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# **Decoding lactate kinetics in septic shock: From flow to metabolism**

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## **Keywords:**

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*No abstract available*

In their excellent narrative review, Castro and his colleagues took on the challenging task of unraveling the intricate pathophysiology of hyperlactatemia in septic shock [1]. They propose a clear framework that distinguishes an early phase, during which hyperlactatemia primarily reflects inadequate oxygen delivery and/or insufficient cardiac output, from a later phase, during which persistent hyperlactatemia stems from metabolic reprogramming and mitochondrial dysfunction. While the early phase is well described, its application at the bedside is not always straightforward.

Firstly, the “six-hour window” should not be interpreted as a rigid cutoff. The temporal dynamics of serum lactate decline are contingent upon the management strategies implemented prior to admission to the intensive care unit (ICU), as well as the patient’s baseline conditions. A substantial body of research has demonstrated that the efficacy of sepsis bundles is contingent upon the duration of delays preceding ICU admission [2]. Therefore, baseline serum lactate levels should be evaluated within the context of the patient’s overall trajectory, rather than in terms of a strict temporal threshold.

Secondly, the phenomenon of over-resuscitation persists as a genuine concern, even during the initial hours following septic shock onset. The CLASSIC trial demonstrated that a restrictive fluid strategy did not result in delayed serum lactate normalization [3]. This finding underscores the notion that hyperlactatemia persistence alone should not be used as a basis for aggressive fluid loading. The early integration of bedside perfusion indices, such as capillary refill time or mottling score, has the potential to prevent unnecessary escalation [4]. Thirdly, persistent hyperlactatemia in the initial hours should prompt a broader differential diagnosis instead of simply escalating fluid volume and vasopressor doses. Early septic cardiomyopathy may manifest as a decrease in serum lactate clearance despite adequate preload and perfusion pressure, thus necessitating an echocardiographic assessment. In addition, hepatic dysfunction alters serum lactate clearance and must be considered when analyzing hyperlactatemia. Multimodal monitoring, incorporating the venous-arterial carbon dioxide (PCO<sub>2</sub>) gap [5], is strongly recommended. In clinical practice, serum lactate during the early phase serves as a useful indicator. Whether measured from arterial or venous blood is of minor importance; what matters is its trend over time rather than the absolute value. This biomarker is best interpreted in conjunction with clinical and hemodynamic evaluations. The message is not to normalize lactate at all costs; rather, it is to interpret its kinetics in context, a nuance that Castro et al. rightly emphasize and that is critical for avoiding both under- and over-treatment.

Beyond the initial phase of fluid resuscitation, the “second phase” of lactate clearance—defined as a persistent elevation in serum lactate levels after the first six hours of shock—is more of a challenge than a useful tool for managing shock in the clinical setting. Castro et al. have demonstrated that, beyond the sixth hour of shock, the onset of the Warburg effect (a metabolic shift described in tumor cells in which glycolysis is used to generate energy and biosynthetic intermediates regardless of oxygen availability) and subsequent mitochondrial dysfunction may be responsible for reduced lactate clearance and persistent hyperlactatemia, independently from tissue perfusion. Conversely, a persistent disparity between oxygen delivery and consumption can also occur.

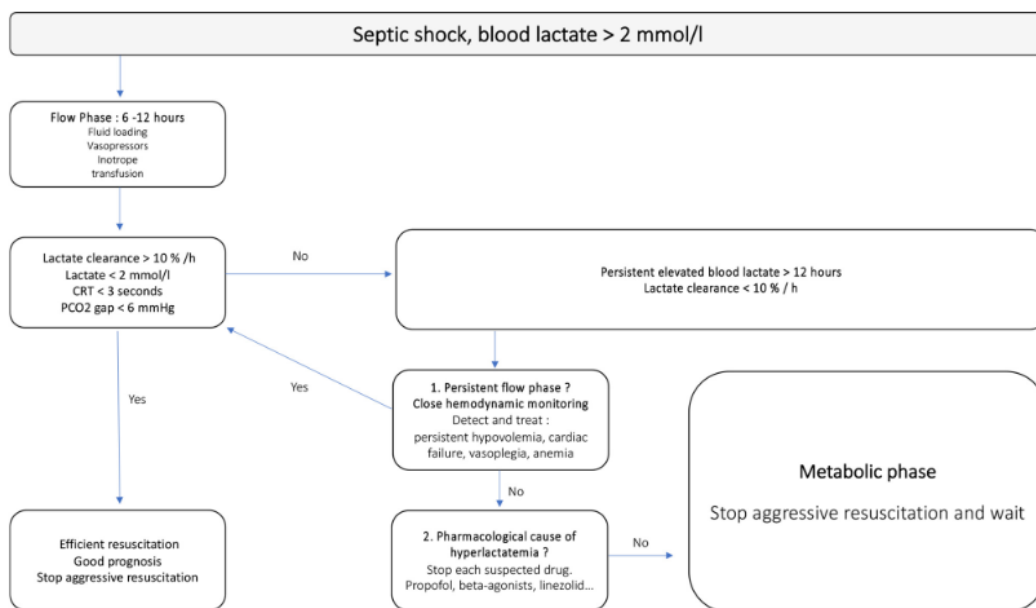


Fig. 1. Proposition of integrative use of blood lactate kinetics during septic shock. Abbreviations: CRT: Capillary refill time, PCO2: CO2 pressure

Consequently, the “second phase” poses three primary questions (Fig. 1):

1. is there a persistent flow phase?
2. Is there is a pharmacological cause of persistent hyperlactatemia?
3. is it a pure “metabolic phase”?

The persistence of the flow phase would suggest the presence of persistent hypovolemia, cardiac dysfunction, and/or anemia. The only method of detecting and closely treating this condition is to closely monitor hemodynamics in all patients with persistent hyperlactatemia. This can be achieved through repeated echocardiography and by incorporating continuous hemodynamic monitoring with trans- pulmonary thermodilution or pulmonary artery catheterization in the most severe patients, particularly in cases of severe sepsis-associated cardiac dysfunction with inotropic requirement [6]. Recent studies have demonstrated that, in

cases of cardiogenic shock, continuous monitoring of cardiac output, left and right cardiac filling pressure, and oxygen central venous saturation is associated with a more favorable prognosis, in addition to septic shock [7–9]. During this phase, calculating the PCO<sub>2</sub> gap can also be beneficial. A high PCO<sub>2</sub> gap value (>6 mmHg) has been shown to indicate inadequate cardiac output [10], whereas a normal PCO<sub>2</sub> gap value (<6 mmHg) can confirm the “pure metabolic phase.”

A systematic evaluation of the potential pharmacological cause of persistent hyperlactatemia is imperative, entailing the cessation of all implicated medications (Fig. 1). For instance, Propofol-Related Infusion Syndrome (PRIS) has been identified as a primary reversible cause of persistent hyperlactacidemia in sedated patients. Epinephrine, terbutaline, albuterol, acetaminophen, metformin, and linezolid have also been identified as frequent drug-induced causes of persistent hyperlactatemia in ICU patients [11,12].

The elimination of these two mechanisms would likely facilitate the accurate identification of the “pure metabolic phase,” thereby substantiating the rationale for de-escalation resuscitation and subsequent wait. As Castro et al. have reported, at this stage, the continuation of aggressive resuscitation is not only futile, but also hazardous. Concomitant with hemodynamic monitoring, favorable trends in PCO<sub>2</sub> gap and capillary refill time values could provide substantial rationale for discontinuing aggressive resuscitation measures.

In the forthcoming years, a promising research domain will emerge centered on the assessment of the efficacy of pharmaceutical agents that expedite mitochondrial and cellular restoration, as well as the identification of novel biomarkers capable of differentiating between the “persistent flow phase” and the “pure metabolic phase.”

### **CRediT authorship contribution statement**

Inès Lakbar: Conceptualization, Writing – original draft, Writing – review & editing. Marc Leone: Conceptualization, Writing – original draft, Writing – review & editing. Laurent Muller: Conceptualization, Writing – original draft, Writing – review & editing.

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