

Hypomagnesemia: the 12th pitfall in interpreting hyperlactatemia in sepsis

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Elevated serum lactate is a hallmark of critical illness, often interpreted as a marker of impaired tissue perfusion and anaerobic metabolism. However, the pathophysiology of hyperlactatemia is more complex, involving not only circulatory failure but also cellular metabolic derangements.^[1,2] In their widely cited editorial, Hernandez et al. identified 10 pitfalls in the interpretation of lactate clearance in sepsis, emphasizing the need to distinguish between lactate production, utilization, and clearance pathways.^[3] Ricci and Romagnoli subsequently added an 11th pitfall, thiamine deficiency, highlighting its overlooked role in mitochondrial metabolism.^[4] Here, we propose a 12th pitfall that remains underrecognized: hypomagnesemia.

Magnesium (Mg) is the second most abundant intracellular cation and an essential cofactor for more than 300 enzymatic processes, particularly those governing glucose metabolism and mitochondrial energy production.^[5,6] Among these, its central role in aerobic pyruvate metabolism is often underrecognized.

The pyruvate dehydrogenase complex (PDH) catalyzes the irreversible decarboxylation of pyruvate to acetyl-CoA, thereby linking cytosolic glycolysis to the mitochondrial tricarboxylic acid (TCA) cycle and enabling efficient aerobic energy generation. PDH activity requires thiamine pyrophosphate (TPP), the formation and function of which are Mg dependent.^[6,7] In addition, Mg acts as a cofactor for pyruvate dehydrogenase phosphatase (PDP), the enzyme that dephosphorylates and activates PDH. Consequently, Mg deficiency impairs PDH activity, leading to intracellular accumulation of pyruvate and its diversion to lactate via lactate dehydrogenase, even in the presence of adequate oxygen^[1] (Fig. 1).

Beyond PDH, several TCA cycle enzymes, including isocitrate dehydrogenase and α -ketoglutarate dehydrogenase, also require Mg for optimal catalytic activity. Magnesium is further indispensable for mitochondrial integrity and bioenergetic function. Nearly all intracellular adenosine triphosphates (ATP) exists as Mg-ATP, the biologically active form that stabilizes phosphate bonds and serves as the true substrate for ATP-dependent enzymes.^[5] In magnesium-deficient states, oxidative

phosphorylation is compromised, impairing mitochondrial ATP synthesis despite preserved oxygen delivery.

To meet energy demands under these conditions, cells increase glycolytic flux, a rapid but inefficient pathway independent of mitochondria, which generates excess pyruvate and subsequently lactate.^[5–7] Importantly, this metabolic reprogramming occurs independently of tissue hypoxia or systemic hypoperfusion.^[1,2]

These mechanisms provide a biologically coherent explanation for how hypomagnesemia can contribute to hyperlactatemia. In sepsis, where mitochondrial dysfunction, relative hypoxia, and high energy demand already coexist, magnesium deficiency may further aggravate lactate accumulation and complicate its clinical interpretation.^[1,2,5–7]

Evidence suggesting an association between hypomagnesemia and hyperlactatemia in sepsis, though limited, is biologically coherent. Noormandi et al. performed a prospective, double-blind, randomized controlled trial involving 58 patients with severe sepsis and elevated lactate.^[8] Patients received intravenous magnesium sulfate titrated to maintain serum magnesium around 3 mg/dL for 3 days, or placebo. Lactate clearance was significantly higher in the magnesium group on both day 2 (27.5% vs. 23.8%; $P < 0.001$) and day 3 (49.8% vs. 37.0%; $P < 0.001$). The time to lactate clearance was shorter (47.3 vs. 61.2 hours; $P = 0.03$), and intensive care unit (ICU) length of stay was reduced (8 vs. 15 days; $P < 0.01$), although mortality did not differ significantly.

Tonai et al. retrospectively analyzed 759 patients with sepsis admitted to a single 16-bed ICU.^[9] At ICU admission, 105 (13.8%) patients had hypomagnesemia (Mg < 1.6 mg/dL) and showed higher median lactate levels (3.9 vs. 2.1 mmol/L; $P < 0.01$) and more frequent lactic acidosis (70% vs. 51.6%; $P < 0.01$) compared with those with normomagnesemia (1.6–2.4 mg/dL). Moreover, from day 1 to day 5, lactate levels and the prevalence of lactic acidosis remained consistently higher in the hypomagnesemia group. In multivariable analysis, hypomagnesemia was independently associated with lactic acidosis (adjusted odds ratio [OR]: 2.76; 95% confidence interval [CI]: 1.60–4.76).

Moskowitz et al. conducted a large retrospective cohort study of 8922 critically ill patients, investigating the association between admission magnesium levels and the risk of lactic acidosis (lactate > 2 mmol/L).^[10] After adjusting for confounders, hypomagnesemia (Mg < 1.6 mg/dL) was independently associated with increased odds of hyperlactatemia (OR: 1.71 [95% CI: 1.51–1.94] for lactate > 2 mmol/L; OR: 1.56 [95% CI: 1.32–1.84] for lactate > 4 mmol/L) compared with the reference quartile (Mg 1.8– < 2.1 mg/dL). In the sepsis subgroup ($n = 1765$), hypomagnesemia remained significantly associated with lactic acidosis (OR: 2.03; 95% CI: 1.50–2.76).

Despite accumulating evidence, magnesium is rarely considered in the interpretation of lactate levels. Routine lactate monitoring in septic shock is common and often informs decisions on fluid resuscitation, vasopressor therapy, and prognostication. However, when lactate remains elevated despite apparent restoration of perfusion, clinicians frequently attribute this to hepatic dysfunction or mitochondrial failure, overlooking micronutrient deficiencies such as magnesium and thiamine.

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Emergency and Critical Care Medicine (2026) 6:1

Received: 7 September 2025; Accepted: 19 September 2025

Published online: 30 March 2026

<https://dx.doi.org/10.1097/EC9.000000000000163>

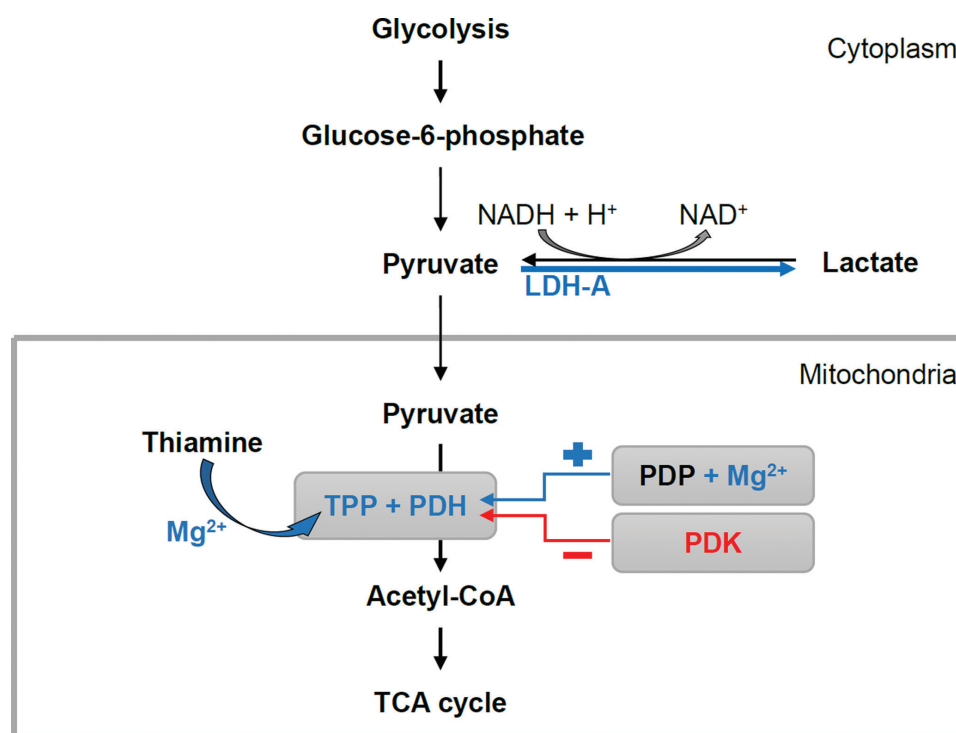


Figure 1. The interplay between magnesium, pyruvate, and lactate metabolism. LDH, lactate dehydrogenase; Mg, magnesium; NAD⁺, nicotinamide adenine dinucleotide; PDH, pyruvate dehydrogenase complex; PDK, pyruvate dehydrogenase kinase; PDP, pyruvate dehydrogenase phosphatase (Mg-dependent); TCA, tricarboxylic acid; TPP, thiamine pyrophosphate (Mg-dependent coenzyme of PDH).

Unlike thiamine, which has received increasing attention in recent years,^[11,12] magnesium remains a biochemical blind spot. It is typically measured only in the presence of arrhythmias, hypokalemia, or neuromuscular symptoms. Yet, hypomagnesemia occurs in up to 65% of critically ill patients,^[5] often unrecognized and untreated.

Given its physiological role, epidemiologic associations, and potential reversibility, hypomagnesemia warrants greater attention in the evaluation of hyperlactatemia, particularly in sepsis. We propose that magnesium assessment and correction be incorporated into hyperlactatemia assessment in critical care, alongside fluid resuscitation, vasopressor therapy, microcirculatory optimization, and thiamine supplementation.

Future studies should determine whether magnesium repletion improves not only lactate kinetics but also patient-centered outcomes. In the meantime, measuring and correcting serum magnesium in patients with persistent hyperlactatemia and sepsis appears both reasonable and low risk.

In conclusion, clinicians should look beyond perfusion and consider the broader metabolic context when interpreting elevated lactate in sepsis. Hypomagnesemia represents a potential “twelfth pitfall” in the complex landscape of hyperlactatemia. Routine recognition and correction of magnesium deficiency could improve lactate interpretation and provide a simple, low-risk therapeutic adjunct in critically ill patients.

Conflict of interest statement

The authors declare no conflict of interest.

Author contributions

The authors conceived the concept, performed the literature review, wrote the manuscript, and approved the final version.

Funding

None.

Ethical approval of studies and informed consent

Not applicable.

Acknowledgments

None.

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How to cite this article: Nguyen TL, Pham PT, Ho VHN. Hypomagnesemia: the 12th pitfall in interpreting hyperlactatemia in sepsis. *Emerg Crit Care Med.* 2026;6(1):3–5. doi: 10.1097/EC9.000000000000163.