



# Lactate – A Marker for Sepsis and Trauma

## NEW CONCEPTS AND EMERGING TECHNOLOGIES FOR EMERGENCY PHYSICIANS

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Dear Colleagues,

It is our pleasure to provide this EMCREG International newsletter which discusses lactate as a marker in resuscitation for sepsis and trauma. While lactate testing has been in medical arena for over a century, its utility in the emergency department for the evaluation of these potentially critically ill patients is only now being recognized. This newsletter aims to review the present literature on lactate testing in the clinical environment as it pertains to its use for emergency department patients.

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We hope this EMCREG-International newsletter provides clinically useful information which will help you in the care of your patients.

Sincerely,



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### Objectives:

- 1) Describe the process by which lactate would become elevated for a given patient.
- 2) List conditions which may cause elevated serum lactate other than trauma and sepsis.
- 3) Explain the significance of "lactate clearance."
- 4) Discuss the potential uses for lactate in the emergency department.

### Background and Introduction

It seems that each month, our journals publish the findings of a new study which describes the use of a certain marker or set of markers for the diagnosis, prognosis, or treatment of some emergency medical condition. Manuscripts and symposia discussing marker clearance, marker change, marker panels, and point-of-care markers reside in every issue and every meeting. In this newsletter, lactate, a serum marker older than any cardiac marker cousin, assumes center stage in two of the most difficult and resource intensive emergency medicine conditions – sepsis and trauma. This EMCREG-International newsletter aims to familiarize the emergency physician with lactate and its potential use the emergency department (ED).

Lactic acid or lactate, as its name implies, was first isolated from sour milk in the 18<sup>th</sup> century. In 1918, scientists observed cases in which metabolic acidosis was associated with decreased blood flow and shock. In the 1970's and 80's, the seminal works of Huckabee and Cohen finally described the clinical syndrome of lactic acidosis as we know it today.<sup>1,2</sup> The clinical and physiologic condition of metabolic acidosis has been recognized for nearly a century, yet we are only now discovering new approaches for its diagnosis and treatment.

### Biochemistry of Lactate Production and Lactic Acidosis

Understanding how lactate levels might be used in our clinical practice requires an understanding of how the body produces and clears lactate. In a normal steady state with adequate tissue resources and oxygenation, more cellular energy can be extracted aerobically by means of the citric acid cycle and the electron-transport chain. In this case, cells convert pyruvate to acetyl CoA through oxidative decarboxylation.



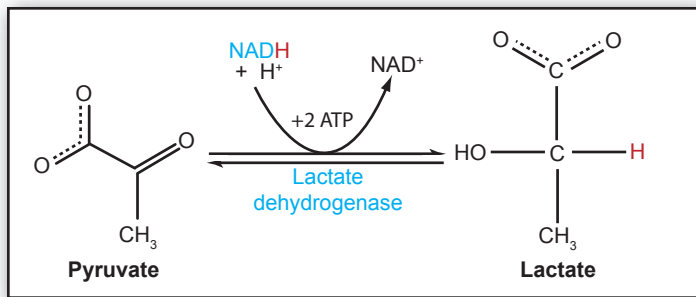


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In contrast, when the body experiences inadequate tissue perfusion, it undergoes anaerobic metabolism to create some energy, even in a small amount. In this case, pyruvate metabolizes to lactate ultimately generating fewer ATPs (2 vs. 36) than through the normal, aerobic mechanism (Figure 1).



**Figure 1.** Anaerobic metabolism and production of lactate.

Lactate production occurs in all tissues, namely skeletal muscle, brain, red blood cells, and kidneys. Even at baseline, under normal healthy oxygen rich conditions, this process occurs to some degree. Lactate in normal human subjects clears very quickly at a rate up to 320 mmol/L/hr, mostly by liver metabolism and re-conversion of lactate back to pyruvate. This action keeps “basal” levels of lactate below one mmol/L in both arterial and venous blood.<sup>2</sup>

Heavy exercise, seizures, and shivering are examples of common conditions which can also cause lactic acidosis (Table 1).<sup>3</sup> In these cases, the body clears lactate quickly and significant serum increases generally do not occur. In select rare metabolic conditions, lactate increases due to inadequate oxygen utilization rather than inadequate oxygen supply. The astute clinician should factor these potential causes into the assessment of any patient with a lactic acidosis.

**Table 1.** Causes of Lactic Acidosis

| Inadequate oxygen delivery               | Disproportionate oxygen demands | Inadequate oxygen utilization  |
|--|---------------------------------|--|
| Volume depletion or profound dehydration | Hyperthermia                    | Systemic inflammatory response syndrome  |
| Significant blood loss                   | Shivering                       | Diabetes mellitus  |
| Septic shock                             | Seizures                        | Total parenteral nutrition   |
| Profound anemia                          | Strenuous exercise              | Thiamine deficiency  |
| Severe hypoxemia                         |                                 | HIV infection  |
| Prolonged carbon monoxide exposure       |                                 | Drugs such as metformin, salicylate, antiretroviral agents, isoniazid, propofol, cyanide |
| Trauma                                   |                                 |  |

Rather than thinking of lactate solely as a byproduct of inadequate blood perfusion, it may be useful to consider lactate as a marker of strained cellular metabolism. For the purposes of the ED patients with sepsis or trauma, volume depletion, blood loss, septic shock, and systemic inflammatory syndrome can alter lactate levels. Knowing these levels, particularly early in the patient’s presentation, can provide valuable information to help guide patient assessment and treatment.



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### Lactate in Trauma

Several studies show the utility of lactate measurements in critically ill trauma patients. For instance, Abramson et al. prospectively evaluated 76 consecutive multi-trauma patients admitted to the ICU and measured serial lactates and lactate clearance over 48 hours. All of the 27 patients in whom lactate normalized (to  $\leq 2$  mmol/L) in 24 hours survived, and only three of the 22 (13.6%) of patients who did not clear their lactate by 48 hours lived. The authors concluded that the time needed to normalize lactate levels could be used as a prognostic indicator in severely injured patients.<sup>4</sup>

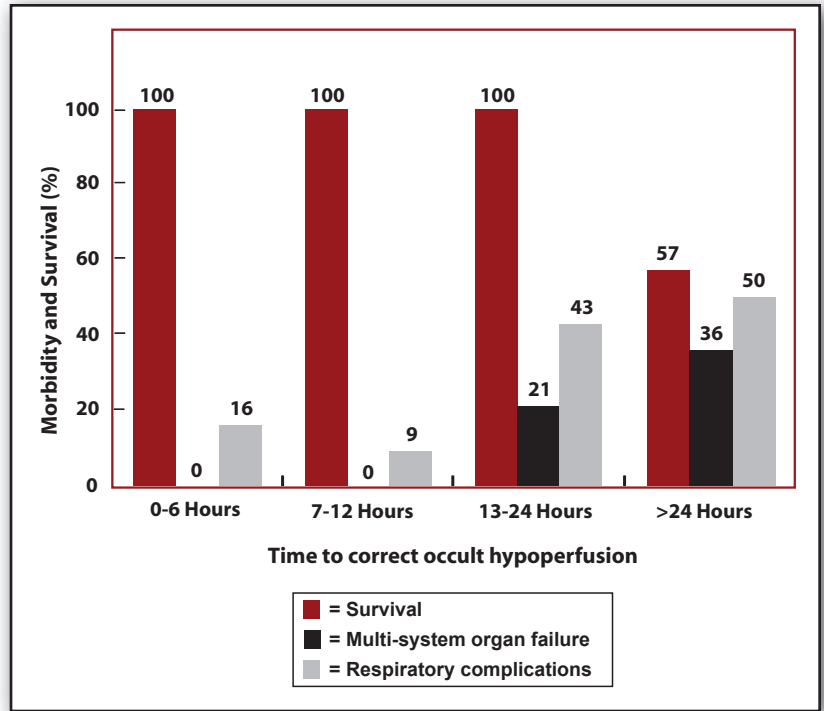
Emergency physicians and emergency medical service providers pay much attention to the “golden hour” critical time period in trauma resuscitation. In his manuscript on the importance of 24-hour lactate clearance, Dr. Blow extends the critical period of a “golden hour” to a new lactate driven adage of the “silver day.” This retrospective observational study followed by a

prospective trial included trauma patients presenting to a Level I trauma center who survived greater than 24 hours and had an Injury Severity Score (ISS) greater than 20. Arrival and subsequent serial serum lactates were obtained and levels and time of lactate clearance measured. These patients (n=85) underwent aggressive resuscitation to clear lactate to a level less than 2.5 mmol/L and thereby treating what the authors call "occult hypoperfusion." Of the patients that corrected their lactate and occult hypoperfusion within 24 hours, all survived. The longer it took for lactate to clear, the higher the rate of multi-system organ failure and mortality. It was found that 43% of the patients died if lactate clearance took more than 24 hours (Figure 2).<sup>5</sup>

If we can conclude that lactate levels in trauma patients are prognostic and that rapid lactate normalization benefits trauma patients, then rapid assessment of lactate levels becomes desirable. To support this conclusion, Asimos et al. conducted a before-and-after study of implementation of a point-of-care testing platform for major trauma patients. Routine trauma labs included hemoglobin, sodium, glucose, potassium, chloride, blood urea nitrogen, pH, P<sub>CO2</sub>, P<sub>O2</sub>, HCO<sub>3</sub>, base deficit, and lactate. Only hemoglobin, glucose, blood gas, and lactate resulted in "emergency appropriate" management changes.<sup>6</sup>



**We have all heard of the trauma resuscitation "Golden Hour." Lactate clearance helps identify and treat for the "Silver Day."**



**Figure 2.** Morbidity and survival vs. time to correct occult hypoperfusion.<sup>5</sup> Reprinted with permission from Blow et al. J Trauma 1999; 47:964-9.

## Myths and Misconceptions Regarding Lactate Measurement in Trauma Patients

### I. "You need to use arterial blood to measure lactate."

Several studies find serial lactate measurements to be useful in trauma patient care. Initial ICU investigations used only arterial lactate and some of the more current literature does not indicate whether arterial or venous blood was used in the study population. Previous experience and clinical use of lactate in the ICU setting suggests that only arterial lactate is useful. Lavery *et al.* investigated this very issue and correlated the use of venous lactate and arterial lactate in triaged patients presenting to a trauma center. In this study, the authors sought to determine the correlation between arterial and venous lactate as well as determine if venous lactate could identify those patients with serious injuries.

As we know, the acquisition of specifically arterial lactate, despite its demonstrated utility, limits its usefulness in the undifferentiated patient population of the ED. Without an arterial line, arterial blood gas acquisition requires the special skills of a physician, nurse, or respiratory therapist. Patients find this procedure more painful and frequently refuse repeated attempts or serial sampling. Arterial punctures can also cause greater complications of bleeding, hematoma, and arterio-venous fistulas.



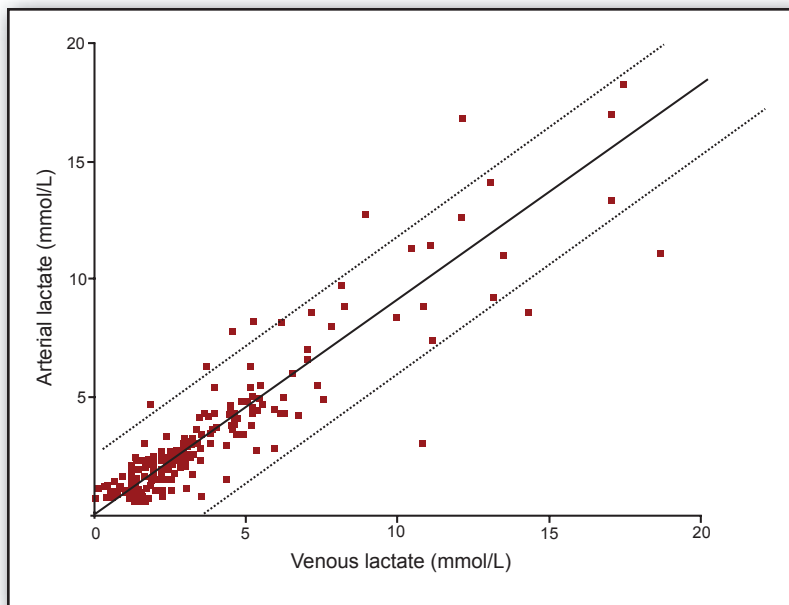
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In this study, patients arriving to a trauma center (n=375) had both arterial and venous lactates performed within 10 minutes. Collected data included injury mechanism, demographics, admission vital signs, disposition, length of stay, hospital outcomes and injury severity score. The mean arterial lactate concentration was 3.11 mmol/L (SD 3.45, 95% CI 2.67-3.55) and the mean venous lactate concentration was 3.43 mmol/L (SD 3.41, 95% CI 2.96-3.90) demonstrating no significant differences between the two sources of blood lactate. The correlation between venous and arterial lactate levels was 0.94 (Figure 3).<sup>7</sup>

Furthermore, an elevated venous lactate was associated with and correctly predicted moderate to severe injury as defined by the Abbreviated Injury Score (AIS). Lactate levels  $\geq 2$  mmol/L portended an increased risk of an ISS  $> 13$ , death, admission to the ICU, and length of stay great than 48 hours. It appears that both venous and arterial lactate can adequately predict injury severity and mortality, suggesting that either can be used in ED clinical practice.<sup>7</sup>



**Figure 3.** Scatter plot, regression line, and 95% confidence intervals for venous and arterial lactate. The equation for the line is  $y=0.076 + 0.889x$ .<sup>7</sup> Reprinted with permission from Klein et al. Acta Med Austriaca 1976; 3:69-73.

### II. "I can use the anion gap and don't need another lab test."

A variety of laboratory parameters can help identify patients with severely compromised or strained metabolisms. Among these are the anion gap (AG), pH, and lactate levels. In a retrospective cohort study, Adams et al. included all ED patients over a seven month time period in whom a lactate level was measured for any reason. They considered an AG  $>12$  abnormal and conducted sensitivity analyses of the AG for detecting the presence of a lactate  $>2.5$  mmol/L. The AG was 52.8% sensitive, 81.0% specific with a negative predictive value of 89.7% for the prediction of lactic acidosis.<sup>8</sup> While the three parameters of AG, pH, and lactate are related, they are not absolutely co-dependent. Critically-ill patients have impaired acid-base regulation and are thought to generate more unmeasured cations, such as magnesium and calcium, thereby affecting the AG. Furthermore, hypoalbuminemia affects the AG and is also prevalent in the ED population.<sup>8,9</sup> From these studies, it appears that the AG cannot be considered a surrogate for lactate testing.



**Both venous and arterial lactate can adequately predict injury severity and mortality, suggesting that either can be used in ED clinical practice.**

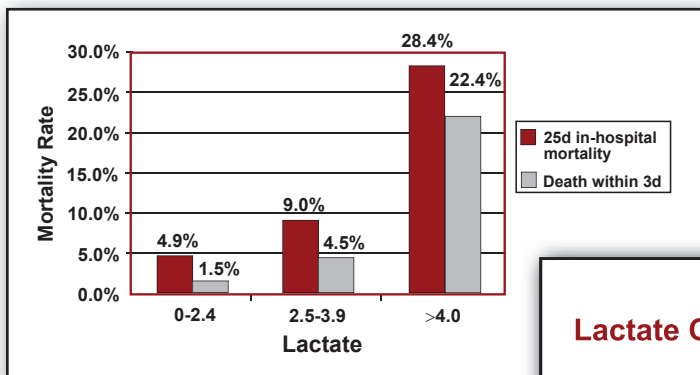
**Lactate screening may prove beneficial even in normotensive, hemodynamically stable patients.**

## Lactate in Sepsis

In the United States alone, sepsis accounts for over 751,000 cases, 215,000 deaths, and 16.7 billion dollars in health care costs annually.<sup>10-12</sup> With the more aggressive emphasis towards rapid discharges and outpatient surgeries, and the paucity of primary care, sepsis ranks as one of the higher prevalence, higher mortality, and more expensive conditions that an emergency physician will encounter. Recent emphasis on goal-directed resuscitation and new aggressive treatment adjuncts such as intensive insulin therapy, activated protein C, and steroid therapy stand to improve outcomes in this everyday emergency condition.<sup>12</sup> Emergency physicians have an opportunity to make a significant impact in this challenging patient population.

Landmark studies in this area support the use of serum lactate in both the diagnostic and treatment phases for septic shock.<sup>11,13,14</sup> Lactate levels are a critical parameter indicating sepsis induced hypoperfusion and triggering guideline driven early goal directed therapy (EGDT) in the Surviving Sepsis Campaign.<sup>15</sup> In a multivariate analysis of over 20 hemodynamic (i.e. pulmonary artery pressures, total blood volume index) and regional variables of organ dysfunction (i.e. mucosal-arterial PCO<sub>2</sub>, gastric intramucosal pH), lactate was the only ED attainable parameter that was predictive of outcome.<sup>13</sup> While previous resuscitation literature may have given the notion that directed care of septic shock patients required invasive measurements such as pulmonary artery pressures, oxygen delivery index, and systemic vascular resistance, more recent investigations support testing more easily acquired in the ED such as mean arterial pressures (MAP), central venous pressures (CVP), and lactate levels.<sup>11,13</sup>

**Figure 4.** Lactate as a predictor of mortality.<sup>12</sup> Reprinted with permission from Shapiro et al. Ann Emerg Med. 2005; 45:524-28.



It also appears that lactate screening may prove beneficial even in normotensive, hemodynamically stable patients. Shapiro et al. in a study with 1,278 patients with infection, demonstrated that increasing lactate levels were associated with increased mortality. Lactate levels less than 2.5 mmol/L were associated with a 4.9% mortality rate compared to patients with lactate levels  $\geq 4$  mmol/L who had an in-hospital mortality of 28.4%. A lactate concentration  $\geq 4$  mmol/L was 36% (95% CI 27-45%) sensitive and 92% (95% CI 90-93%) specific for any death (Figure 4).<sup>12</sup>

Just as in the trauma population, serial lactate measurements and attention to lactate clearance or “lac-time” may provide additive information useful in the treatment and prognosis of the individual patient. For instance, Bakker et al. found that while initial blood lactates did not differ between survivors and non-survivors in patients with septic shock, survivors had a significant decrease in lactate levels and lower “lac-times.”<sup>16</sup> Levraut et al. used a novel method of determining lactate clearance by infusing exogenous lactate and measuring clearance as well as basal lactate production. An increase in blood lactate of  $\geq 0.6$  mmol/L 60 minutes after the start time of lactate infusion was 53% sensitive and 90% specific and was associated with an odds ratio of 14.2 (p=0.042) for 28-day mortality.<sup>17</sup> Nguyen et al. examined a cohort of 111 ED and ICU patients with severe sepsis and septic shock. In this study, lactate clearance was defined as the percentage lactate decrease over the initial six hour ED evaluation and treatment period (Figure 5). All patients were followed for 72 hours and received protocol-driven early goal directed therapy EGDT. Multivariate logistic regression analysis of statistically significant univariate variables showed an inverse relationship with mortality - the higher the lactate clearance, the lower the mortality. In fact, mortality was reduced approximately 11% for each 10% increase in lactate clearance. Patients with a lactate clearance  $>10\%$  had a greater improvement in Acute Physiology And Chronic Health Evaluation (APACHE) II scores and lower 60-day mortality.<sup>18</sup> These findings suggest an important role for serial sampling and lactate clearance as a prognostic indicator.

**Figure 5.** Definition of lactate clearance.<sup>18</sup>

$$\text{Lactate Clearance} = \frac{(\text{Lactate}^{\text{ED Presentation}}) - (\text{Lactate}^{\text{Hour 6}})}{\text{Lactate}^{\text{ED Presentation}}} \times 100$$



## Conclusions

Using lactate as an indicator of impaired metabolism in trauma and sepsis patients may help emergency caregivers further diagnosis, risk stratify, and treat patients in the ED. Serial lactate measurements over the early diagnostic and treatment period can assist in monitoring treatment progress. Mainstream adaptation to the diverse ED environment will require further ED-based studies and observation of lactate utility in routine care of critically-ill and injured patients.

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### CME Post Test

After you have read the monograph carefully, record your answers by circling the appropriate letter answer for each question.

1) Lactate is a product of anaerobic metabolism.

- a) True      b) False

2) Seizures can cause a transient elevation in serum lactate.

- a) True      b) False

3) Stable or increasing serum lactate levels are associated with improved mortality in septic patients.

- a) True      b) False

4) Lactate is cleared by the liver, kidney, brain, and red blood cells.

- a) True      b) False

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