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Thiamine: An Essential Component of the Metabolic Resuscitation Protocol*

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Thiamine deficiency is common among septic patients, with a range in prevalence between 20% and 70% (1–3). It is likely that metabolic stress, age, nutritional deficiency, and the presence of comorbidities are risk factors for thiamine deficiency. Thiamine pyrophosphate, the active form of thiamine, is a required cofactor in two enzyme-mediated carbohydrate metabolism pathways, namely the Krebs cycle and the Pentose phosphate pathway (4). The pyruvate dehydrogenase (PDH) complex and alpha-ketoglutarate dehydrogenase are the two main Krebs cycle enzymes that require thiamine as a cofactor. A deficiency in thiamine leads to decreased activity of thiamine-dependent enzymes that triggers a sequence of metabolic events leading to energy compromise and decreased adenosine triphosphate (ATP) production. Thiamine deficiency has added significance in patients with sepsis. The production of reactive oxygen species (ROS) plays a key pathophysiologic role in sepsis. The unbalanced production of mitochondrial ROS impairs mitochondrial structure and enzymatic function and ATP production (5, 6). This further compromises the bioenergetic failure associated with thiamine deficiency. This phenomenon is likely compounded by cytokine and oxidative mediated down-regulation of the PDH complex (7). As suggested by Graetz and Hotchkiss (8), it is likely that these factors lead to bioenergetic failure with "cellular hibernation" and organ failure particularly in those organs which have a high mitochondrial content and metabolic demand (heart, kidney, and brain).

In this issue of *Critical Care Medicine*, Woolum et al (9) report on the effect of thiamine administration on lactate clearance and mortality in patients with septic shock. In this retrospective, single-center, matched-cohort study, the authors demonstrated that the cohort who received IV thiamine had a significantly greater fall in serum lactate (lactate clearance) and a lower 28-day mortality than the control group. The results of the study by Woolum et al (9) are biologically plausible and consistent with other studies (3). The major limitation of the study by Woolum et al (9) is that patients with liver disease were overrepresented; nevertheless, it is likely that the results of the study by Woolum et al (9) are generalizable to a heterogeneous population of real-life patients with septic shock. In a pilot randomized controlled trial, Donnino et al (3) randomized 88 patients with septic shock to receive 200 mg thiamine bid for 7 days. In the predefined subgroup of patients with thiamine deficiency, those in the thiamine treatment group had statistically significantly lower lactate levels

*See also p. 1747.

Key Words: delirium; sepsis; septic shock; thiamine; Wernicke's

Dr. Marik disclosed off-label product use of thiamine, which is approved by the U.S. Food and Drug Administration for patients with "established thiamine deficiency", but it is not specifically approved for the treatment of sepsis.

DOI: 10.1097/CCM.0000000000003336

at 24 hours and a lower mortality at 30 days. Furthermore, in a secondary analysis of the study by Donnino et al (3), the need for renal replacement therapy and the serum creatinine were greater in the placebo group (10). Furthermore, it is likely that thiamine deficiency plays a contributory role in the etiology of ICU delirium (11). ICU delirium has many of the features of Wernicke's encephalopathy, namely, confusion, mental sluggishness, apathy, impaired awareness, and inability to concentrate. A decrease in ATP production in the brain is associated with a diffuse decrease in cerebral glucose metabolism, an increase in production of dopamine metabolites, and a decrease in cholinergic neurotransmission (11, 12). Areas in the brain commonly affected by thiamine deficiency are the mediodorsal thalamic nucleus, mammillary bodies, the periaqueductal gray matter, the floor of the fourth ventricle, and the hippocampus (11). These areas affect memory circuits and explain the neurologic consequences of thiamine deficiency (11, 12). In addition, thiamine deficiency impairs the activity of the thiamine-dependent enzyme transketolase, which disrupts the pentose phosphate pathway impairing myelin sheath maintenance (13). O'Keeffe et al (14) demonstrated that thiamine deficiency was especially common in hospitalized elderly patients, with thiamine-deficient patients having a greater risk of developing delirium during the index hospitalization. Reduction of PDH activity has been reported in animals resuscitated from cardiac arrest, and this is associated with the degree of neurologic injury (15, 16). In a mouse model of cardiac arrest, Ikeda et al (17) reported that thiamine reduced the 10-day mortality, improved neurologic outcome, prevented histologic neurologic injury, and restored PDH levels. The study by Woolum et al (9) supports the notion that thiamine may have a neuroprotective effect in conditions associated with increased oxidative stress (16).

In clinical practice, clinicians administer thiamine almost exclusively in patients with prolonged alcohol ingestion. However, the data suggest that diverse groups of patients are at risk of thiamine deficiency, most notably elderly patients and those with sepsis. The long turnaround time for thiamine assays precludes treatment based on thiamine levels. Since thiamine administration appears to have little risk, it may be reasonable to treat all septic patients with thiamine. This is the rationale for including thiamine in the hydrocortisone, ascorbic acid, and thiamine protocol (18). The optimal dosing strategy of thiamine is unclear. Based on the study of Donnino et al (3), we have suggested a dose of 200 mg IV 12 hourly for 4 days. The most common dose in the study by Woolum et al (9) was 500 mg IV every 8 hours for 72 hours. Patients with alcohol use disorders have traditionally been treated with a "banana bag" which consists of 1 L of IV fluid infused over 24 hours and containing 100 mg of thiamine, 1 mg of folic acid, and a multivitamin formulation. In a systematic review, Flannery et al (13) suggest that this traditional dosing regimen is suboptimal, will not adequately replete thiamine body stores, will not improve clinical signs and symptoms, and will not prevent Wernicke's encephalopathy. Based on thiamine pharmacokinetics, these authors suggest abandoning the banana bag and providing 200–500 mg IV thiamine every 8 hours for least 72 hours (13).

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Effect of Thiamine Administration on Lactate Clearance and Mortality in Patients With Septic Shock*

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Objectives: Mounting evidence has shown that critically ill patients are commonly thiamine deficient. We sought to test the hypothesis that critically ill patients with septic shock exposed to thiamine would demonstrate improved lactate clearance and more favorable clinical outcomes compared with those not receiving thiamine.

Design: Retrospective, single-center, matched cohort study.

Setting: Tertiary care academic medical center.

Patients: Adult patients admitted with an *International Classification of Diseases,* 9th Edition, or *International Classification of Diseases,* 10th Edition, diagnosis code of septic shock to either the medicine or surgery ICU.

Interventions: None.

Measurements and Main Results: Patients who received IV thiamine supplementation within 24 hours of hospital admission were identified and compared with a matched cohort of patients not receiving thiamine. The primary objective was to determine if thiamine administration was associated with a reduced time to lactate clearance in septic shock. Secondary outcomes included 28-day mortality, acute kidney injury, and need for renal replacement therapy, and vasopressor and mechanical ventilation-free days. Two-thousand two-hundred seventy-two patients were screened, of whom 1,049 were eligible. The study consisted of 123 thiamine-treated patients matched with 246 patients who did not receive thiamine. Based on the Fine-Gray survival model, treatment with thiamine was associated with an improved likelihood of lactate clearance (subdistribution hazard ratio, 1.307; 95% CI, 1.002–1.704). Thiamine administration was also associated with a reduction in 28-day mortality (hazard ratio, 0.666; 95% CI, 0.490–0.905). There were no differences in any secondary outcomes.

Conclusions: Thiamine administration within 24 hours of admission in patients presenting with septic shock was associated with improved lactate clearance and a reduction in 28-day mortality compared with matched controls. (*Crit Care Med* 2018; 46:1747–1752)

Key Words: critical care; intensive care; lactate; sepsis; septic shock; thiamine

Septic shock is a metabolically demanding state that possesses a clinical presentation very similar to thiamine deficiency. Not surprisingly, a collective amount of evidence has shown that critically ill patients are commonly thiamine deficient, with metabolic stress, decreased or poor nutritional intake, and the presence of comorbidities likely serving as risk factors for the deficient state (1–5).

A recent pilot study by Donnino et al (3) evaluated thiamine administration in 88 patients with septic shock and found no benefit in the overall cohort of patients. However, in those patients with septic shock and a laboratory-confirmed thiamine deficiency, thiamine administration was associated with a reduced lactate at 24 hours and possibly a reduction in mortality (3). In clinical practice, clinicians administer thiamine for suspected thiamine deficiency, particularly in patients with prolonged alcohol ingestion or other risk factors for thiamine deficiency. We sought to evaluate a larger number of patients

***See also p. 1869.**

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Drs. Bastin and Flannery disclosed off-label product use of thiamine supplementation in septic shock. Dr. Flannery received funding from Nova Biomedical (speaking fees). The remaining authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/CCM.0000000000003311

from clinical practice to determine if thiamine administration in the setting of septic shock was associated with improved lactate clearance and clinical outcomes compared with those patients with septic shock not receiving thiamine.

MATERIALS AND METHODS

Design and Setting

We performed a retrospective, single-center cohort study to determine if thiamine administration was associated with improvements in clinical outcomes in patients with septic shock based on its hypothesized role as a metabolic resuscitator. The study was conducted at a tertiary academic medical center that serves as a regional referral center for the state and surrounding areas. The research was approved by the institutional review board. Given the observational nature of the study, we followed the STrengthening the Reporting of OBservational studies in Epidemiology checklist for cohort studies (**Appendix**, Supplemental Digital Content 1, http://links.lww.com/CCM/D822) (6).

Study Population

The electronic medical record was queried between January 1, 2013, and January 1, 2017, for patients admitted to the ICU with an *International Classification of Diseases,* 9th Edition (ICD-9), or *International Classification of Diseases,* 10th Edition (ICD-10), diagnosis code for septic shock. Patients were included in the study if they were at least 18 years old, coded for a diagnosis of septic shock at admission to the hospital, and were admitted to either the medical or surgical ICU services. Initial exclusion criteria at this stage of the query included age less than 18 years old or the development of septic shock that was not present at admission.

Patients with septic shock were initially identified using the ICD-9 or ICD-10 diagnosis code criteria. These diagnoses were validated based on the Sepsis-3 criteria of septic shock, specifically a peak lactate greater than 2 mmol/L and need for vasopressor therapy (7). Patients not meeting these criteria, or patients with missing baseline data, were excluded from the study. Thiamine administration was classified as receiving IV thiamine supplementation at any dose within 24 hours of hospital admission. ICD-9 and ICD-10 codes for septic shock and liver disease used for the data query are displayed in **eTable 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/D822).

Definitions and Outcomes

The primary outcome of the study was time to lactate clearance, defined as the time from hospital arrival to documented serum lactate of less than or equal to 2 mmol/L. If a patient survived the episode of septic shock but did not have subsequent documented lactate clearance (due to physician judgement), the lactate clearance time was calculated as the time to the measurement of the lowest lactate level plus an additional 24 hours.

Secondary outcomes included 28-day mortality (censored at hospital discharge), change in Sequential Organ Failure Assessment (SOFA) scores from baseline to day 5 of ICU (or sooner if patient was discharged or died), acute kidney injury (AKI) or need for renal replacement therapy (RRT) within the ICU, and vasopressor-free, ventilator-free, and ICU-free days within the 28 days following ICU admission (8). The serum creatinine component of the Risk, Injury, Failure, Loss, and End-stage criteria was used to define AKI based on the patient's baseline serum creatinine at admission (9). Use of RRT was identified by querying orders for continuous RRT or intermittent hemodialysis within the electronic medical record.

Statistical Analysis

Continuous data were assessed for normality with histograms and use of the Shapiro-Wilk test, reported as medians ± interquartile range, and compared between cohorts using the Mann-Whitney *U* test. Dichotomous data are presented as percentages and compared between cohorts using the chi-square or Fisher exact test, as appropriate. Matching between cohorts was performed in a 1:2 (thiamine:control) fashion using Mahalanobis distance matching based on the following characteristics: ICU service (medical vs surgical), presence of liver disease, peak lactate, SOFA score on day of ICU admission, Elixhauser comorbidity index, age, sex, and race (8, 10, 11). Statistical analysis was performed on the matched cohort for primary and secondary outcomes.

For the primary outcome of time to lactate clearance, a competing risks regression model was constructed using the methods of Fine and Gray, with mortality as a competing event (i.e., if the patient died prior to achieving lactate clearance, lactate clearance could never be achieved) (12). Three models were constructed on the matched cohort: one evaluating thiamine only, one with adjustment for age, sex, and race, and a third model with adjustment for age, sex, and race with additional relevant clinical characteristics hypothesized to influence lactate clearance and death in septic shock (13). A Cox proportional hazards model was constructed for 28-day mortality in similar fashion (lactate clearance was not considered a competing risk for mortality), and models assessed with visual inspection of the Schoenfeld residuals to ensure the proportional hazards assumption was met. A potential interaction with sex was assessed based on the possible potential impact of sex on sepsis outcomes and treatment (14). Statistical analyses were performed using Stata (StataCorp, College Station, TX), SAS (SAS Institute, Cary, NC), and R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Our initial inclusion criteria yielded 2,272 patients from the data extract. Upon validation with the Sepsis-3 criteria, 1,049 patients remained in the unmatched sample. Reasons for exclusion are displayed in **Figure 1**. Of the 1,049 unmatched patients, 123 received thiamine. In the unmatched cohort, patients receiving thiamine had a higher prevalence of liver disease and were at a higher risk of death as illustrated by higher admission SOFA scores and higher peak lactate values (**eTable 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/D822).

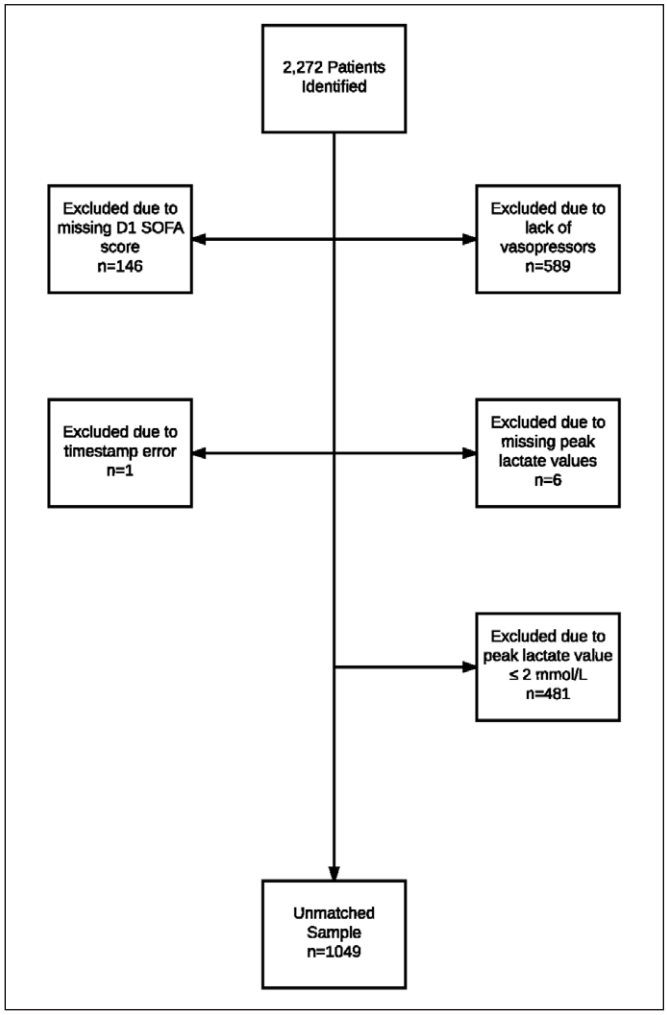

Figure 1. Study flow of inclusion and exclusion. SOFA = Sequential Organ Failure Assessment.

Following the matching procedure, 123 thiamine-treated patients and 246 patients who did not receive thiamine were available for analysis (**Table 1**). The matching process minimized all previously significant baseline demographic differences between the thiamine and control groups. Patients within the matched analysis were admitted predominantly to the medical ICU (> 95%). The matched cohort represented a severely ill patient population with septic shock (median day 1 SOFA score of 10) and a significant amount of baseline liver disease at admission (65%). Detailed data on thiamine administration, including dose and duration, are also displayed in Table 1. The median time from hospital admission to thiamine administration was 6.4 hours (3.8–11 hr). High-dose thiamine (500 mg) was the most frequently ordered dose. Thiamine was administered for a median of 3 days.

The median time to event (lactate clearance or death) in the matched cohort was 31 hours (14–59 hr). For the primary outcome of interest, three competing risks regression models were constructed from the matched cohort (**Table 2**). All three models suggest that thiamine administration is associated with improved lactate clearance with subdistribution hazard ratios (SHRs) of approximately 1.3 (SHR range from the three models, 1.292–1.339). Estimated cumulative incidence functions based on the fully adjusted models, including adjustment for clinical factors, are displayed with shaded CIs in **Figure 2**. A significant interaction was found between thiamine administration and sex, such that female patients were observed to have significant benefits in lactate clearance associated with thiamine administration compared with male counterparts (Table 2; and **eFig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/D822).

The three Cox proportional hazards models for 28-day mortality are shown in **eTable 3** (Supplemental Digital Content). In the final model including adjustment for clinical factors, thiamine was found to be significantly protective against 28-day mortality (**Fig. 3**) with a hazard ratio for death of 0.666 (95% CI, 0.490–0.905). Similar to the lactate clearance analysis, a significant interaction was found between thiamine administration and sex, suggesting a greater benefit in female patients (eTable 3, Supplemental Digital Content 1, http://links.lww.com/CCM/D822 and **eFig. 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/D822). The remainder of the secondary outcomes are displayed in **eTable 4** (Supplemental Digital Content 1, http://links.lww.com/CCM/D822) and **eFigures 3–5** (Supplemental Digital Content 1, http://links.lww.com/CCM/D822), with no significant differences observed between groups.

DISCUSSION

Thiamine is an essential component of aerobic metabolism in humans, serving as a cofactor for pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase within the Kreb's cycle (1, 2). In addition to its role in mitochondrial oxidative metabolism, thiamine also plays a critical role in the pentose-phosphate pathway where it aids in the regeneration of the reducing agent nicotinamide adenine dinucleotide phosphate (5). Deficiency in thiamine pyrophosphate, the phosphorylated and active form of thiamine, inhibits Kreb's cycle function, consequently disabling oxidative metabolism and adenosine triphosphate production. Deleterious sequelae from thiamine deficiency include lactic acidosis, hypotension, and death (1, 2, 5, 15, 16). Septic shock patients may be at particular risk for thiamine deficiency due to increased mitochondrial oxidative stress, possible decreased nutritional intake, and underlying comorbid conditions (15).

Given previous findings by Donnino et al (3) that thiamine supplementation may only improve outcomes in those patients with a laboratory-confirmed thiamine deficiency (which is not common to test for due to availability and long turnaround times), we sought to assess the effects of thiamine over a larger population of patients administered thiamine in clinical practice. Our analysis suggests that thiamine supplementation to a critically ill septic shock population is associated with improved time to lactate clearance and 28-day mortality. These results align with previous findings by other groups who found that metabolic support with IV thiamine may enhance lactate clearance and decrease mortality in critically ill patients with septic shock (4, 17).

TABLE 1. Baseline Demographics and Thiamine Administration in Matched Cohort

Variables	No Thiamine ($n = 246$)	Thiamine ($n = 123$)	p
Baseline demographics			
Age (yr), median (IQR)	54 (45–61)	52 (43–61)	0.238
Sex (male) (%)	56.10	56.10	1.000
Race (white) (%)	91.90	91.90	1.000
Liver disease (%)	65.00	65.00	1.000
Elixhauser comorbidity index, median (IQR)	4 (3–5)	4 (2–5)	0.948
Service (medical) (%)	96.80	96.80	1.000
Sequential Organ Failure Assessment score on ICU admission, median (IQR)	10 (8–12)	10 (8–12)	0.972
Stress dose steroids (%)	52.00	52.90	0.883
Peak lactate (mmol/L), median (IQR)	6 (3.3–10.5)	6 (3.3–12.1)	0.904
WBC count on ICU admission (× 10^3/μL), median (IQR)	14 (8–21)	14 (8–22)	0.844
Infection source (%)			
Bacteremia	37.0	37.4	0.939
Urinary tract	19.9	23.6	0.417
Thiamine administration			
Time from admission to thiamine (hr)	N/A	6.4 (3.8–11)	N/A
Dose (mg) (%)			
100	N/A	27.10	N/A
100–400	N/A	5.90	N/A
500	N/A	67	N/A
Duration (hr), median (IQR)	N/A	66.2 (38.2–119.5)	N/A

IQR = interquartile range, N/A = not applicable.

TABLE 2. Competing Risks Regression Models for Lactate Clearance

Models	Subdistribution Hazard Ratio (95% CI)
Primary models	
Thiamine only	1.339 (1.044–1.717)
Thiamine, age, sex, and race	1.292 (1.003–1.663)
Thiamine, age, sex, race, and clinical factors[a]	1.307 (1.002–1.704)
Interaction models with sex	
Thiamine, age, sex, and race with thiamine-sex interaction term	Female: 1.724 (1.175–2.532); male: 1.065 (0.764–1.484)
Thiamine, age, sex, race, and clinical factors[a] with thiamine-sex interaction term	Female: 1.890 (1.267–2.825); male: 1.032 (0.732–1.456)

[a]Clinical factors include liver disease, Elixhauser comorbidity index, ICU service (medical vs surgical), Sequential Organ Failure Assessment score day 1 of ICU admission, hydrocortisone, and peak lactate.

We were unable to identify any potential benefit surrounding thiamine and its potential renoprotective effects, as suggested from a post hoc analysis of a previous pilot trial (18). Previously, it had been suggested that thiamine supplementation may improve renal mitochondrial function and reduce AKI and need for RRT (18, 19). AKI in sepsis is likely multifactorial, arising due to ischemic injury, microcirculatory dysfunction, and tubular cell stress (20). Although thiamine supplementation may promote enhanced renal mitochondria function, it may be that other unaccounted factors may lead to

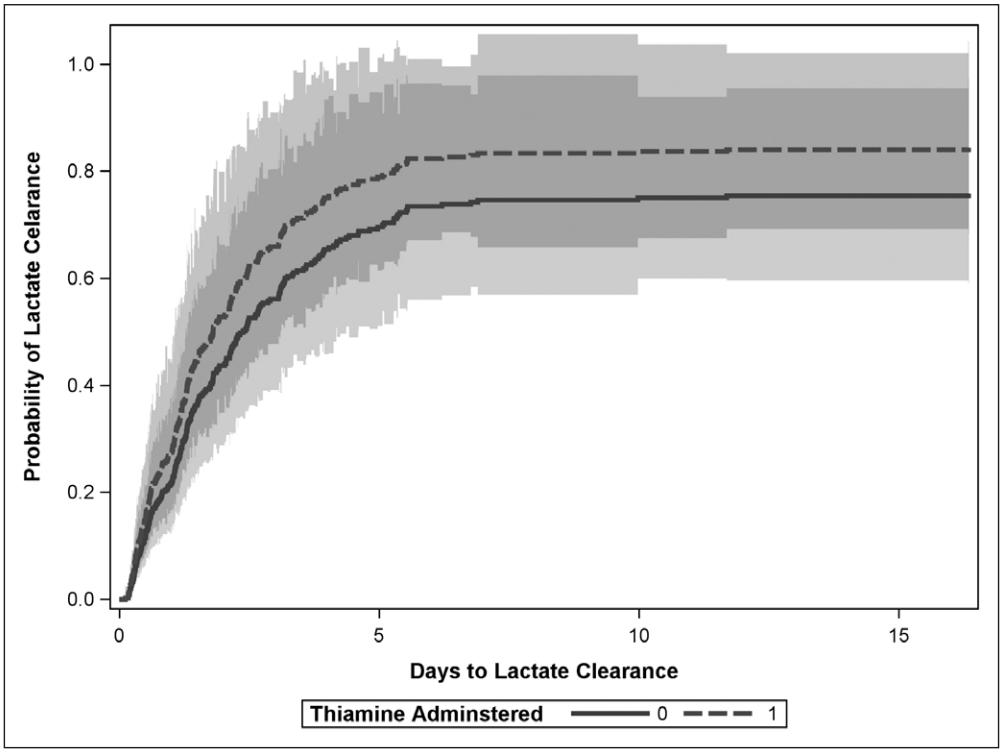

Figure 2. Probability of lactate clearance over time. 0 = no thiamine, 1 = thiamine.

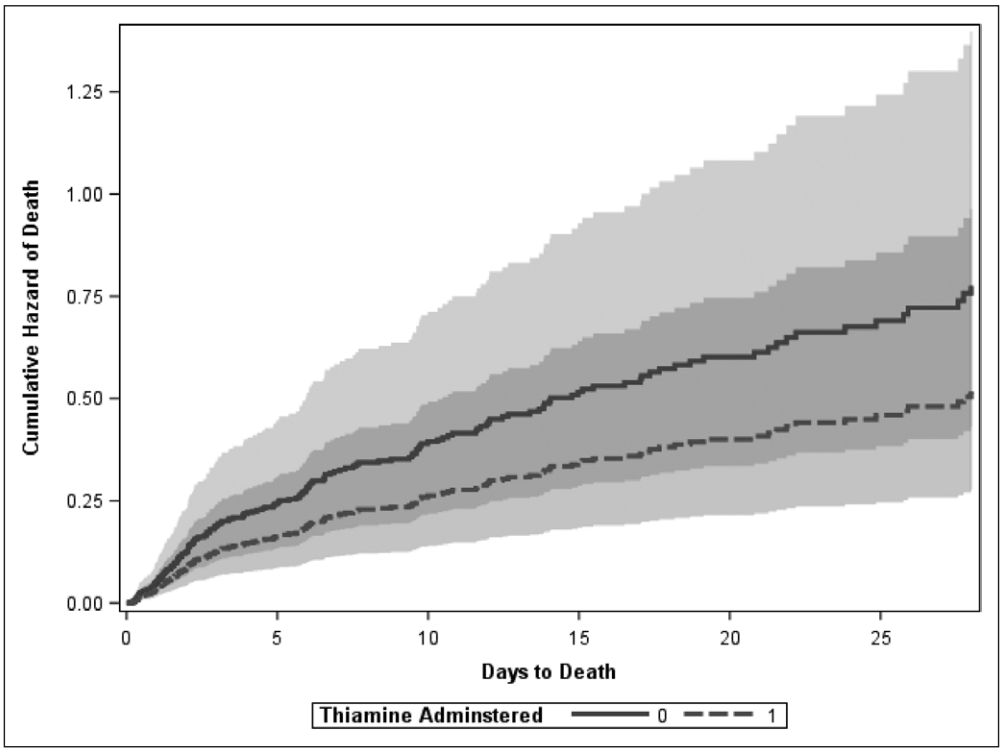

Figure 3. Cumulative hazard of death over time. 0 = no thiamine, 1 = thiamine.

the renal injuries seen in septic shock patients. Additionally, we did not discover any potential benefits regarding thiamine supplementation and improvements in vasopressor-free days, ventilator-free days, or change in SOFA scores from day 1 to day 5.

Nearly two thirds of the thiamine group received high-dose thiamine, which is consistent with a common practice at the study institution of prescribing 500 mg IV every 8 hours for 72 hours. This is a higher dosing of thiamine than evaluated in prior studies of thiamine in septic shock. Higher thiamine doses may offer the advantage of improved passive absorption into the CNS and improvements in thiamine exposure due to the rapid elimination of thiamine from the serum into the urine (21–23). Thiamine is a particularly safe and inexpensive therapy, and although it remains an investigational agent for septic shock, now deserves a larger clinical trial to confirm these findings. The long turnaround time for thiamine assays likely precludes isolation of thiamine-deficient patients for randomization in a clinical trial of patients with septic shock. Until reliable, rapidly available testing to identify thiamine-deficient patients is available, overtreatment with thiamine is likely to occur. However, given the safety profile and low cost of thiamine, the potential benefits may far outweigh the risks.

One surprising finding was the interaction between gender and thiamine response, with females responding more favorably. This could represent a greater likelihood of thiamine deficiency among female patients with septic shock, an improved response to thiamine for another reason or simply be a chance finding. Although women may be at risk of thiamine deficiency during pregnancy and lactation due to increased requirements, this is the first association of a gender interaction with response to thiamine that has been described (24). This should be considered hypothesis generating and addressed in future studies of thiamine in septic shock.

Our study is the largest yet to associate thiamine administration in septic shock with improved clinical outcomes, specifically improved lactate clearance and reduced 28-day mortality. The patient cohort was validated with Sepsis-3 definitions and was well matched following our matching procedure. With such a high mortality rate, we carefully considered the effects of mortality as a competing event in our competing risks analysis and adjusted for relevant covariates. Although not causal inference due to the observational nature of the data, we identified a biologically plausible mechanism (improved lactate clearance due to metabolic resuscitation) and associated that with a mortality benefit in this critically ill population with septic shock.

There are important limitations of this study that deserve mention. First, the prescription of thiamine was not randomized and given in clinical practice upon clinician suspicion of thiamine deficiency given the patient history (as opposed to being given as a treatment for septic shock). Although we have attempted to capture and adjust for differences between these two cohorts, unmeasured confounders may exist. Second, no standardized protocol existed for when and how often to obtain repeat lactate values, which may influence the outcome of lactate clearance. Third, this was a retrospective study, and the data quality is limited to that documented in the electronic medical record. Our study also included a large percentage of cirrhotic patients, who are not representative of the typical patient population observed in traditional trials of septic shock. Perhaps accordingly, our mortality rates were also higher than recent studies in septic shock (25, 26). Furthermore, the categorization of liver disease was done so by ICD-9 or ICD-10 codes, which may have limited our ability to more clearly define this potentially at-risk patient population.

CONCLUSIONS

For patients in septic shock admitted to the ICU, receipt of thiamine within the first 24 hours of admission was associated with improved lactate clearance and a reduction in 28-day mortality compared with a matched cohort of patients who did not receive thiamine. Further randomized trials are warranted to evaluate this safe and inexpensive therapy for septic shock.

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