JPPT | Topic Review

An Overview of Type B Lactic Acidosis Due to Thiamine (B1) Deficiency

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Type B lactic acidosis can occur secondary to several factors, including thiamine deficiency, and is not as common as type A. Recognizing thiamine deficiency–associated lactic acidosis is challenging because serum thiamine concentrations are not routinely obtained, and a thorough and specific history is necessary for clinicians to suspect thiamine deficiency as a root cause. Furthermore, the appropriate dose and duration of thiamine treatment are not well defined. Untreated thiamine deficiency–associated lactic acidosis can lead to critical illness requiring lifesaving extracorporeal therapies. Additionally, if thiamine and glucose are not administered in an appropriate sequence, Wernicke encephalopathy or Korsakoff syndrome may occur. This review aims to summarize therapeutic treatment for thiamine deficiency–associated lactic acidosis, based on case reports/series and nutritional guidance. After a literature search of the PubMed database, 63 citations met inclusion criteria, of which 21 involved pediatric patients and are the focus of this review. Citations describe dosing regimens ranging from 25 to 1000 mg of intravenous (IV) thiamine as a single dose, or multiple daily doses for several days. Specific guidance for critically ill adults recommends a thiamine range of 100 mg IV once daily to 400 mg IV twice daily. Although there are no specific recommendations for the pediatric population, given the relative safety of thiamine administration, its low cost, and our review of the literature, treatment with thiamine 100 to 200 mg IV at least once is supported, with ongoing daily doses based on clinical response of the patient, regardless of age.

ABBREVIATIONS ASPEN, American Society for Parenteral and Enteral Nutrition; ATP, adenosine triphosphate; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; ESPEN, European Society for Clinical Nutrition and Metabolism; IM, intramuscular; IV, intravenous; MeSH, Medical Subject Headings; PDH, pyruvate dehydrogenase; PICU, pediatric intensive care unit; TPN, total parenteral nutrition

KEYWORDS acidosis; lactate; beriberi; malnutrition; thiamine deficiency; Wernicke encephalopathy

J Pediatr Pharmacol Ther 2023;28(5):397–408

DOI: 10.5863/1551-6776-28.5.397

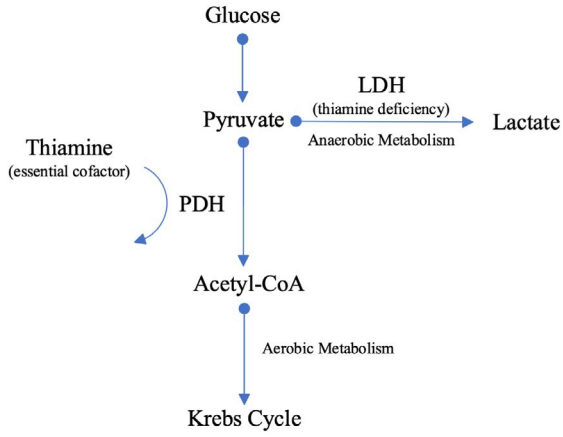
Introduction

Lactic acidosis can be divided into 2 different types (A and B). Lactic acidosis type A is the most common type, characterized by hypoxemia that is typically a result of septic shock. However, it can also be due to hypovolemic shock, cardiogenic shock, and other disease processes that cause tissue hypoperfusion. When the suspected cause of lactic acidosis is due to septic shock, treatment includes rapid fluid resuscitation, in addition to administration of intravenous (IV) antibiotics in an attempt to resolve a potential underlying infection. Type B lactic acidosis is considered when a patient has persistently elevated blood lactate concentrations, but no evidence of inadequate oxygenation. There are several potential causes of type B lactic acidosis, including multiorgan failure, drugs/toxins (e.g., metformin), vitamin deficiencies (e.g., thiamine), and metabolic abnormalities.[1]

Normally, when the body performs aerobic metabolism, pyruvate enters the mitochondria and is oxidized by the pyruvate dehydrogenase (PDH) complex into acetyl-CoA. Acetyl-CoA is used in the Krebs cycle to generate adenosine triphosphate (ATP). Thiamine deficiency leads to lactic acidosis because thiamine is a cofactor of the PDH complex that helps convert pyruvate to acetyl-CoA. If thiamine is deficient and pyruvate cannot be used for the Krebs cycle, it is converted to lactate by the enzyme lactate dehydrogenase in anaerobic metabolism, leading to lactic acidosis (see Figure).[2]

Causes of thiamine deficiency–associated lactic acidosis that have been described in the literature include lack of vitamin supplementation, chronic alcohol abuse, advanced malignancy, and functional deficiency. From case reports describing pediatric patients, the most commonly reported causes of thiamine deficiency–associated lactic acidosis are due to enteral or parenteral nutritional deficits.[3–23] In contrast, adult case reports most commonly identified nutritional deficiency, chronic alcohol abuse, and advanced malignancy as the primary precipitating factors.[24–65]

Figure. Role of thiamine in aerobic and anaerobic metabolism.



LDH, lactate dehydrogenase; PDH, pyruvate dehydrogenase.

Thiamine deficiency disorders have been characterized into 5 different categories by common presenting symptoms in specific age groups. The first category is the acute cardiologic form most commonly present in exclusively breastfed infants beginning with nonspecific signs including colic, restlessness, vomiting, and progressing to cyanosis with difficulty breathing and signs of heart failure. Next, the aphonic form is the second category of thiamine deficiency disorders peaking around the age of 4 to 6 months and is characterized by nonspecific signs including a hoarse cry, restlessness, and breathlessness. Thirdly, the pseudomeningitis form commonly occurs in 7 to 9-month old infants. This form is distinguished by nystagmus, muscle twitching, bulging fontanelle, convulsions, and could lead to unconsciousness. The fourth category is encephalopathy, which generally occurs in older children or adults, but does not exclude infants. Patients may present with apathy, nystagmus, ophthalmoplegia, ataxia, and eventually impaired consciousness/coma. Finally, peripheral neuropathies, most commonly seen in children and adults, are characterized by pain, tingling in hands or feet, muscle wasting, loss of ankle or knee reflexes, and/or cranial nerve impairment. Importantly, it is unlikely for a patient to present with all signs/symptoms within a category, and most symptoms are nonspecific, making the diagnosis challenging.[66]

Several questions arise when considering thiamine replacement treatment options, including dose of thiamine, duration, effects of extracorporeal therapies (e.g., extracorporeal membrane oxygenation [ECMO] and continuous renal replacement therapy [CRRT]) on thiamine supplementation, and the timing of coadministration of glucose-containing fluids. To our knowledge, no specific studies have addressed these questions in the pediatric population. Thus, this review describes the data identified in pediatric case reports/series.[3–23] Additional data identified from reports in adults are summarized in the Supplemental Table.[24–65]

Potential Complications

Several complications have the potential to be detrimental to thiamine-deficient patients if not taken into consideration, which include the use of extracorporeal therapies in critical illness and risks associated with administering IV glucose-containing products prior to thiamine supplementation.

Untreated lactic acidosis of thiamine deficiency can lead to the progression of critical illness and the need for lifesaving extracorporeal therapies. Additionally, pharmacokinetic changes have been documented for several micronutrients while on extracorporeal therapies.[67–71] The extent of alteration depends on several factors including the medication administered and circuit components, but thiamine is likely to have altered pharmacokinetics in both ECMO and CRRT (e.g., increased volume of distribution, aggravated losses) and this must be considered when treating patients with thiamine deficiencies while on extracorporeal therapies. Lastly, identification and treatment of thiamine deficiency in these patients is pivotal for improvement.

In a state of thiamine deficiency, the body reverts to anaerobic metabolism, converting pyruvate to lactate. If glucose is given prior to correcting the thiamine deficiency, the body will initiate glycolysis, creating more pyruvate, but no ATP. Pyruvate accumulates and continues to produce more lactate, worsening the lactic acidosis. In an ATP-deficient state, cells are unable to maintain their normal biologic functions, including protecting the cell from outside stressors such as reactive oxygen species, leading to damage of many intracellular structures and eventual programmed cell death.[72] These acute cellular changes can lead to a cognitive impairment known as Wernicke encephalopathy that is characterized by a triad of symptoms including gait ataxia, vision changes, and confusion.[73] Although Wernicke encephalopathy is most commonly associated with the adult population, infantile thiamine deficiency can also present in this manner. Infants most commonly present with vomiting, low Glasgow Coma Scale scores, seizures, vacant stares, and ptosis according to a retrospective review of infants in a tertiary care hospital.[11] According to adult guidance, administration of thiamine 100 mg IV once or 250 mg intramuscularly (IM) daily for 3 to 5 days, with the first dose prior to glucose-containing IV fluids in patients at risk of thiamine deficiency, may prevent the development of Wernicke encephalopathy.[72,74] To the best of our knowledge, there are no reported data on the prevention of Wernicke encephalopathy in pediatric patients, therefore, dosing must be extrapolated from adult data. However, a review on infantile thiamine deficiency recommends a 2 mg/kg daily dose of thiamine in infants younger than 6 months to mitigate the risk of thiamine deficiency

while managing patients who have severe acute malnutrition.[75] Wernicke encephalopathy in adults should be treated with thiamine 500 mg IV, 3 times daily for 2 to 3 days, followed by 250 mg IV daily for 3 to 5 days. Although no fixed guidance, treatment for pediatric patients has been suggested as thiamine 50 to 100 mg daily or about 14 mg/kg of thiamine. However, thiamine 100 mg daily is most routinely recommended.[74,76] If left untreated, a state of chronic thiamine deficiency can progress from Wernicke encephalopathy to Korsakoff syndrome, which is characterized by amnesia that is usually irreversible and is associated with a poor prognosis. Wernicke encephalopathy and Korsakoff syndrome are most commonly reported in patients with alcohol use disorder; however, they can also occur in situations where patients have other etiologies of thiamine deficiency.[73]

Overview of Nutritional Guidance

Reported normal recommended dietary allowance of thiamine, based on patient age, to maintain sufficient nutrient requirements is reported below[74,77]:

1 to 3 years: 0.5 mg/day
4 to 8 years: 0.6 mg/day
9 to 13 years: 0.9 mg/day
14 to 18 years: 1 to 1.2 mg/day
Adult men: 1.1 mg/day
Adult women: 1.2 mg/day
Pregnant women: 1.4 mg/day

Of note, these are recommendations for average daily requirements, not for patients who have deficiency. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on parenteral nutrition in intensive care recommend an adult daily IV dose of 100 to 300 mg of thiamine during the first 3 days in the intensive care unit when thiamine deficiency is possible.[78] Frank[77] suggests that in adult patients presenting with critical illness, a dosing range of thiamine 100 mg IV once daily up to 400 mg IV twice daily can be considered. The American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines recommend that patients receiving long-term parenteral nutrition receive daily thiamine, ascorbic acid, pyridoxine, and folic acid, stating that thiamine is critical, because several deaths have resulted from cardiac failure due to thiamine deficiency after receiving long-term parenteral nutrition without vitamin supplementation for 3 to 4 weeks.[79] These nutritional guidelines do not mention any pediatric-specific dosing guidance.

Review of Literature

Sixty-three citations were identified through a search of the PubMed medical database (performed February 2023; inclusive of 1965–2023) using the following MeSH (Medical Subject Headings) terms: *lactic acidosis*, *beriberi*, *malnutrition*, *thiamine deficiency*, and *Wernicke encephalopathy*.[3–65] Citations were included if available in English, with description of type B lactic acidosis, and a documented thiamine deficiency and/or a response to thiamine administration. Of the 63 citations, 21 described pediatric patients; 20 with thiamine deficiency due to an enteral or parenteral nutritional deficit, and 1 describing a presumed functional deficiency.[3–23] Citations will be summarized by mechanism of deficiency. Adult case reports were also identified, and the most common causes of thiamine deficiency among these individuals included nutritional deficits, alcohol use, and advanced malignancy. Adult cases will not be discussed in detail within this review, but a brief summary of each case can be found in the Supplemental Table.[24–65]

Enteral-Associated Deficiency. Enteral-associated deficiencies occurred by 2 main mechanisms. Infantile cases were secondary to thiamine-deficient formula or diet in the mother, whereas older patients were described to have limited diets or chronic illnesses that resulted in reduced intake.

Baird and Ravindranath[3] describe a report of an 11-year-old male with a history of autism spectrum disorder and developmental delay. He presented to the hospital altered from baseline and his laboratory test results demonstrated a metabolic acidosis, hyperlactatemia (peak blood concentration of 170.27 mg/dL), and pyridoxine deficiency. The patient's family reported that his diet consisted solely of chicken nuggets and french fries 3 times daily for several years without supplementation of any fruits, vegetables, or milk products. He was given thiamine 25 mg IV daily that was continued for 9 days and within hours of administration of the first dose, the lactic acidosis significantly improved. Pretreatment serum thiamine concentration was not obtained. On day 12 of hospital admission, the patient developed generalized tonic-clonic seizures. A parenteral dose of pyridoxine 100 mg was administered, followed by daily supplementation. His neurologic status gradually improved.

A case report by Derespina et al[4] describes a 22-month-old female diagnosed with high-risk neuroblastoma who was admitted to the hospital to receive an autologous stem cell transplant. Five cycles of chemotherapy had been completed previously, leading to the development of grade IV mucositis and vomiting, ultimately causing decreased enteral intake over the previous 4 months. On day 12, the patient developed a metabolic acidosis with a blood lactic acid concentration of 109.01 mg/dL. The acidosis continued to worsen through day 14, with concentrations reaching 253.25 mg/dL and subsequently exceeding detectable levels. Type B lactic acidosis was suspected, and thiamine 25 mg IV was administered with profound improvement to a concentration of 45.05 mg/dL within 7.5 hours. Pre-supplementation serum thiamine concentration was confirmed and a deficiency at 2.13 mcg/dL (reference range, 2.64–6.25 mcg/dL) was noted. Acid-base status normalized, and thiamine 10 mg IV

continued for a month until her serum thiamine concentrations remained within normal range.

Fujita et al[5] report a case of a 21-month-old female with no reported past medical history who was given an isotonic sports drink daily from 10 months of age, with no supplementation of milk or substantial meals. At the age of 19 months, the patient became unwilling to walk. About 2 weeks prior to presentation, she began vomiting and lost a kilogram of weight. At presentation, she was found to be hyponatremic. Despite correction, she remained tachycardic with hepatomegaly and cardiomegaly. Metabolic acidosis progressed to cardiogenic shock secondary to right-sided heart failure with a blood lactate concentration of 45.3 mg/dL. A serum thiamine concentration obtained was 2.1 mcg/dL (reference range, 3.0–5.0 mcg/dL). After developing pulmonary edema she was subsequently intubated. Thiamine was given (dose and duration not reported) and within 24 hours, the patient's clinical status improved. However, on day 5, hypoxemia persisted with a chest radiograph showing diffuse bilateral alveolar infiltrates, and a diagnosis of acute respiratory distress syndrome was made. On day 9, the patient developed emphysema, and on day 23, the patient died of respiratory failure.

A case report by Vicinanza et al[6] describes a case of a 6-year-old male with no significant past medical history who was brought to the emergency department with hypothermia and unconsciousness. He was intubated and underwent rewarming. He was acidotic with a blood lactate concentration of 49.55 mg/dL. Persistent hyperlactatemia occurred in the pediatric intensive care unit (PICU). Six hours after rewarming, he developed cardiogenic shock and went into cardiac arrest. Return of spontaneous circulation was obtained but the patient had continual degradation of cardiac function despite vasopressor and inotropic support, necessitating ECMO cannulation. Prior to ECMO initiation, a nutritional screening was performed and revealed that the patient was in a severe state of malnutrition with numerous vitamin deficiencies (thiamine was not assessed). Total parenteral nutrition (TPN) was initiated with 2.5 mg of thiamine daily. Cardiologic function dramatically improved, and the patient was weaned off mechanical ventilation and ECMO within 6 days. A week after stopping ECMO, the patient was transitioned to full enteral nutrition. Refeeding syndrome developed after a few days, along with acute pulmonary edema and cardiologic dysfunction. It was suspected that the patient was still thiamine deficient owing to prolonged malnutrition; therefore, thiamine 500 mg orally daily was given. Clinical improvement occurred within a few days and within 2 months, the patient made a full recovery.

Chong et al[7] recount a case of a 6-year-old male with Down syndrome, congenital heart disease, and autism spectrum disorder. He was highly food selective and rejected all foods with the exception of a specific brand of custard pudding. He presented with severe dehydration due to a streptococcal pharyngitis infection and was admitted for fluid resuscitation. Upon admission, he developed acute circulatory failure and cardiopulmonary arrest. Return of spontaneous circulation was obtained shortly after. Blood lactate concentration was 129 mg/dL. Thiamine was given (dose and duration not reported) owing to a suspected micronutrient deficiency given the patient's history. Subsequently, cardiac function improved and returned to normal by day 3. A serum thiamine concentration obtained prior to the administration of thiamine was found to be 1.1 mcg/dL (reference range, 2.4–6.6 mcg/dL). Although cardiac function normalized, magnetic resonance imaging indicated hypoxic ischemic encephalopathy with absent coughing and swallowing reflexes. He subsequently required tracheostomy placement and was bedridden.

A case series by Fattal-Valevski et al[8] describes 9 infants (aged 2.5 to 12 months) with thiamine deficiency who presented to different medical centers in Israel. Common early clinical symptoms were nonspecific and included gastrointestinal symptoms (constipation, vomiting, diarrhea, lack of appetite, and abdominal distention), neurologic manifestations (lethargy, irritability, and developmental delay), as well as respiratory symptoms. Upon investigation of patient histories, it was discovered that the only commonality was the use of a specific non-dairy, soy-based formula. An investigation into the contents of the formula revealed an undetectable thiamine concentration. Each of the 9 infants met laboratory criteria indicating thiamine deficiency, based on abnormal transketolase activity, an indirect, functional marker of thiamine status. Additionally, 6 of the 9 infants had measured blood lactate concentrations, with elevation noted in 4, ranging from 21.62 to 52.79 mg/dL. In patients with the most severe thiamine deficiency, neurologic symptoms later progressed to nystagmus, convulsions, and unconsciousness. Each patient was treated with 50 mg IM thiamine daily for 14 days. Additionally, a switch to a different enteral formula was made. Clinical symptoms improved or disappeared in all patients within the 2 weeks of thiamine treatment.

Abu-Kishk et al[9] describe a case of a 5.5-month-old infant female who presented with acute neurologic deterioration and seizures but was otherwise considered healthy. She presented with sleepiness, irritability, and loss of eye contact. Drug or poison exposure was ruled out. As in the case report by Fattal-Valevski et al,[8] this patient had been exclusively fed a soy-based formula for the previous 5 months. Owing to a manufacturer error, this formula did not contain any thiamine. The initial blood lactate concentration was 52.79 mg/dL (a lumbar puncture revealed a lactate value of 59.46 mg/dL in the cerebrospinal fluid). After receiving a dextrose-containing fluid she became apneic, requiring mechanical ventilation a few hours after presentation. Enteral

thiamine was given at a dose of 500 mg/day. Improvement was noted after 1 day of thiamine therapy and she was extubated within 2 days.

Qureshi et al[10] studied 23 infants (aged 32 days to 4 months) who were exclusively breastfed from presumed thiamine-deficient mothers and presented to the hospital with a blood potential hydrogen <7.0. All patients had a blood lactate concentration above the detectable range (>135.14 mg/dL). Clinical presentation amongst the infants was mostly nonspecific, including reflux, irritability, and decreased feeding. Seizure-like episodes occurred in 6 of 23 patients. An initial dose of thiamine 100 mg IV was given to all patients, followed by 50 mg IV daily until discharge. After discharge, patients received enteral thiamine 50 mg daily to complete 14 total days of therapy. Within 4 hours of administration of the first dose of thiamine, all patients' blood lactate concentrations declined to <36.04 mg/dL and clinical status significantly improved. Thiamine deficiency was diagnosed in 6 patients, based on laboratory confirmation. Serum thiamine concentrations were not obtained for all patients owing to financial reasons, but thiamine deficiency was assumed from clinical improvement after thiamine administration.

Additionally, the authors of the above study by Qureshi et al[10] performed a retrospective evaluation[11] of 189 infants suspected of having thiamine deficiency due to exclusive breastfeeding from presumed thiamine-deficient mothers. Of the 189 patients, 43 (aged 1 to 11 months) were determined to have thiamine deficiency on the basis of rapid clinical response to thiamine therapy. Most commonly they presented with nonspecific symptoms that included tachypnea, moaning, vomiting, and irritability. Their blood lactate concentrations ranged from 45.05 mg/dL to >135.14 mg/dL. Following administration of thiamine, all 43 patients had rapid resolution of their clinical status, symptoms, and laboratory values.

Samprathi et al[12] report a case series of 6 previously healthy, exclusively breastfed infants of presumed thiamine-deficient mothers who presented with an acute nonspecific illness. Of the 6 cases, 2 met criteria to be included in this review. The first case describes a 2-month-old male who was experiencing reduced feeding, vomiting, tachypnea, and respiratory distress. Blood tests indicated a severe metabolic acidosis with a blood lactate concentration of 207.21 mg/dL. He was given thiamine 500 mg IV, which resulted in a dramatic improvement of his symptoms and resolution of acidosis within 12 hours. Similarly, a 3.5-month-old male, also exclusively breastfed, presented with a mild fever, tachypnea, and excessive crying. Delayed capillary refill, cool extremities, and a mean arterial pressure in the 50th percentile were noted. Blood lactate concentration was obtained and reported at 45.05 mg/dL. An echocardiogram revealed a massively dilated right atrium and ventricle with tricuspid valve regurgitation. He was given thiamine 400 mg IV, resulting in improvement of clinical symptoms over the next 12 hours, and the patient was discharged within 12 hours on oral thiamine. Four weeks later an echocardiogram revealed normal results.

Bhat et al[13] report a case series of 29 infants (17 male, 12 female) who were exclusively breastfed by presumed thiamine-deficient mothers and presented with right-sided heart failure and shock that developed into pulmonary hypertension. Twelve infants required mechanical ventilation and 4 were started on peritoneal dialysis. Blood lactate concentrations were elevated in 27 of the 29 infants. Only 2 patients had a serum thiamine diphosphate concentration (active form of thiamine) obtained, which revealed thiamine deficiency. Thiamine 100 mg/kg IV was administered, followed by oral thiamine 10 mg/day until complementary feeds were initiated. Metabolic abnormalities and cardiologic manifestations were reversed nearly completely. A repeated echocardiogram performed 4 to 6 weeks later demonstrated complete resolution of pulmonary hypertension in 25 infants.

Tanné et al[14] recount a case of a 2-month-old female with no reported past medical history who was exclusively breastfed from a presumed thiamine-deficient mother. Initially, she presented to the emergency department with rhinitis, coughing, and regurgitation that was diagnosed as bronchiolitis, then discharged home. Within 48 hours, the patient presented again with persistent cough, fever, and difficulty feeding. She required oxygen supplementation and, ultimately, required high-flow oxygen therapy. Initial blood lactic acid concentration was elevated at 67.57 mg/dL and peaked at 77.48 mg/dL. An echocardiogram was performed that showed pulmonary hypertension and signs of acute right-sided heart failure. Thiamine was administered (dose not reported) and within a few hours she showed signs of clinical improvement including a normal follow-up echocardiogram the following day. Serum thiamine concentration obtained prior to thiamine administration was found to be 1.28 mcg/dL (reference range, 2.63–6.24 mcg/dL).

Parenteral-Associated Deficiency. Shah and Wald[15] recount the presentation of a 4-year-old male with medulloblastoma who was primarily dependent on TPN and presented with lactic acidosis initially thought to be secondary to septic shock. Adequate fluid resuscitation, norepinephrine, and hydrocortisone were given to maintain blood pressures. Antibiotics were also administered for the treatment of sepsis. Despite all these interventions, the patient's blood lactate remained elevated between 90.09 and 108.11 mg/dL. Type B lactic acidosis was considered, and the patient was given a bolus of 25 mg of IV thiamine and 25 mg/kg of IV levocarnitine. The patient's blood lactate fell to 43.24 mg/dL within 4 hours and to 21.62 mg/dL within 24 hours. A thorough

history revealed that no vitamins were provided in the home TPN, therefore, the patient was likely thiamine deficient on presentation. Levocarnitine was administered in addition to thiamine because carnitine is an important cofactor in the transport of fatty acids into the mitochondria. In carnitine deficiency, ATP production is impaired, which can also lead to the development of a lactic acidosis.

A case series by Salvatori et al[16] describes 2 neonates on TPN who developed thiamine deficiency–associated lactic acidosis. The first neonate was born preterm and required parenteral nutrition, which was not supplemented with any vitamins owing to an oversight. At day 40 of life, the infant developed hypotonia, hypotension, and severe metabolic acidosis, requiring intubation. Suspecting thiamine deficiency, a serum thiamine concentration was obtained and revealed that it was 1.01 mcg/dL (reference range, 2.03–6.76 mcg/dL). Intravenous thiamine 150 mg was administered, and the metabolic acidosis quickly improved. Resolution of hypotension and acidosis occurred within 24 hours after administration, and the patient was able to be extubated. A second preterm neonate was also initiated on TPN that was not supplemented with vitamins, again, owing to an oversight. At day 45 of life, the patient developed refractory metabolic acidosis with an elevated blood lactate concentration requiring intubation. Thiamine deficiency was suspected, and 150 mg of IV thiamine was administered, improving the acidosis shortly after administration and within 24 hours, it completely resolved. Five days after administration, the patient was successfully extubated.

Teagarden et al[17] report a case of a full-term female neonate who had initially presented to the PICU with acute respiratory failure secondary to pertussis. Respiratory failure progressed, requiring intubation in addition to venoarterial ECMO. Starting on hospital day 3, TPN was initiated. Hyperlactatemia was identified by hospital day 9, prompting a septic workup. Blood lactate concentration continued to rise despite appropriate interventions and initiation of CRRT. Supplementation with levocarnitine and coenzyme Q10 was provided, which appeared ineffective. Hyperlactatemia persisted for 10 days, with the highest concentration reaching 93.69 mg/dL. On hospital day 20, the team noticed this patient's TPN was being made without standard multivitamins and trace elements since initiation. A serum thiamine concentration was sent for evaluation and empiric IV thiamine supplementation was administered at 50 mg daily for 2 weeks. Blood lactate concentrations rapidly declined to 11.71 mg/dL within 30 hours and to 9.01 mg/dL by 60 hours of empiric thiamine therapy. Pretreatment serum thiamine concentrations eventually resulted as subtherapeutic at 1.86 mcg/dL (reference range, 2.36–6.08 mcg/dL). Decannulation from ECMO occurred after day 4 of thiamine supplementation.

Besci et al[18] describe a case report of a 6-year-old female on chronic TPN without multivitamin supplementation for an entire month owing to supply shortages, who presented to the hospital with encephalopathy, blurred vision, tachycardia, and hyperlactatemia (maximum blood concentration reaching 117.12 mg/dL). Within an hour after receiving 1 dose of thiamine 100 mg IM, her blood lactate concentration declined to 18.02 mg/dL. After daily replacement for 2 days, she showed some improvement in mental status and therapy was continued for an additional 12 days. Some neurologic sequelae persisted indefinitely, likely secondary to the prolonged duration of thiamine deficiency.

Anderson et al[19] detail a report of a 17-year-old male with a history of Crohn disease and a subtotal colectomy on chronic TPN who was admitted for treatment of a small-bowel obstruction and underwent a laparotomy procedure for a stricture resection and placement of an ileostomy. Prior to admission, the patient had developed hives associated with TPN administration, which were suspected to be due to the vitamin K supplementation within the TPN. As a result, all fat-soluble and B vitamins were removed from his home TPN. Postoperatively, he developed an anion gap metabolic acidosis with a blood lactate concentration of 123.42 mg/dL. He required initiation of vasopressors to maintain his mean arterial pressure and the blood lactate value subsequently increased to 157.66 mg/dL. Concern for type B lactic acidosis secondary to thiamine deficiency was considered, then empiric thiamine 100 mg IV was given. Within the hour after initiation of thiamine, vasopressors were quickly weaned and within 10 hours the blood lactate concentration was 23.42 mg/dL. Initial serum thiamine concentration was discovered to be 1.11 mcg/dL (reference range, 2.25–6.76 mcg/dL) when reported several days later.

La Selve et al[20] describe a case of a 12-year-old female with no reported past medical history who presented to the hospital with hemorrhagic diarrhea and malnutrition, resulting in a diagnosis of ulcerative colitis. She required TPN for a total of 4 weeks, receiving only 2 mg of thiamine once weekly. On day 30, the patient developed a marked metabolic acidosis and profound shock. Blood lactic acid concentration increased to a maximum of 288.29 mg/dL. In addition, the patient developed elevated cardiac output and pulmonary arterial pressure. Five days after the onset of this critical illness, a dose of thiamine 1000 mg IV was given, after which the patient rapidly improved. Blood lactic acid concentration continued to improve to 20.72 mg/dL by the next day. Transketolase activity obtained prior to administration of thiamine, revealed deficiency.

Greenspon et al[21] recount a case of a 28-month-old male with no past medical history who presented with an acute abdomen. An exploratory laparotomy revealed a necrotic bowel, requiring extensive resection,

including removal of the ileocecal valve. After surgery, the patient was initiated on TPN. Six weeks into his hospital stay, he developed a severe allergy, which was believed to be due to the polysorbate vehicle contained in the IV multivitamin component of the TPN. Therefore, multivitamins were removed from the order. Multiple desensitization attempts were unsuccessful. Multivitamin supplementation was continued orally and the patient tolerated without issue and was discharged home. Four days after discharge, the patient presented to the emergency department after developing a fever, lethargy, somnolence, and abdominal pain. A blood lactate test revealed a concentration of 86.49 mg/dL. Upon admission to the PICU, his blood lactate concentration increased to 90.09 mg/dL and he ultimately required intubation. Thiamine and folate deficiency was suspected owing to the lack of parenteral multivitamins for 41 days. Thiamine 100 mg IV and folate 1 mg IV were administered, via a polysorbate-free product. Within a few hours, the patient's vitals normalized, and the blood lactate concentration improved to 36.94 mg/dL. Additionally, the patient was successfully extubated and made a full recovery. Of note, a thiamine concentration was obtained prior to administration of thiamine and sent to an outside laboratory but was subsequently lost. However, an initial folate concentration was found to be subtherapeutic.

Cottini et al[22] detail a case report of a 17-year-old female with congenital jejunal atresia who had spent the previous 2 months in a pediatric hospital after a surgical duodenal-jejunal anastomosis and subsequently required chronic TPN for nutrition. The patient was transferred to a cardiology intensive care unit from the outlying pediatric hospital owing to the development of cardiogenic shock. Despite multiple vasopressors, she was still profoundly hypotensive. A blood lactate test revealed a concentration of 257.66 mg/dL and the patient was intubated and mechanically ventilated. Her hemodynamic state continued to worsen despite inotropic therapy and required ECMO and CRRT support. Prolonged TPN therapy led investigators to suspect thiamine deficiency, and thiamine 100 mg IV was administered after the initiation of ECMO, then continued at a dose of 500 mg IV, 3 times daily until discharge. Blood lactate concentrations progressively declined and normalized within 12 hours after the initial dose. Serial cardiac function examinations improved within a few hours and completely normalized within a few days. Extracorporeal therapies were stopped after 7 days, and 6 months after the event, the patient was in good clinical condition. Although the mechanism of thiamine deficiency was not readily identifiable, inadequate vitamin supplementation in TPN and inadequate absorption of vitamins in the small intestine due to atresia, are plausible explanations.

Functional Deficiency. Elias et al[23] describe a case of a 14-year-old male with a history of Wilms tumor who had undergone a total nephrectomy, 27 weeks of IV chemotherapy, and whole abdominal radiation post resection. Subsequently, he developed end-stage renal failure requiring renal replacement therapy with hemodialysis for approximately 2.5 years. More than 50% of his recommended caloric intake via nutritional supplementation through a gastrostomy tube occurred during this time. A renal multivitamin that contained water-soluble vitamins, including thiamine 1.5 mg/day, was also given. Initial laboratory values on admission to the PICU, after a deceased donor renal transplant, were mostly unremarkable, including an absence of acidosis and a normal blood lactate concentration. Two hours post transplant the patient developed oliguria and at 4.5 hours post transplant he developed marked hemodynamic deterioration, lactic acidosis (blood lactate concentration of 124.32 mg/dL), and hyperglycemia. Inotropic support was required to maintain mean arterial pressure and 7 hours post transplant the patient required intubation. Renal ultrasonography showed good perfusion with no evidence of bleeding. However, a bedside echocardiogram revealed generalized myocardial dysfunction. One dose of thiamine 50 mg IV was given 9 hours post transplant. Within 1 hour, the patient had rapid improvement in blood lactate concentrations (12.61 mg/dL) and hyperglycemia and was weaned off all inotropic support. Thereafter, he remained hemodynamically stable with no recurrence of lactic acidosis or hyperglycemia. Additional doses of thiamine 50 mg IV were given on day 1 and 2 post transplant. By the time of discharge, there were no signs of any cognitive or metabolic impairments. The suspected mechanism of thiamine deficiency is complex and unlike previously described case reports. In patients undergoing dialysis for renal failure, erythrocyte transketolase activity has been shown to be vastly decreased owing to accumulation of renal toxins such as oxythiamine. Oxythiamine is an antimetabolite of thiamine that competitively inhibits transketolase activity. During dialysis, thiamine is cleared from the serum, but oxythiamine is sequestered in red blood cells. As a result, thiamine deficiency develops.

Discussion

Thiamine is a water-soluble vitamin that is relatively safe with limited adverse effects (injection site reactions with rapid IV push reported in <1% of patients; flushing and weakness with an undefined frequency) and drug interactions.[80,81] None of the above pediatric case reports describe any adverse effects associated with thiamine administration. No defined tolerable upper intake level of thiamine has been described; and large oral doses of thiamine, up to 500 mg daily, when given for more than 1 month, have been described without adverse effects. Additionally, parenteral administration

has been shown to be safe, resulting in a low incidence (approximately 1% or less) of adverse events including local irritation, generalized pruritus, and rarely, serious allergic reaction.[74,77] Given the small risk, it is recommended to dilute and infuse over 30 minutes to decrease infusion reactions.[74] Furthermore, in comparison to other treatments that critically ill patients often require, the cost of thiamine or other micronutrients is negligible.[81]

Type B lactic acidosis is often difficult to identify. If typical therapies targeting the underlying cause of lactic acidosis fail, obtaining a thorough patient history can help recognize a risk factor for type B lactic acidosis, enabling the clinician to initiate prompt therapy. Indicators in a pediatric patient's history that might signal a thiamine deficiency include history of long-term TPN use, limited enteral diet, or malignancy. Ongoing and inevitable future supply shortages, including many IV pediatric multivitamin formulations, are likely to continue. For patients on chronic TPN, this should be considered as a potential inciting cause for lactic acidosis in this population. Additionally, plans for conservation of resources during shortages should be executed. For example, a health care facility transitioned from providing infants with 1.5 mL of daily multivitamin in TPN to 3.25 mL 3 times weekly to help conserve supply during a pediatric multivitamin shortage.[82] Implementing plans to balance conservation of supply while avoiding total lack of supplementation can help to avoid poor outcomes, especially in the very low birth weight infant population.

In many institutions, serum thiamine concentrations must be sent to another laboratory to be processed and it could take a week or longer to obtain results.[83] Given this delay and the likelihood of the critical nature of the illness, it may not be feasible to delay therapy pending the results of the serum thiamine concentration. A reasonable approach would be to provide thiamine supplementation to any patient with unimproved lactic acidosis after conventional therapies, while monitoring for signs of improvement in the acidotic state.

Additionally, critical illness and its associated organ dysfunction may require many patients to be supported by complex, lifesaving extracorporeal therapies, including CRRT and/or ECMO. It is important to consider what implications these treatment modalities could have on thiamine treatment. One study in critically ill pediatric patients demonstrated a significant fall in serum folate concentrations in patients receiving CRRT, concluding that standard pediatric folate treatment may not be adequate for these patients.[67] Although this study did not specifically assess serum thiamine concentrations, folate is another water-soluble B vitamin, and results can likely be extrapolated to serum thiamine concentrations. Another study looked at critically ill adult patients and found that the mean serum thiamine concentration losses in the effluent of CRRT were very high. Of note, these patients had received 100 mg of IV thiamine, in addition to daily multivitamins in their parenteral nutrition to help prevent thiamine deficiency. These authors concluded that normal doses of thiamine treatment are insufficient to cover losses experienced while a patient is receiving CRRT, and additional supplementation may be required.[68] ESPEN guidance states that CRRT contributes to a loss of water-soluble micronutrients, varying between the equivalent of 1 to 2 extra adult doses of selenium, zinc, and thiamine each day.[84] Therefore, we recommend that the therapeutic dose of IV thiamine be increased by 100% to 200% for the duration of CRRT therapy.

An ECMO circuit can alter the pharmacokinetics of multiple medications, especially micronutrients.[69] Water-soluble vitamins, such as thiamine, are likely to be affected. Excessive loss due to sequestration and adsorption of hydrophilic medications in the hydrophilic circuit may occur. Additionally, dilutional effects from the introduction of priming solutions used in the ECMO circuit result in increased volume of distribution. Ultimately, this results in decreased plasma concentrations of hydrophilic compounds.[70] One study compared the influence of ECMO on the concentration of nutritional supplements to a control group via an *ex vivo* model. No significant differences in concentrations were found between the ECMO circuits and the controls for cobalamin or folate, both of which are water-soluble B vitamins.[71] It is difficult to assess whether these results have clinical significance. However, given the pharmacokinetic changes mentioned previously, serum thiamine concentrations would likely be depleted by the ECMO circuit and it would likely be reasonable to administer larger than normal thiamine treatment doses to critically ill patients on ECMO given a risk-benefit assessment. Although no specific data exist guiding increased thiamine treatment dose supplementation in patients undergoing ECMO, we believe thiamine doses should be increased by 100% to 200% up to 500 mg IV every 8 hours while on ECMO and then regular treatment dosing of thiamine can be resumed.

Lastly, prevention of Wernicke encephalopathy and Korsakoff syndrome in thiamine-deficient patients is important to consider. To avoid a potentially devastating outcome, it is reasonable to suggest administering thiamine prior to giving any IV glucose-containing products in patients suspected to be thiamine deficient. Patients more likely to receive glucose-containing IV fluids include neonates and infants; therefore, extra vigilance should be observed when lactic acidosis is present in these patients and suspected to be secondary to thiamine deficiency.[72,73]

Conclusion

Although no specific recommendations on the dosing and duration of IV thiamine for the treatment of lactic acidosis secondary to thiamine deficiency are

established, case reports document a range from 25 to 1000 mg IV given as a single dose, or multiple daily doses for several days. Given the relative safety and modest cost of IV thiamine, it may be reasonable to consider any of these dosing regimens, followed by frequent assessment for clinical improvement. Additionally, when traditional treatments for lactic acidosis fail, early administration of thiamine in patients suspected to be deficient may help to prevent progression of critical illness. Guidance for critically ill adults recommends a range of anywhere from thiamine 100 mg IV once daily to 400 mg IV twice daily. Although no specific guidance for the pediatric population exists, it is our opinion, based on available literature, that it would be reasonable to administer thiamine 100 to 200 mg IV at least once, with ongoing daily doses based on clinical response of the patient. Although no specific data exist to guide increased thiamine dose supplementation in patients necessitating extracorporeal therapies such as CRRT and/or ECMO, we believe the therapeutic dose should be increased. For CRRT, we recommend the therapeutic dose be increased by 100% to 200% for the duration of CRRT therapy. For ECMO, we recommend the therapeutic dose be increased by at least 100% to 200%, up to 500 mg IV, 3 times daily for the duration of ECMO therapy. Lastly, it is judicious to consider administering thiamine in patients prior to administering IV glucose in patients with lactic acidosis to avoid potential permanent neurologic deficits. Thiamine deficiency–associated lactic acidosis is often not an obvious cause and relies on identification of key risk factors to ensure prompt treatment.

Article Information

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Disclosures. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

Submitted. December 23, 2021

Accepted. June 8, 2022

Supplemental Material. DOI: 10.5863/1551-6776-28.5.397.S

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