Review Article

The origins of the Lacto-Bolo reflex: the mythology of lactate in sepsis

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Abstract: The use of lactate as a marker of the severity of circulatory shock was popularized by Dr. Weil in the 1970's. Dr. Weil promoted the idea that blood lactate concentration increased in circulatory shock due to anaerobic metabolism following decreased oxygen delivery. This concept becomes entrenched with 1992 ACCP/SCCM consensus conference definition of sepsis. Since then, the central role of lactate in the definition and management of septic shock has only been expanded and become more ingrained. This review will discuss the wisdom of such an approach, an updated model describing the origins of hyperlactatemia in sepsis, and how such improvements in our knowledge of the underlying physiology should change our approach to resuscitation in patients presenting with septic shock.

Keywords: Sepsis; septic shock; lactate; myth; metabolic failure; the Lacto-Bolo reflex

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The Lacto-Bolo reflex: a well-known pathological reflex observed in the majority of house staff and a large portion of attending physicians. It involves the reflexive administration of IV crystalloid in response to a serum lactate above what is considered normal. Also known as Lacto-Crystalis, Lacto-Saline, and even Lacto-Lactated (ringers) reflex.

Discovered in sour milk by a Swedish apothecary assistant, Karl Wilhelm Scheele, in 1780 (1), lactic acid first achieved prominence as a prognostic aide in the initial 1992 definition of sepsis. Since then its role in septic shock has only expanded and become more entrenched (2). With recent publications (2) suggesting potential harms associated with the use of a lactate guided approach, one cannot help but wonder, how, from its humble beginnings, lactate reached the vaulted position it holds today, as the irrefutable guide in the management of patients with sepsis and septic shock.

The syndrome of hyperlactatemia was first described by William Huckabee in 1961. Dr. Huckabee published a case series of nine patients in which he described a syndrome of decreased serum bicarbonate levels with a corresponding increase in serum lactate values, noting this constellation of laboratory values was associated with poor outcomes (3). In 1970, Weil *et al.* published an experimental study using a hemorrhagic rat model, reporting the presence of hyperlactatemia correlated with the presence of shock (4).

In 1992 Bone *et al.* published the results of the first ACCP/SCCM consensus conference on the definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis (1). The authors asserted that elevations of serum lactate should be considered a marker of end-organ dysfunction, and inadequate tissue oxygenation (1). In the 2001 consensus updated by Levy *et al.*, the authors views on lactate remained essentially unchanged, specifying

elevations in serum lactate levels should be considered as a marker of organ hypoperfusion (5).

In 2004 the Surviving Sepsis Campaign (SSC) published the first iteration of their sepsis guidelines reasserting that elevations in serum lactate levels should be considered a marker of tissue hypoperfusion. Over the ensuing years lactate's place in sepsis resuscitation only grew more ensconced as subsequent iterations of SSC treatment guidelines began to link its elevation to the administration of intravenous (IV) fluids (6-8).

In 2015 the SSC's recommendations were given regulatory support when the Center of Medicare and Medicaid Services (CMS) announced the initiation of their own quality measure, the SEP-1 criteria. This document essentially mandated hospitals to track clinicians' performance of completion of treatment bundles at 3 and 6 hours. Similar to the SSC's bundles, lactate was featured heavily as marker to guide fluid resuscitation, only now tying compliance with such a strategy to the threat of financial compensation.

Subsequent versions of the SSC conceded that all elevations in serum lactate are not necessarily due to end-organ dysfunction and hypoperfusion (9,10). Despite this concession, the recommendations regarding the use of serum lactate to guide fluid resuscitation remained unchanged, relegating this important acknowledgment to a gesture of words alone.

As we have watched lactate's role in the management of sepsis grow in prominence since its initial appearance in the 1992 sepsis definition, we have coordinately observed a growing body of evidence demonstrating potential harms associated with early aggressive fluid resuscitation strategies (11-13); culminating in the recent ANDROMEDA-SHOCK Trial, suggesting potential harm associated with a lactate guided strategy (2). How should we reconcile mounting evidence suggesting harms associated with our current resuscitative strategies with more than a decade of consecutive guidelines recommending this very approach? What exactly is the role of serum lactate in modern sepsis management?

The concept of lactate as a marker of end-organ hypoperfusion, or a surrogate for anaerobic metabolism at a cellular level is deeply rooted in the critical care literature. Much of this originates from research examining lactate production in exercising muscle. While multiple models of shock have demonstrated an association between lactate and tissue hypoxia, in sepsis this is rarely the case, where blood flow to the organs is often increased and partial pressure of oxygen (PO2) at the level of the tissue is normal or even high (14-17). In fact, elevations in lactate can and often occurs even in the setting of increased blood flow, with no clear association between oxygen delivery and serum lactate values (14,18,19). This was most recently demonstrated in a reanalysis of the Albumin Italian Outcome in Sepsis (ALBIOS) Study, in which they found that up to lactates of 5.6 mmol/L were independent of oxygenation (19).

If hypoperfusion induced anaerobic metabolism is not the source of hyperlactatemia in sepsis, then what is? Lactate is derived from pyruvate by lactate dehydrogenase (LDH). Lactate and pyruvate are maintained at an equilibrium of roughly 10:1 (20). In sepsis this ratio shifts to favor lactate (21). Catecholamine stimulation, via the beta 2 pathway is associated with increased pyruvate (22), by default leading to an increased lactate (14). When patients are administered epinephrine to combat sepsis-related shock, increases in serum lactate levels are observed (22). In the setting of septic shock, not only is there catecholamine increased aerobic glycolysis but pyruvate dehydrogenase (the enzyme responsible for shifting pyruvate into Krebs cycle metabolites) is dysfunctional, so more pyruvate is shifted to lactate (22,23). A similar phenomena is seen in patients receiving albuterol for asthma exacerbation, and epinephrine in septic shock (24,25).

The causative role of these pathways in producing hyperlactatemia is illustrated in studies where investigators inhibit their progression, leading to decreases in lactate production (14,22). Esmolol infusions, to blunt the catecholamine pathways of septic shock cause falls in serum lactate levels alongside a decrease in oxygen delivery, reinforcing the concept that a large portion of the hyperlactatemia observed in sepsis is due to an elevation in circulating catecholamines (26). Similarly, the use of dexmedetomidine has been observed to be associated with a significant decrease in circulating intrinsic catecholamines and serum lactate levels (27,28). While the lactate production might be in partly secondary to dysfunctional metabolism, it is not useless, it is an essential fuel for tissues undergoing stress (29,30).

Taken together this suggests a complex picture of metabolic failure in sepsis that simply cannot be explained by tissue hypoperfusion and hypoxemia. In the setting of increased oxygenation, and catecholamine stimulation, pyruvate generation is increased. However, the pathway into the Krebs cycle is inhibited leading to greater lactate generation and an increase in the lactate to pyruvate ratio, and decreased adenosine triphosphate (ATP) (especially in

non survivors) (31). When viewed from this perspective, it is obvious that resuscitation strategies intended to improve oxygen delivery by augmenting cardiac output with aggressive fluid resuscitation are destined to fail (32). And trending serum lactate levels to assess the effectiveness of such strategies is nonsensical.

If lactate was never a specific marker for sepsis, and its elevation rarely represents end-organ hypoperfusion, why have all the previous trials, used by the SSC to support their recommendations, found a benefit where ANDROMEDA-SHOCK found potential harm?

Most of the literature examining lactate clearance as a resuscitative marker in sepsis is observational. These trials demonstrate that improvements in lactate clearance is a prognostic marker. They do not demonstrate that our active attempts to lower lactate levels leads to improved outcomes (33,34). There is little to no randomized clinical trial (RCT) data demonstrating the use of a lactate guided resuscitation strategy improves outcomes in sepsis. In 2010, Jones *et al.* published the results of the Shocknet Trial which compared a lactate guided approach to the more traditional early goal-directed therapy (EGDT) approach employing central venous oxygen saturation (ScvO2) to guide resuscitative efforts (35). The authors found the two resuscitative strategies were similar. The only RCT claiming to find a benefit in a lactate-guided approach was Jansen *et al.*, published in AJRCCM in 2010. The authors conducted a RCT of 348 intensive care unit (ICU) patients, admitted to the ICU with a lactate >3, and randomized them to a lactate guided resuscitation protocol *vs.* usual care. The goal was for a decrease in lactate of 20% every 2 hours. The lactate guided therapy resulted in larger volumes of IV crystalloid administration as well as more frequent use of vasodilators without a statistically significant improvement in mortality in the unadjusted analysis. It was only after statistical adjustments for baseline imbalances, that the authors identified a benefit to the use of a lactate-guided resuscitation strategy. However, only a minority of the patients (135 patients total) enrolled in this trial had sepsis or septic shock (36).

Gu *et al.* published a meta-analysis, which included both the Jones *et al.* and Jansen *et al.* trials along with two additional small RCTs examining the use of lactate to guide resuscitative efforts in septic shock. The authors reported a mortality benefit [relative risk (RR), 0.65, 95% confidence intervals (CI), 0.49–0.85, P=0.002], but this was based on a total of 547 patients, with only two of the trials found to be at low risk of bias (37). It is important to note, none of the trials referenced by the SSC used serum lactate to guide fluid administration, in the fashion that is suggested by the SSC guidelines. In each of these four trials, fluid administration was driven by a central venous pressure (CVP) goal. Lactate levels helped determine the administration of inotropic agents, vasodilators, or the transfusion of packed red blood cells (pRBCs).

Compare this to the ANDROMEDA-SHOCK trial, a well-done multicenter RCT, employing a lactate-guided strategy similar to the SSC recommendations, enrolling almost as many patients combined as all four trials included in the Gu *et al.* meta-analysis (2). Published in *JAMA*, by Hernández *et al.*, the authors randomized adult patients presenting with septic shock (defined as a serum lactate ≥2.0 mmol/L, requiring vasopressors to maintain a mean arterial pressure (MAP) of 65 mmHg after a fluid bolus of at least 20 mL/kg), to one of two resuscitation strategies for the first 8-hour of management. Patients were randomized to have end-organ perfusion assessed using either capillary refill time (CRT), the peripheral perfusion group, or serum lactate. If perfusion was determined to be inadequate, patients were placed into a resuscitative algorithm, which included IV crystalloid boluses, vasoactive and inotropic support.

The authors enrolled 424 patients over a 1-year period from 28 sites; the majority (71%) being enrolled from the Emergency Department. A lactate-guided strategy led to a higher volume of fluid administered, more vasopressor use, and more frequent use of epinephrine. This strategy failed to translate into improvements in clinical outcomes. In fact, when patients underwent a lactate guided strategy they tended to fare worse when compared to a perfusion-targeted approach; 28-day mortality was 34.9% in the peripheral perfusion group and 43.4% in the lactate group [hazard ratio, 0.75 (95% CI, 0.55 to 1.02); P=0.06]. This 8.5% absolute difference, while not statistically significant, tiptoed along the border of demonstrating harm associated with a lactate guided resuscitation approach.

There are a number of conclusions that can be drawn from the results of the ANDROMEDA-SHOCK trial. One could deduce that there is no difference between these two resuscitative strategies and either approach to the early hemodynamic management of patients in septic shock is adequate. An alternative interpretation is a lactate guided-therapy is harmful, and the study was immensely underpowered to detect an 8.5% in 28-day mortality. Since the majority of lactate produced in the early stages of sepsis is not due to end-organ malperfusion,

incorporating it into a treatment algorithm that treats it as a marker of tissue hypoxia cannot help but lead us astray. A third possibility is neither of these strategies are the ideal method for resuscitating a patient in septic shock, rather the peripheral perfusion approach merely represents the lesser of two evils. Given the growing body of literature suggesting harm associated with overly aggressive fluid resuscitation, the peripheral perfusion strategy may have appeared superior simply because it triggered activation of the ANDROMEDA-SHOCK resuscitation pathway less frequently, sparing a greater proportion of patients from overly enthusiastic therapeutic intentions.

While not definitive, the results of the ANDROMEDA-SHOCK trial should force us to reevaluate the role of lactate as a resuscitation marker in patients with septic shock.

Lactate is not without its uses. There is a fairly robust body of evidence suggested serum lactate can serve as a prognostic tool during resuscitative efforts (38-41). In the past we have understood this to mean that in the face of non-clearing lactate levels we should redouble our resuscitative efforts. With the growing evidence that lactate is a poor surrogate for tissue hypoperfusion and suggested harms associated with a lactate-guided resuscitation strategy, the wisdom of such a response is now in question. Rather, a non-clearing lactate level should alert clinicians of the ongoing stress experienced by the patient, prompting an inquiry into whether source control is truly achieved or if additional antimicrobials or interventions are required. It is our opinion that the interpretation of lactate should be separate from decisions regarding ongoing fluid resuscitation. We must strive to once and for all sever the deep-rooted neuronal pathways that lead to the almost universal and pathological Lacto-Bolo reflex.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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