

# Biological significance and clinical utility of lactate in sepsis

Juan B. Dartiguelongue<sup>a</sup> 

## ABSTRACT

Sepsis is a global health problem; progression to septic shock is associated with a marked increase in morbidity and mortality.

In this setting, increased plasma lactate levels demonstrated to be an indicator of severity and a predictor of mortality, and are usually interpreted almost exclusively as a marker of low tissue perfusion. However, a recent paradigm shift has occurred in the exegesis of lactate metabolism and its biological properties. Indeed, metabolic adaptation to stress, even with an adequate oxygen supply, may account for high circulating lactate levels. Likewise, other pathophysiological consequences of sepsis, such as mitochondrial dysfunction, are associated with the development of hyperlactatemia, which is not necessarily accompanied by low tissue perfusion.

Interpreting the origin and function of lactate may be of great clinical utility in sepsis, especially when circulating lactate levels are the basis for resuscitative measures.

**Keywords:** *sepsis; septic shock; lactate; hyperlactatemia; energy metabolism.*

doi: <http://dx.doi.org/10.5546/aap.2023-10149>.eng

**To cite:** Dartiguelongue JB. Biological significance and clinical utility of lactate in sepsis. *Arch Argent Pediatr* 2024;122(2):e202310149.

<sup>a</sup> *Emergency Department, Hospital General de Niños Ricardo Gutiérrez, City of Buenos Aires, Argentina.*

**Correspondence to** Juan B. Dartiguelongue: [jbdartiguelongue@hotmail.com](mailto:jbdartiguelongue@hotmail.com)

**Funding:** None.

**Conflict of interest:** None.

**Received:** 7-6-2023

**Accepted:** 10-31-2023



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## INTRODUCTION

The clinical definition of sepsis is the presence of organ dysfunction caused by a dysregulated response to infection.<sup>1,2</sup> Tissue aggression mediated by an inflammatory storm causes endothelial damage, microvascular dysfunction, and an alteration in cellular metabolism, which may sometimes progress to septic shock. This is a critical situation, resulting from a serious imbalance between oxygen (O<sub>2</sub>) supply and demand.<sup>3</sup> Clinically, shock is characterized by the presence of hemodynamic compromise, which may rapidly lead to multiple organ failure.<sup>4,5</sup> Sepsis and septic shock are part of a continuum, which, in the absence of an adequate management, is associated with a marked increase in mortality.<sup>4-7</sup>

Lactic acid, almost completely dissociated into lactate and protons at the physiological pH level of body fluids, has been extensively studied in sepsis and shock, based on its role as a biochemical marker of tissue perfusion.<sup>8-10</sup> Hyperlactatemia, i.e., an elevation of lactate levels above 2 mmol/L (normal value: 0.3–1.8 mmol/L) was correlated to increased mortality in observational studies of pediatric patients with sepsis,<sup>11-15</sup> particularly if persistent.<sup>16-18</sup> Likewise, early lactate normalization was shown to decrease the risk of multiple organ failure.<sup>19</sup> In this regard, the latest publication of the Surviving Sepsis Campaign (SSC) guidelines for children<sup>20</sup> included lactate measurement (along with clinical and advanced monitoring parameters) to assess hemodynamic response to fluid therapy and guide treatment. This recommendation has been recently replicated,<sup>7</sup> although capillary refill was shown to be superior to lactate as a resuscitation target.<sup>7,21</sup> Also, it has been recently proposed to add lactate measurement to the quick Sequential Organ Failure Assessment (qSOFA), a clinical scoring system that predicts mortality in septic patients.<sup>22</sup>

It is evident that circulating lactate levels are intimately related to sepsis and septic shock. However, the information available in pediatrics was obtained from observational studies, with dissimilar designs in terms of cut-off points for defining hyperlactatemia (2 to 5 mmol/L), the time of measurement (at admission, at 1, 2, 4, 24 hours, etc.), follow-up, and results; moreover, they were carried out in very heterogeneous populations.<sup>10-19</sup> Therefore, the recommendation made by the SSC guidelines is weak, with very low quality evidence to support it.<sup>7,20</sup>

To properly interpret the role of lactate in

the complex scenario of sepsis, first of all, it is necessary to ask: Where does lactate come from? What is its role? Is it just a marker of hypoxia or is it a molecule with other biological properties? And, secondly, what is the clinical utility of its measurement? Should it condition hemodynamic recovery measures?

The objective of this review is to guide the answers to these questions, based on the scientific evidence that motivated the reinterpretation of classical physiological concepts, responsible for restricting lactate as only a marker of tissue hypoxia.

## LACTATE PRODUCTION

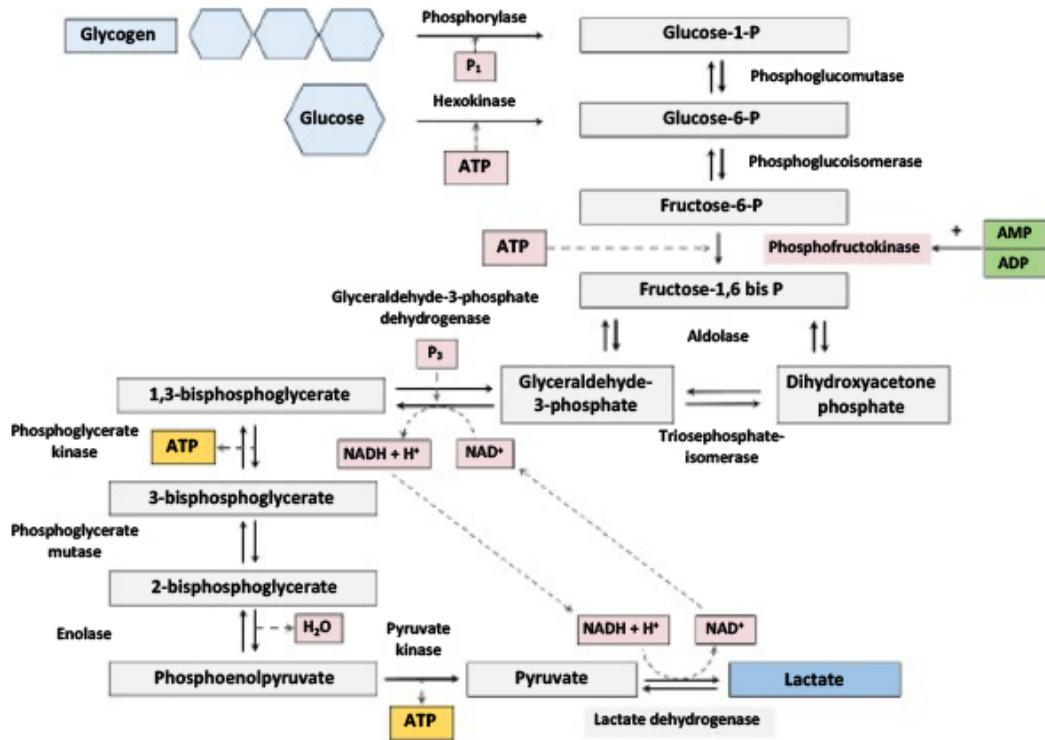
### General concepts and classical perspective

Glycolysis is the initial pathway of glucose catabolism and occurs in most cells in the body.<sup>23</sup> From an evolutionary stance, it is the oldest energy-producing mechanism, possibly present in the first microorganisms when the earth's atmosphere was still devoid of O<sub>2</sub>. It is also an outstanding example of the unity of the biological kingdom; it functions in all living organisms, even those phylogenetically very distant, following exactly the same metabolic steps (*Figure 1*). The variation among organisms lies in the final destination of the pyruvate formed; for example, in anaerobic microorganisms, pyruvate results in the formation of lactate (lactic fermentation), whereas the final product in yeasts is ethanol together with carbon dioxide (alcoholic fermentation). Normally, during glycolysis, 2 moles of adenosine triphosphate (ATP) are obtained per mole of glucose metabolized.<sup>23,24</sup>

In aerobic organisms, such as humans, glycolysis is the first part of glucose catabolism. According to the classical paradigm, it provides the mitochondria with pyruvate, its end product under aerobic conditions. In the mitochondria, pyruvate is decarboxylated into acetyl-coenzyme A (acetyl-CoA) during oxidative decarboxylation (mediated by the pyruvate dehydrogenase complex), which then enters the tricarboxylic acid cycle (Krebs cycle) and, after transfer of the electrons obtained in the mitochondrial transport chain (oxidative phosphorylation), the maximum energy yield per mole of glucose (36–38 moles of ATP) is reached.<sup>23</sup>

The regulation of glycolysis occurs primarily by allosteric modulation of phosphofructokinase 1 (PFK-1), the enzyme that catalyzes the third metabolic step (*Figure 1*); adenosine monophosphate (AMP) and adenosine

FIGURE 1. Glycolytic pathway



Source: Developed by the author.

ATP: adenosine triphosphate; AMP: adenosine monophosphate; ADP: adenosine diphosphate; NAD: nicotinamide adenine dinucleotide.

diphosphate (ADP) stimulate its function, while ATP, citrate, and fructose-2,6-bisphosphate inhibit it. Physiologically, the beta-adrenergic stimulus on the Na<sup>+</sup>/K<sup>+</sup> ATPase pump is accompanied by the activation of glycolysis by supplying ADP to PFK-1.<sup>23</sup> It also increases substrate availability by promoting glycogenolysis.

Moreover, glycolysis represents the main source of energy when tissue oxygenation is significantly compromised, for example, during severe hypovolemia. In this context, an intracellular O<sub>2</sub> pressure ≤ 0.5 mmHg (dysoxia) limits oxidative phosphorylation and, consequently, mitochondrial ATP production. According to the classical paradigm, under these circumstances, pyruvate is not metabolized in the mitochondria, but is reduced to lactate by cytoplasmic lactate dehydrogenase (LDH), which maintains the intracellular redox balance (simultaneously oxidizing nicotinamide adenine dinucleotide [NADH] to NAD<sup>+</sup>) (Figure 1) and, in turn, justifies the increase in circulating lactate.<sup>23</sup>

From this perspective, lactate is presented exclusively as a by-product of hypoxia or

hypoperfusion, with potentially toxic biological properties (lactic acidosis, etc.) in complex pathophysiological settings.

### Current paradigm

Although glycolysis and its regulation are still valid, the apothegm that assimilated lactate as a mere indicator of hypoxia, strongly rooted in the medical community, led to a series of confusing interpretations that, at times, motivated clinical decisions that were not entirely correct.<sup>25</sup> Although lactate elevation under conditions of dysoxia is well established,<sup>23,25,26</sup> this situation is the exception rather than the rule. Indeed, lactate is always the end product of glycolysis, regardless of the extent of tissue oxygenation.<sup>26</sup> This concept began to be overlooked in the mid to late past century in typical studies of exercise physiology (skeletal muscle is glycolytically a very active tissue), where the permanent efflux of lactate during muscle contraction, in the clear absence of dysoxia (intracellular O<sub>2</sub> pressures > 2–3 mmHg), was documented by different methods.<sup>27,28</sup> Moreover, lactate may be taken

up by the liver and kidney to produce glucose (gluconeogenesis) or be used by other muscle fibers and different tissues as metabolic fuel.<sup>29</sup> Later, studies on brain metabolism described similar findings, which were also observed in other parenchyma;<sup>25,30–32</sup> which progressively led to a paradigm shift.<sup>25,26,33</sup>

The biochemical principles that support these findings are based on the following:

1. The reaction catalyzed by cytoplasmic LDH is bidirectional (*Figure 2*) and exergonic (it releases free energy, so it occurs spontaneously), and its equilibrium constant is strongly biased toward lactate production ( $1.62 \times 10^{11} \text{ M}^{-1}$ ).<sup>23,26</sup> This normally maintains a lactate/pyruvate ratio of  $\sim 10/1$ . Furthermore, its activity is much higher than that of the enzymes that regulate glycolysis and it produces NAD<sup>+</sup>, an electron acceptor that ensures the continuity of the pathway. Therefore, as long as glycolysis is active, pyruvate will be reduced to lactate, regardless of the extent of tissue oxygenation.
2. The resulting lactate enters the mitochondria by facilitated diffusion through the monocarboxylate transporter-1 (*MCT1*).<sup>34</sup> In the intermembrane space, it is oxidized to pyruvate by mitochondrial LDH, which is part of the mitochondrial lactate oxidation complex (mLOC) anchored to the inner mitochondrial membrane<sup>35</sup> (*Figure 3*). Pyruvate is then transported to the mitochondrial matrix (via the mitochondrial pyruvate carrier [MPC]), which functions as a “sink” for pyruvate, where it is converted into acetyl-CoA to enter the tricarboxylic acid cycle.<sup>35</sup> Simultaneously, the mitochondrial LDH reaction generates NADH + H<sup>+</sup>, whose electrons are “launched” into the mitochondrial matrix by the malate-aspartate transporter and the glycerol phosphate transporter (*Figure 3*),<sup>26</sup> an event that contributes to the Krebs cycle.

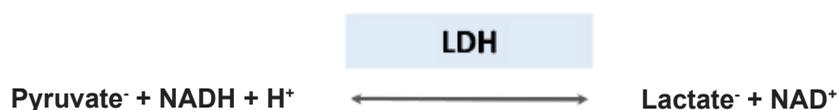
It is worth explaining that the production of lactate is not synonymous with an accumulation or increase in its circulating levels. Normally, lactate finds a steady state between entry into the mitochondria, exit from the cells, and peripheral utilization,<sup>36</sup> as long as the rate of production, i.e., glycolytic activity, resembles the rate of mitochondrial oxidation (metabolic coupling). In these conditions, its plasma level remains within the normal range, with a resting rate of production varying between 0.9 and 1.0 mmol/kg/h.<sup>37</sup> If oxidative phosphorylation is inhibited (dysoxia), the rate of lactate production exceeds the mitochondrial capacity to oxidize pyruvate and NADH, thereby increasing intracellular lactate and its outflow across the membrane (via *MCT4*). Even with adequate O<sub>2</sub> supply, if glycolytic activity is stimulated above mitochondrial oxidative capacity (high intensity exercise, sustained beta-adrenergic stimulation) or if mitochondrial activity is inhibited (cytopathic hypoxia), metabolic uncoupling occurs which, if not buffered, justifies the development of hyperlactatemia.<sup>25,26</sup>

Normally, the main sources of lactate are skeletal muscle (25%), skin (25%), brain parenchyma (20%), gastrointestinal tract, and red blood cells. It is metabolized mainly by the liver (50–60%) and the kidney ( $\sim 30\%$ ), via oxidation and gluconeogenesis and, to a lesser extent, by the myocardium and other tissues.<sup>36</sup> However, during intense exercise, skeletal muscle is both the site of maximum production and consumption ( $\sim 70\%$ ).<sup>38</sup> In the case of sepsis and septic shock, lactate is the main oxidative source in the myocardium (60–70%);<sup>8</sup> its oxidation is also increased in the brain and various tissues, where it acts as an additional metabolic substrate.

## BIOLOGICAL PROPERTIES

As observed, lactate is a ubiquitous molecule that functions as an energy intermediate within

**FIGURE 2. Reaction catalyzed by lactate dehydrogenase**



Source: Developed by the author.

LDH: lactate dehydrogenase; NAD: nicotinamide adenine dinucleotide.

and among cells.<sup>25,36</sup> The 2 molecules formed during glycolysis possess 93% of the energy contained in glucose (686 kcal/mol), which is used in mitochondrial oxidation to obtain the maximum yield of ATP.

It is also the quantitatively most important precursor of liver and kidney gluconeogenesis, which decreases glycogen utilization; it is also an additional source of energy during metabolic stress and functions as a lipolysis inhibitor and glucose saver.<sup>25</sup>

In addition, it is able to promote its own metabolism and efflux from cells by stimulating the expression of hypoxia-inducible factor-1 $\alpha$  (*HIF-1 $\alpha$* ), a transcription factor that, among other functions, stimulates cellular glucose transport, glycolysis enzymes, lactate oxidation, and *MCT4* expression.<sup>25,39,40</sup>

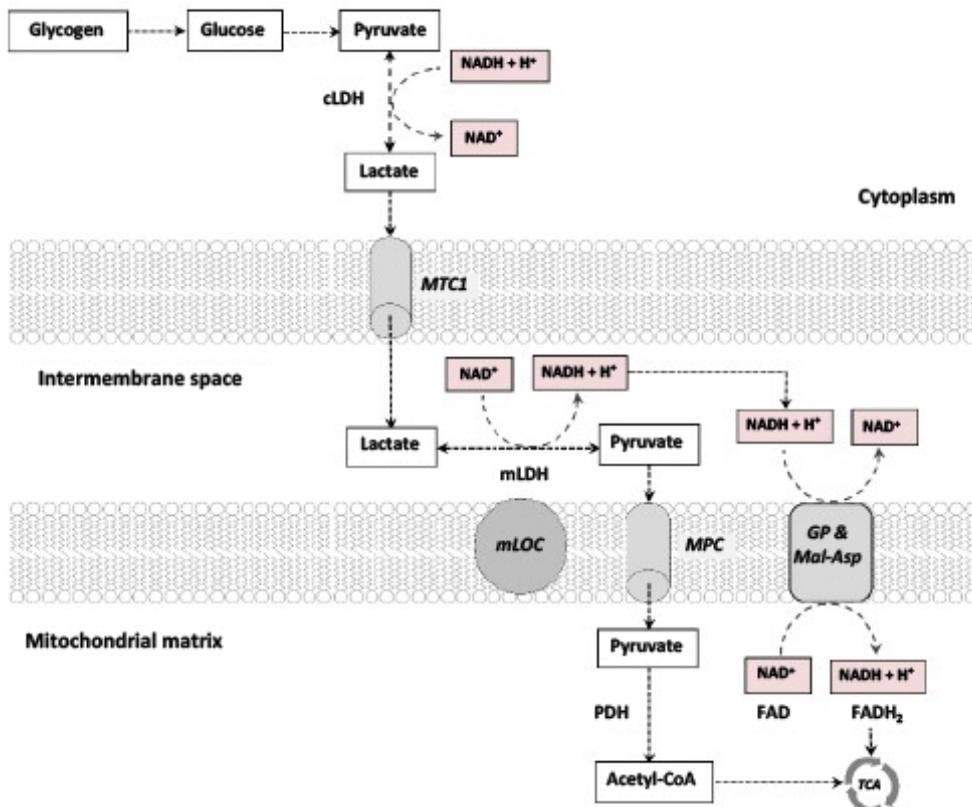
## LACTATE IN SEPSIS

### Where does it come from?

Several pathophysiological mechanisms explain the increase in lactate levels in sepsis.<sup>2,3</sup> The complexity involved in its metabolism, especially in patients with sepsis, often hinders the clinical interpretation of hyperlactatemia.

In addition to microcirculatory disorders, which may severely compromise tissue perfusion (dysoxia),<sup>8,41</sup> other metabolic circumstances may increase circulating lactate levels. The hyperadrenergic state that characterizes sepsis is a permanent stimulus for glycolysis, lactate formation, and aerobic energy uptake (by the beta-adrenergic effect on the Na<sup>+</sup>/K<sup>+</sup> ATPase pump, glycogenolysis, and glycolysis) (*Figure 4*); this implies an adaptive change in the metabolic profile, which may overcome the mitochondrial

**FIGURE 3. Generation of lactate, transfer to the intermembrane space, oxidation to pyruvate, transfer to the mitochondrial matrix, oxidative decarboxylation, and entry into the tricarboxylic acid cycle**



Source: Developed by the author.

TCA: tricarboxylic acids; cLDH: cytoplasmic lactate dehydrogenase; MCT1: monocarboxylate transporter 1; mLDH: mitochondrial lactate dehydrogenase; mLOC: mitochondrial lactate oxidation complex; MPC: mitochondrial pyruvate carrier; PDH: pyruvate dehydrogenase complex; GP & Mal-Asp: glycerol-phosphate and malate-aspartate transporters; FAD: flavin adenine dinucleotide.

capacity to metabolize pyruvate and, by the law of mass action, increase lactate levels (*Figure 4*).<sup>8,42–44</sup> In a study conducted in adults, stimulation of glycolysis and lactate production after adrenaline infusion improved the prognosis of septic shock, which may suggest that this mechanism involves an adaptive response.<sup>45</sup> Likewise, during sepsis, 50–60% of the lactate produced is oxidized by different tissues and up to 30% enters liver and kidney gluconeogenesis, favoring glycogen synthesis;<sup>8</sup> this reinforces the hypothesis of metabolic adaptation to stress.

In addition, proinflammatory cytokines, nitric oxide, and lipopolysaccharide from gram-negative bacteria may result in mitochondrial dysfunction and

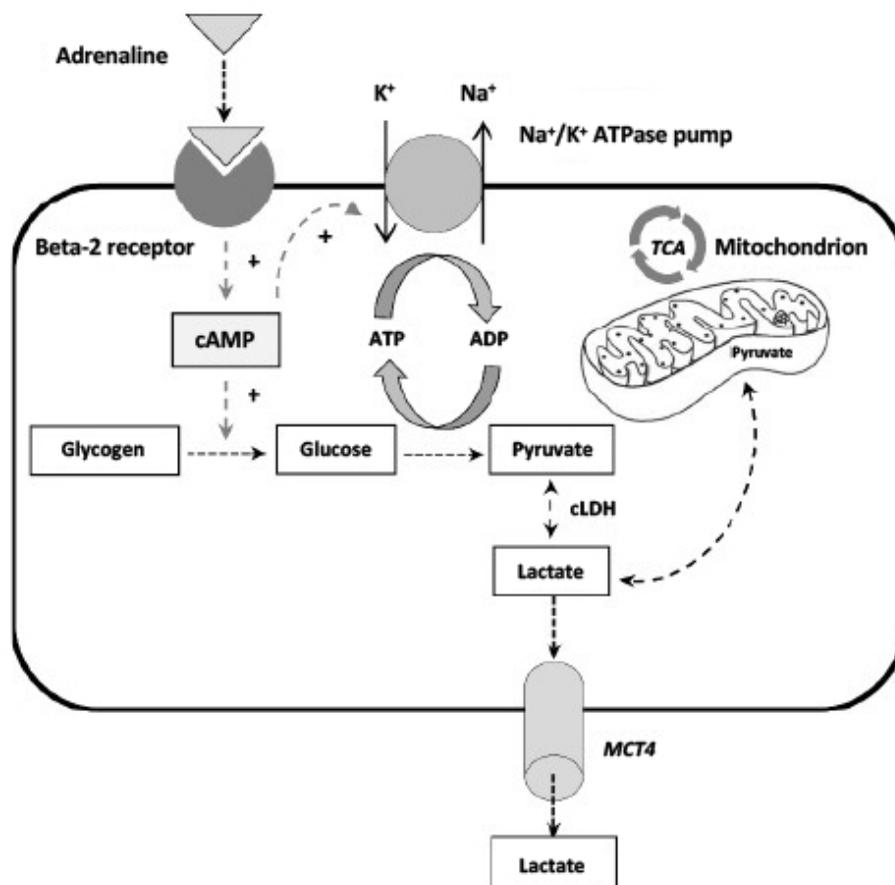
cytopathic hypoxia during sepsis.<sup>3</sup> Dysfunction of the pyruvate dehydrogenase complex, responsible for the oxidative decarboxylation of pyruvate to acetyl-CoA, is associated with an increase in circulating lactate levels.<sup>44,46</sup>

In addition, ischemic hepatitis and other mechanisms that cause liver dysfunction in sepsis and shock may compromise lactate metabolism, increasing its circulating levels.<sup>3,44,47</sup>

Based on the above, 4 possible origins of hyperlactatemia in sepsis have been described:

- Territories with marked hypoperfusion, particularly where severe microcirculatory disturbances (dysoxia) develop.
- Sustained beta-adrenergic stimulation,

**FIGURE 4. Activation of cellular metabolism by catecholamines**



By acting on beta-2-adrenergic receptors, adrenaline stimulates the development of cyclic adenosine monophosphate (cAMP). This compound is able to activate glycogenolysis, glycolysis, and the activity of the Na<sup>+</sup>/K<sup>+</sup> ATPase pump. ATP consumption by this pump produces ADP, which reactivates glycolysis and lactate production. Oxidation of lactate to pyruvate, its decarboxylation to acetyl-CoA, and entry into the tricarboxylic acid (TCA) cycle occur within the mitochondrion. If lactate production exceeds the mitochondrial oxidative rate, its intracellular level and output through monocarboxylate transporter-4 (MCT4) increase.

cLDH: cytoplasmic lactate dehydrogenase; ATP: adenosine triphosphate; ADP: adenosine diphosphate.

Source: Developed by the author, modified from: Dartiguelongue JB, Cheistwer A, Montero D. *Medicina interna pediátrica*. City of Buenos Aires: Journal; 2023.

which activates the glycolytic rate above the mitochondrial oxidative capacity.

- Mitochondrial dysfunction due to involvement of the pyruvate dehydrogenase complex, the electron transport system, or altered mitochondrial ultrastructure (cytopathic hypoxia).
- Compromised liver metabolism due to multifactorial parenchymal and microcirculatory disturbances.

Technically, it is difficult to determine the exact sites of lactate production during sepsis; however, the lung and skeletal muscle appear to be its main sources,<sup>8,25</sup> in addition to sources of infection and inflammation.

### What is the clinical utility of determining lactate levels?

In the case of sepsis, hyperlactatemia is an indicator of severity and its persistence is a predictor of mortality. While there is limited evidence to support this assertion in pediatrics,<sup>10–19</sup> it is consistent in adults.<sup>48</sup>

Whenever accompanied by clinical findings of hemodynamic compromise, increased lactate levels should alert to the presence of hypoperfusion; in this setting, a vigorous restoration of an effective blood volume markedly improves prognosis.<sup>7,20,44</sup> However, in the absence of clinical indicators of hypoperfusion, it should not motivate the implementation of resuscitative measures.<sup>7,20</sup> Likewise, if lactate levels remain elevated after hemodynamic recovery, i.e., after restitution of capillary refill, pulses, diuresis, consciousness, and skin temperature, it is unlikely to be a marker of low perfusion and is possibly due to another of its causes (for example, sustained beta-adrenergic stimulation). The paradigm of “hidden hypoperfusion,” which assimilated isolated hyperlactatemia as evidence of low tissue perfusion, seems to be incorrect and motivated the implementation of unnecessary measures, which may cause toxicity due to excessive resuscitation.<sup>44,49,50</sup> Therefore, the restoration of clinical parameters is above the lowering of lactate levels in terms of hemodynamic recovery goals.<sup>7,21,44</sup> It should also be mentioned that, in order to adequately determine lactate variations, lactate levels should be determined every 1–2 hours.<sup>9</sup>

Possibly, persistent hyperlactatemia is related to the magnitude of the metabolic response to stress and the extent of compromise of body homeostasis, which affects the severity of the

condition and its prognosis.<sup>7,8,20</sup> This hypothesis is supported by the fact that early lactate normalization was shown to be associated with better results.<sup>19</sup>

The dynamism of such a complex scenario as sepsis may justify that several causes of hyperlactatemia are present in the same patient at the same time (for example, dysoxia and metabolic adaptation to stress), and that these causes vary with treatment and the course of disease. This demonstrates the metabolic complexity of lactate and the clinical challenge of correctly interpreting its extent and implications.

### CONCLUSIONS

- Lactate is a ubiquitous molecule, the end product of glycolysis, which functions as an energy intermediate within and among cells.
- It is the main gluconeogenic substrate and an additional source of energy during metabolic stress.
- Lactate levels increase when there is a decoupling among lactate production, oxidative rate, and its tissue metabolism.
- In the case of sepsis, hyperlactatemia is a marker of severity and its persistence increases mortality. When accompanied by clinical indicators of hemodynamic compromise, it reinforces the decision to implement resuscitative measures.
- In the absence of clinical findings of hypoperfusion, isolated hyperlactatemia should not prompt hemodynamic recovery strategies. ■

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