Obbic glycolysis is a much less efficient pathway for ATP production as pyruvate (glycolysis end substrate) is converted into lactate (Fink, M. 1997). Thiamine (Vit B1), a water-soluble vitamin B with limited storage capacity, is an important cofactor in the aerobic metabolism pathway via pyruvate dehydrogenase enzyme. So in malnourished septic critically ill patients, thiamine deficiency associated hyperlactatemia is highly probable. Thiamine infusion as an adjunctive nutritional and therapeutic intervention might facilitate the glucose driven ATP production and reduce mortality at the cellular level. In this article review, we postulate a new nutritional/therapeutic strategy that may probably have a positive clinical impact and possibly mitigate the sepsis-associated mortality in septic malnourished critically ill patients.

**Keywords:** Thiamine Associated Hyperlactatemia, Lactic Acidosis, Vitamin B1, Septic Shock, Malnutrition Critically Ill Patients, Elevated Anion Gap Metabolic Acidosis.

**INTRODUCTION**

Septic patients are commonly manifested by specific and non-specific signs and symptoms that including but not excluded to hypotension/hypoperfusion, hyperdynamic cardiac reflex, elevated shock indices (e.g., shock index and modified shock index), stress-induced hyperglycemia, and hyperlactatemia (Gauer, R. 2013, July 1). Lactate hyperproduction accompanied with/without a low clearance rate is commonly encountered in septic critically ill patients and is primarily associated with elevated anion gap metabolic acidosis (Ganesh, K. et al., 2016).

Metabolically, glucose is the preferred energy-yielding macronutrient as it has the least oxygen consumption rate (VO2) but in the case of sepsis-related hypoperfusion and cellular hypoxemia, aerobic metabolism is automatically shifted toward the anaerobic pathway. It is well known that anaerobic glycolysis is a much less efficient pathway for ATP production as pyruvate (glycolysis end substrate) is converted into lactate via pyruvate dehydrogenase instead of the Krebs cycle entering and processing (Beltramo, E. et al., 2008). Thiamine (water-soluble vitamin) has diverse physiologically functions as a co-factor for transketolase (TK), pyruvate dehydrogenase, and α-ketoglutarate dehydrogenase complexes. One of the key enzymes in the glycolysis pathway and ATP production is pyruvate dehydrogenase which necessarily needs thiamine in its metabolic processing. Without thiamine, pyruvate is reversibly converted into lactate (Fink, M. 1997).
In case of malnutrition associated thiamine deprivation as in the case of septic critically ill patients, thiamine stores can be completely depleted as soon as few days and thiamine deficiency related cardiovascular, neurological, immunological, and metabolic signs and symptoms could have early ensued after admission into intensive care unit (ICU). Several published data had revealed that hyperlactatemia was associated with septic mortality independent from mortality confounders (Suetrong, B., & Walley, K. 2016). In addition to stress-induced response syndrome (SIRS), decreasing glucose turnover rate efficacy may amplify the stress-induced hyperglycemia and other metabolic dysfunctions clinical consequences in these hyperdynamic/hypermetabolic malnourished septic critically ill patients (Mikkelsen, M. E. et al., 2009).

Thiamine deficiency is theoretically seemed to exacerbate the lactate hyperproduction in severe malnutrition hyperlactatetemia associated septic critically ill patients. Based on the aforementioned concepts, we speculate that thiamine infusion may be considered as an innovative adjunctive nutritional/therapeutic strategy that may be early used in selected cases of severe malnourished septic critically ill patients accompanied with hyperlactatetemia in hope of reducing the high mortality rate as much as possible in these victim cohorts.

**DISCUSSION**

Biochemically, thiamine is a precursor of thiamine diphosphate (TDP), the active cofactor for diverse anabolic and catabolic intermediary metabolic enzymes, which is required at several stages of, such as the intracellular glucose metabolism (glycolysis, Krebs cycle, pentose-phosphate cycle). Deficiency in thiamine leads to several disorders such as; Beriberi, neurological and cardiovascular disease, and metabolic disorders. Chronic thiamine deficiency can be clinically manifested as pain in the limbs, weakness of the musculature, distorted skin sensation, and cardiomyopathy associated-heart failure. In more severe cases of acute thiamine deficiency, as in severe malnourished hospitalized patients, Wernicke–Korsakoff syndrome, cerebral beriberi, and metabolic complications related to refeeding syndrome may be early manifested after admission. Wernicke–Korsakoff syndrome is a neuropsychiatric disorder, diagnosed clinically by paralysis of eye movements, abnormal stance and gait, and markedly deranged mental function which may rapidly progress into irreversible neuro-complications if thiamine is not urgently administered (Loiacono, L. A., & Shapiro, D. S. 2010).

Lactate is a marker of aerobic mitochondrial dysfunction and anaerobic tissue metabolism. Lactate can convert to pyruvate in the liver by cori cycle and the body maintains constant lactate to pyruvate ratio. In clinical conditions where tissue oxygenation is low, the body system is overwhelmed and the buffering system cannot maintain the normal blood pH. Hypoxia affects the metabolism of pyruvate and its intracellular level increases. Accumulation of lactate reduces blood pH below 7.35. In sepsis, tissue-related hypoxic injury is the result of hypoxemia and hyperperfusion and cytokine-mediated mitochondrial dysfunction termed cytopathic hypoxia. As known, oxidation of pyruvate efficiency and rate is substantially affected by thiamine deficiency with the subsequent further accumulation of lactate that ultimately leads to lactate acidosis (O’Donnell, K. 2017).

While hyperlactatetemia is a common finding in septic critically ill patients, the lactate level is one of the diagnostic and prognostic criteria for sepsis. As previously explained, malnourished critically ill patients have a higher propensity of thiamine deficiency which may exacerbate hyperlactetetemia. One possible explanation for increased lactate production in sepsis is down-regulation of the activity of the enzyme complex, pyruvate dehydrogenase (PDH), which regulates the oxidation of pyruvate to acetyl-CoA. The pyruvate accumulates within the cytosol since the consumption of this partially oxidized metabolic fuel via the TCA cycle is blocked. During anaerobic glycolysis, NAD is reduced to NADH as a consequence of the reaction catalyzed by glyceraldehyde-3-phosphate dehydrogenase. To regenerate NAD under anaerobic conditions, cells convert pyruvate to lactate in the reaction catalyzed by lactate dehydrogenase (Gunnerson, K., & Harvey, C. 2018).

Thiamin deficiency in sepsis-related hypotension/hyperperfusion malnourished critically ill patients may overestimate the diagnostic and prognostic efficacy of lactate indicator. So, the correction of thiamine deficiency in septic critically ill patients may improve the prognostic capability of sepsis-related hyperlactetetemias prognosticator and improve overall survival rate. Thiamine supplementation as an adjunctive treatment may potentially improve septic state and possibly reducing the lactate level significantly (Samra, J. S. et al., 1996). Because thiamine is safe, inexpensive, and readily available to use, we propose giving thiamine infusion in addition to other supportive and therapeutic recommended interventions, in hope of reducing malnourished septic critically ill patients' mortality rate.

**CONCLUSION**

Thiamine deficiency is highly suspected in severely malnourished septic critically ill patients, and it is usually underinvestigated. Adjunctive thiamine supplementation via intravenous infusion in these critically ill cohorts may help in mitigating the high mortality risk. Thiamine infusion may result in rapid correction of lactate level in our selected...
studied patients. Further clinical trials and investigations are needed to support thiamine infusion in septic malnourished patients.

REFERENCES