to occur as a result of inadequate nutritional support (9).

Estimates of thiamine deficiency prevalence amongst critically ill patients vary substantially as a result of population characteristics, disease states, disease severity, and measurement techniques. Among patients with sepsis, estimates of thiamine deficiency range from 10% to 70% (12-15). Thiamine deficiency can be assessed in a number of ways including direct detection of free thiamine and measurement of TPP in whole blood or erythrocytes (9). While erythrocyte TPP accounts for most of the thiamine content in whole blood, the measurement of plasma free thiamine may be more representative of recent nutritional intake. The optimal measurement technique to assess for clinically significant thiamine deficiency is not known. There is no point-of-care test available to assess for thiamine deficiency.

## Sepsis and organ injury

Organ injury resulting from a dysregulated host response to infection is a defining feature of sepsis (16). While impaired oxygen delivery resulting from a distributive physiology was previously considered to be the primary driver of organ injury in septic shock, there is increasing recognition that non-oxygen delivery dependent mechanisms may play an important role. A number of studies have found, for instance, that septic organ injury often occurs even if hemodynamics is preserved. In addition, histopathologic organ injury patterns more commonly reflect apoptotic, as opposed to ischemic, cell death. While current management recommendations for septic shock focus heavily on the maintenance of hemodynamic stability via the infusion of vasopressors and intravenous fluid, there is an increasing focus on non-oxygen delivery dependent mechanisms of septic organ injury including mitochondrial dysfunction (17). In that setting, the role of thiamine as a key cofactor for mitochondrial aerobic respiration and the maintenance of redox status, has gained attention.

## Thiamine supplementation in septic shock

A number of animal and human clinical studies have explored a potential role for thiamine as an adjunctive therapeutic agent in septic shock and other critical illnesses. In one canine model of septic shock, 14 dogs undergoing invasive hemodynamic monitoring were randomized to receive TPP or placebo after exposure to endotoxin. The 7 dogs who received TPP had substantially higher pH, mean arterial pressure, cardiac index, and oxygen consumption (18). In a cardiac arrest mouse model, thiamine improved mitochondrial function as measured by cellular oxygen consumption, restored cerebral PDH activity, reduced histologic signs of brain injury, and improved neurologic outcomes (19). These animal studies build on prior pre-clinical work demonstrating impaired PDH function in the setting of *in vitro* endotoxin exposure and in septic rodent models (20,21).

PDH activity in human septic shock has likewise been shown to be impaired (22,23). Thiamine, *in vitro*, improves PDH function in sepsis and in other disease states (24-26). Observational studies exploring the relationship between thiamine deficiency and outcome in critically ill patients have had mixed results, with some studies suggesting an association between thiamine deficiency and worse outcomes and other studies finding no relationship (13,15,27-30). In the study by Corcoran *et al.* the sample

 

size was small and a microbiologic thiamine assay was used, which may be less reliable than other available measurement methods (29-31). In the study by Costa *et al.* the proportion of patients with thiamine deficiency was quite high (71.3%) which may reflect on the population studied or the measurement technique (30).

More recently, a number of observational studies have explored whether there is any relationship between thiamine administration and outcome in septic shock. These studies have typically been small, single center retrospective studies. In one study, 123 patients with septic shock who received parenteral thiamine within 24 hours of hospital admission were matched with patients who had not received thiamine. In this study, receiving thiamine was associated with more rapid lactate clearance and reduced 28-day mortality (32). In a small pediatric study, thiamine administration in septic shock patients with prolonged hyperlactatemia resulted in rapid lactate clearance and improved outcomes when compared to matched controls (33). Finally, among alcoholic patients admitted with septic shock and high lactate levels at a single center, 36% did not receive any thiamine. Mortality rates were higher in those who did not receive thiamine (34).

These observational studies all carry significant risk of bias owing to their retrospective, observational designs with inadequate controls for various biases including the immortal time bias (35). To date, only one randomized trial has been conducted comparing thiamine to placebo in a septic shock population. In that trial, a total of 88 patients at increased risk of symptomatic thiamine deficiency based on a serum lactate >3 mmol/L after volume resuscitation (and exclusion of other causes of lactic acidosis) were randomized to receive 200 mg of parenteral thiamine *vs.* placebo. Overall there was no difference in the primary outcome of median lactate level at 24 h, though there was a statistically significant lower lactate in the thiamine group when evaluating lactate levels at serial timepoints in the first 72 h. In a pre-defined subgroup of patients with thiamine deficiency (35% of the cohort), the administration of thiamine reduced lactate levels and improved mortality (14). In a post hoc analysis of that study, patients without baseline end-stage renal disease who were given thiamine had better renal outcomes than those randomized to placebo (36).

As no rapid test exists to determine a patient's thiamine status, and the current evidence base does not support the routine administration of thiamine to all septic shock patients, the front-line clinician must rely on observable patient characteristics when deciding whether to administer thiamine in septic shock. The pathophysiologic rationale described in detail above suggests that the population of patients most likely to benefit are those with persistent lactic acidosis. Moreover, the one randomized trial suggests that thiamine is not necessarily beneficial for all-comers, but may be beneficial for those with deficiency. Thus, the provision of thiamine to patients with persistent lactic acidosis, particularly with one or more identified nutritional risk factors (e.g., alcoholism, high-dose diuretic exposure, malnourished state, cannabinoid and other hyperemesis syndromes etc.), may be prudent.

Clinicians should be aware that classic thiamine deficiency syndromes (i.e., cardiovascular and gastrointestinal beri-beri) can mimic septic shock with high lactate levels and other signs of organ dysfunction. As differentiating beri-beri from septic shock may be difficult, a trial of thiamine supplementation might serve as both a diagnostic (lactate levels fall quickly in response to thiamine in these conditions) as well as therapeutic intervention.

In 2016, Marik *et al.* published an observational before-and-after study of the combination of thiamine (200 mg every 12 h), ascorbic acid (1,500 mg every 6 h), and hydrocortisone (50 mg every 6 h) in septic shock (37). In that study, patients admitted with septic shock were treated with the above medication 'cocktail' and their outcomes compared to a matched retrospective cohort. Patients receiving thiamine, ascorbic acid, and hydrocortisone had substantially better outcomes. This study has resulted in tremendous interest in the area of so-called 'metabolic' resuscitation for sepsis that focuses less on impaired oxygen delivery and more on enhancing oxygen utilization and maintenance of redox balance (2). While many focus on the potential benefits of the ascorbic acid component of this drug cocktail [and results from a recent randomized trial is promising in that regard (38)], there has been less focus on the thiamine component (39). However, subjects in these trials are not necessarily in the high-risk categories for symptomatic thiamine deficiency.

Parenterally administered thiamine, even at doses up to 500 mg three times daily, is safe, well tolerated, and has been the mainstay of treatment for Wernicke's Encephalopathy for decades (40). Anaphylaxis has been reported with the administration of parenteral thiamine, however most of these events occurred with the use of parentrovite (a combination of B-vitamins and vitamin C) (41). In one study of bolus dose thiamine administered to 989 consecutive patients, there were no episodes of anaphylaxis (42). In a study of parenterally 'push' dosed thiamine in doses up to 500 mg, there were no anaphylactic reactions after

 

8,530 administrations in 2,591 patients. While these studies suggest a very low risk of allergic response to thiamine, administering thiamine as an infusion over 15–30 minutes may further mitigate any potential risk.

## The future of thiamine in septic shock

Given an excellent safety profile, good biologic rationale, and promising clinical studies, thiamine is an appealing adjunctive therapy for patients with septic shock. However, the results of the one randomized trial conducted in a cohort of septic shock patients selected to be at an increased risk of thiamine deficiency did not result in an overall clinical benefit, but did show promise in the subgroup with serologically identified thiamine deficiency (14). Many questions remain and emerged from this and previous studies. For instance, while the group overall did not have an improvement in mortality, a post-hoc, hypothesis-generating sub-analysis did show improved renal function in the patients who received thiamine (36). Therefore, one question is whether thiamine has reno-protective properties. A phase II randomized trial (NCT03550794) is underway to test the impact of thiamine in generalized septic subjects with renal injury.

Another organ system with high metabolic demands that is known to be susceptible to thiamine deficiency is the central nervous system. Thiamine deficiency is a well-described cause of gross neurologic impairment (i.e., the Wernicke-Korsakoff syndrome) and may be associated with more subtle neurologic impairment in survivors of critical illness. In one study in an animal model of cardiac arrest, thiamine was found to be neuroprotective (19). This study has prompted further work in human cardiac arrest victims with two clinical trials presently enrolling patients (NCT03450707 & NCT03450707). Given the substantial rates of long-term cognitive sequelae from sepsis (43), determining whether thiamine supplementation improves cognitive outcomes in septic shock is an important area of future study.

The ability to rapidly identify patients at highest risk for symptomatic thiamine deficiency would better allow for the selective administration of thiamine to those most at need. Unfortunately, there remains no rapid serologic test for thiamine deficiency in critically ill septic shock patients. Existing commercial options for the measurement of thiamine status can take days to result. Efforts towards the development of a rapid serologic test of thiamine status are certainly welcome, but in the interim clinicians must use other indirect clues, as described above, to identify patients most at risk. Along these lines, it may be helpful to consider more targeted sepsis resuscitation with a focus on improving oxygen delivery in patients with low central venous oxygen levels and a focus on metabolic resuscitation/thiamine administration in patients with high lactate and high central venous oxygen levels (44).

Building on the above, the overall benefit of thiamine to a community of sepsis patients likely depends largely on the underlying prevalence of thiamine deficiency in that community. While most developed nations fortify food staples with thiamine, this is less commonly seen in the developing world. Certain populations, especially those in which polished rice is a staple food (e.g., parts of West Africa), are at increased risk for beri-beri and likely also have a high prevalence of undiagnosed thiamine deficiency, which may manifest during sepsis (https://www.who.int/nutrition/publications/en/thiamine_in_emergencies_eng.pdf) Whether early thiamine supplementation for sepsis in these populations improves outcomes is an important area for future study.

The popularity of the 'metabolic resuscitation' bundle, and an increasing recognition of thiamine deficiency as a potential contributor to lactate production, represent challenges to the ongoing study of thiamine in sepsis as the number of critically ill patients treated with thiamine has increased. Pooled subgroup analyses from ongoing/completed trials of the 'metabolic resuscitation' bundle focused on patients with symptomatic (i.e., elevated lactate) thiamine deficiency, may help fill knowledge gaps around thiamine supplementation for patients with sepsis.

## Conclusions

Thiamine supplementation in septic shock appears to be safe and may benefit certain septic shock populations at increased risk for thiamine deficiency. More research is needed to determine the optimal timing, dosage, and sepsis population where thiamine supplementation may be most effective.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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