

Type B Lactic Acidosis Secondary to Thiamine Deficiency in a Child With Malignancy

Sareen Shah, MD^a, Eric Wald, MD, MSCI^b

Type B lactic acidosis is an underrecognized clinical entity that must be distinguished from type A (hypoxic) lactic acidosis. We present the case of a 4-year-old boy with medulloblastoma who presented with lactic acidosis in the setting of septic shock. His hyperlactatemia persisted to high levels even after his hemodynamic status improved. After administration of intravenous thiamine, his lactate level rapidly normalized and remained stable. It was determined that his total parenteral nutrition was deficient in vitamins due to a national shortage. Because thiamine is an important cofactor for pyruvate dehydrogenase, he was unable to use glucose through aerobic metabolism pathways. We briefly review type A versus type B lactic acidosis in this case report.

Tissue hypoxia is the most common cause of clinically significant lactic acidosis, usually secondary to disease processes such as sepsis, multiorgan failure, and malignancy. Type A or hypoxic lactic acidosis must be differentiated from type B or nonhypoxic etiologies of lactic acidosis in the appropriate clinical context. Numerous drugs, toxins, and inherited or acquired enzymatic defects in metabolic pathways can lead to either overproduction or underutilization of lactate.¹ Because most clinicians are more familiar with hypoxic lactic acidosis, the evaluation is usually directed toward trying to uncover a source of tissue hypoperfusion or hypoxia, potentially leading to a delay in recognizing a type B presentation (especially when there is a mixed clinical picture of both type A and type B). We present the case of a child with medulloblastoma who presented with type B lactic acidosis associated with sepsis and thiamine deficiency. We also briefly discuss the biochemistry of lactate production and potential links between thiamine and cancer.

CASE PRESENTATION

A 4-year-old boy with a history of medulloblastoma status-post partial resection and port placement presented to the PICU with fever, hypotension, and tachycardia. His mentation was normal. Initial laboratory test results demonstrated neutropenia (ANC 288), a venous blood gas of pH 7.30, CO₂ of 34.7 mm Hg, HCO₃⁻ of 17.1 mEq/L, a base deficit of 9, and lactate level of 12.8 mEq/L. Kidney function and liver test results were normal on admission. The urine culture grew *Enterococcus* species sensitive to the prescribed antibiotics. He received adequate fluid resuscitation with normal saline, antibiotics for the treatment of septic shock, and norepinephrine and stress-dose hydrocortisone to maintain appropriate blood pressures.

Despite achieving adequate blood pressures for age and improved perfusion, the patient's lactate remained in the 10- to 12-mEq/L range. He was noted to be polyuric from the beginning of admission and

abstract

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Dr Shah helped conceptualize the case report; helped write the first draft of the manuscript; participated in the literature search, editing, and drafting of the final manuscript; and prepared the figures in the manuscript. Dr Wald conceptualized the case report and participated in all drafts of the manuscripts, including literature search as well as review, editing, and drafting of the final manuscript. Both authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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began to develop substantial electrolyte wasting during hospital day 2. Urinalysis was notable for granular casts, suggesting the diagnosis of acute tubular necrosis (although no oliguric phase had been noted).

The patient was weaned from vasoactive medications on hospital day 3. That evening, he developed a worsening lactic acidosis (peak lactate of 19 mEq/L; pH of 7.21) and concomitant hyperglycemia along with altered mental status. Given his adequate perfusion and the concern for type B lactic acidosis, the patient was started on insulin therapy. This therapy was chosen given the theoretical benefit of stimulating the oxidation of pyruvate through the pyruvate dehydrogenase (PDH) pathway, but lactate levels remained elevated. An abdominal radiograph was concerning for possible free air; given the acute rise in lactate with concern for intra-abdominal pathology, he was taken for exploratory laparoscopy. No signs of perforation, ischemia, or bowel compromise were evident.

Because of a high suspicion that the patient's lactic acidosis did not result from tissue hypoxia, he received a 25-mg dose of intravenous thiamine and 25 mg/kg of intravenous levocarnitine after his return from the operating room. Within 4 hours, his lactate level had fallen to 4.8 mEq/L, and within 24 hours, it had decreased to 2.4 mEq/L (Fig 1). Concurrently, he developed a dramatic metabolic alkalosis secondary to intrinsic bicarbonate that was produced as a consequence of higher serum lactate. His respiratory drive decreased to compensate for this change in acid-base status, and he was placed on noninvasive positive-pressure ventilation to improve his minute ventilation and was given acetazolamide to counteract the metabolic alkalosis. His urine output normalized, and his hyperglycemia resolved.

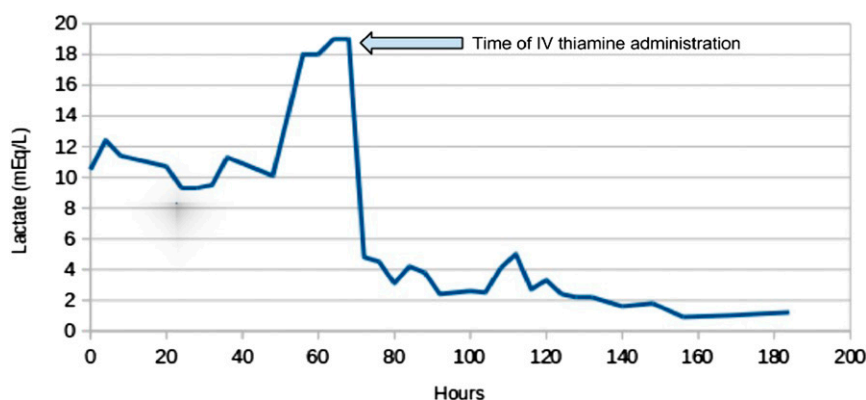


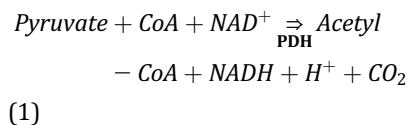
FIGURE 1 Effect of thiamine administration on lactate level. Patient's lactate levels dropped after administration of intravenous (IV) thiamine.

Additional history revealed that he had been taking very little nutrition by mouth before admission secondary to intractable vomiting and was primarily dependent on total parenteral nutrition (TPN). There were no vitamins in his TPN, and thus he was likely deficient in thiamine on initial presentation.

PATHOGENESIS OF LACTIC ACIDOSIS

There are 2 categories of lactic acidosis. In type A lactic acidosis, there is marked tissue hypoperfusion or hypoxia (eg, due to sepsis or hypovolemia). With type B lactic acidosis, there is no impairment in oxygenation. There are many potential causes for type B lactic acidosis, including multiorgan failure, certain drugs or toxins, and metabolic abnormalities.

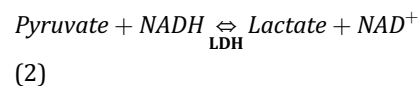
In aerobic metabolism, pyruvate enters mitochondria, where it is oxidized by the PDH complex (equation 1)²:



The acetyl-CoA product can be used for multiple purposes, one of which is entering the Krebs cycle in aerobic metabolism to generate significantly more adenosine triphosphate compared with anaerobic metabolism (Fig 2). The PDH complex has

multiple cofactors including thiamine pyrophosphate, without which it cannot generate acetyl-CoA for the Krebs cycle. Carnitine is also important for aerobic metabolism because it serves to transport fatty acid metabolites into the mitochondria as well as acting as a cofactor at multiple steps in the electron transport chain.³

If pyruvate cannot be used for the Krebs cycle (eg, in thiamine deficiency), it can be converted to lactate by the enzyme lactate dehydrogenase (LDH) (equation 2).



Clinicians typically associate lactic acidosis with tissue hypoperfusion (type A). This condition arises because with decreased oxygen supply to tissues, the electron transport chain cannot oxidize substances such as nicotinamide adenine dinucleotide ([NADH]→NAD+), and there is an abundance of reduced substances. As NAD+ must be regenerated by some other reaction, the forward reaction of equation 2 is favored and lactate is generated.

In both contexts (hypoxic conditions or problems with the PDH complex including thiamine deficiency), pyruvate is preferentially converted to lactate instead of entering the

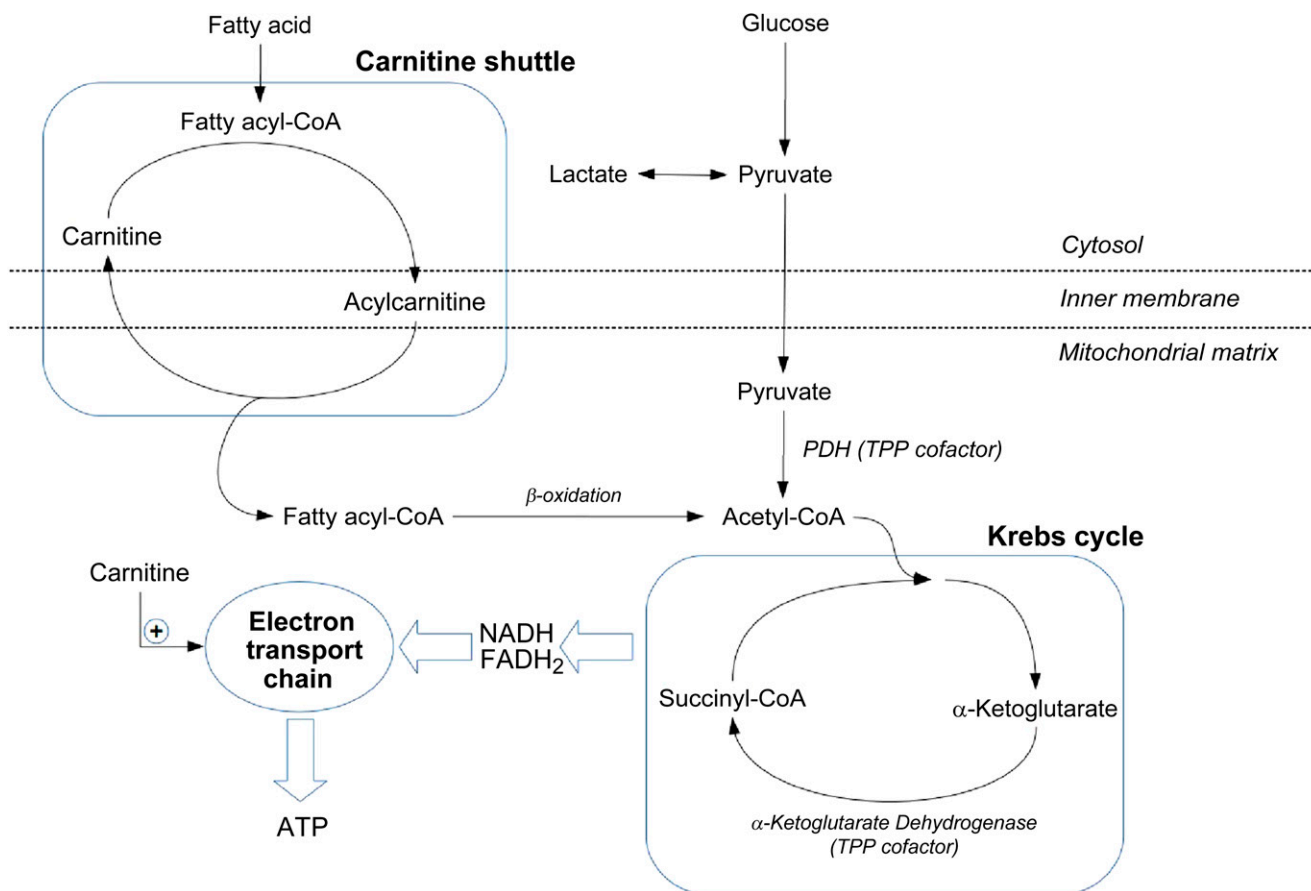


FIGURE 2

Fate of pyruvate in aerobic and anaerobic metabolism. Note the role of carnitine and thiamine in metabolism. ATP, adenosine triphosphate; FADH_2 , reduce form of flavin adenine dinucleotide; NADH, nicotinamide adenine dinucleotide; TPP, thiamine pyrophosphate.

Krebs cycle, and a significant energy loss occurs. However, the reasons behind the lactate generation are different and have vastly different clinical implications.

DISCUSSION

Clinicians must be aware that there are different types of lactic acidosis. If the clinical context and examination are not consistent with tissue hypoxia, but hyperlactatemia persists, then alternative causes of type B lactic acidosis should be investigated.¹ The list is extensive and includes underlying diseases (eg, renal failure, malignancy), drugs, toxins, and metabolic derangements.

Our patient was largely TPN dependent but was not taking multivitamins; without thiamine, his mitochondria were unable to process

pyruvate into acetyl-CoA. Thiamine and L-carnitine were administered empirically to support mitochondrial metabolism. His lactate:pyruvate ratio before thiamine and L-carnitine administration was 20, which more strongly supports a PDH complex impairment rather than an electron transport chain impairment (eg, carnitine deficiency), in which one would expect a higher ratio.⁴ Thus, although both thiamine and L-carnitine were administered simultaneously, we believe that thiamine administration was the more critical component in our patient.

A *Morbidity and Mortality Weekly Report* from 1997 addressed lactic acidosis related to thiamine deficiency in 3 patients who were TPN dependent with little or no oral nutrition.⁵ The report was issued

during a nationwide shortage of intravenous multivitamins that began in November 1996. These patients responded dramatically to thiamine administration, with rapid resolution of lactic acidosis and subsequent improvement in neurologic status. Interestingly, a national shortage of intravenous multivitamins occurred during this child's use of TPN, and reports of thiamine deficiency–related lactic acidosis are once again being described.⁶

Our patient's underlying malignancy may have contributed to his type B lactic acidosis because this phenomenon has been reported in various types of cancers independent of thiamine status (most often with leukemias and lymphoma).⁷ The pathophysiology of this association is not well understood, and several mechanisms have been proposed.

Some studies suggest that rapidly growing malignant cells preferentially use thiamine, leading to a relative thiamine deficiency⁸ and increased cancer proliferation.⁹ Certain tumor cells overexpress glycolytic enzymes such as hexokinase, which may also help facilitate rapid proliferation.¹⁰ The neoplastic tissue beds in solid tumors are relatively ischemic compared with normal tissue,¹¹ and these cells often use anaerobic metabolism, which leads to lactate accumulation. Regardless of the underlying etiology or pathophysiology, type B lactic acidosis in children and adults with malignancy is associated with an extremely high mortality.¹⁰

Our patient's initial presentation with septic shock made both type A and type B lactic acidosis plausible. Although sepsis directly leads to decreased perfusion and tissue hypoxia, it also decreases lactate clearance.¹² Our patient's lactate:pyruvate ratio was 20, which is more consistent with a mixed lactic acidosis rather than purely type B. His initial pH was also only mildly acidotic at 7.30, which may be helpful in determining etiology of lactic acidosis. Type B lactic acidosis is not associated with a primary problem in generating adenosine triphosphate, and therefore the rate at which hydrogen ions accumulate is much lower than in type A lactic acidosis.¹³ Thus, pH may not be as severely depressed as is seen in the type A form. Type B lactic acidosis can be a difficult diagnosis to make unless it is considered at the bedside. On examination when off vasoactive

medications, our patient was warm, well perfused, and not hyperdynamic. His biomarkers of end-organ function (including creatinine, albumin, and coagulation parameters) were normal except for lactate. Because his constellation of signs and symptoms made tissue hypoxia an unlikely etiology of his lactic acidosis, alternative diagnoses were considered. Given their few adverse effects, thiamine and L-carnitine were administered empirically. In critically ill children, there can be multiple etiologies for persistent lactic acidosis, and although tissue hypoxia and hypoperfusion are the most frequent causes, consideration should be given to other potential contributing factors.

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