



Serum lactate is a useful predictor of death in severe sepsis and septic shock

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ABSTRACT

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The severe sepsis and septic shock are as common and lethal that emergency physicians routinely confront. Actually, more than two thirds of sepsis patients present initially to the ED. Only a few laboratory tests for markers of sepsis are currently available. The serum lactate level can help in determining prognosis and to risk-stratify patients with severe sepsis. This independent review of the literature includes 83 studies published in all electronic-based database such as Elsevier, PubMed, and SID during the last 18 years (40–320 patients in each). Data gathered from English language articles and books published between 1995 and 2013. The serum lactate concentrations measured in almost all patients with severe sepsis raised at admission and were higher in patients who had the worst outcomes such as higher Apache-II and SOFA score. Serum lactate was associated with mortality independent of clinically apparent organ dysfunction and shock in patients with severe sepsis admitted to the emergency department and intensive care unit.

This review focuses on the association between initial and serial serum lactate level and mortality in patients presenting to the emergency department with severe sepsis.

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Introduction

Sepsis is a heterogeneous clinical syndrome caused by any class of

microorganism. The incidence of severe sepsis and the number of sepsis-related

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deaths is increasing (1-3). There has not been a scientific basis for identification of high-risk patients or a practical standard for hemodynamic optimization and adjunctive pharmacological therapies in the emergency department (ED) (4).

According to several randomized, controlled trials, during the past few years, overall mortality rate among patients with severe sepsis and septic shock is declining (5-7). The concept of empirical therapy has changed in order to antimicrobial resistance to several agents (8,9).

Although there is no specific laboratory test for the diagnosis of severe sepsis and septic shock, the improvement in imaging and noninvasive interventional techniques have led to new diagnostic and therapeutic strategies for early source control.

Despite dramatic improvement in our knowledge about severe sepsis, there is always a long delay in diagnosis of sepsis and initiation of treatment, which increase the incidence of organ failure and mortality. It seems that the management of severe sepsis is time-dependent suggesting a "golden hour" and "silver day" giving the ED a more important role in the care of these patients.

The cornerstone of treatment of severe sepsis is the early diagnosis, administration of appropriate antibiotics, and early hemodynamic resuscitation.

Systemic inflammatory response syndrome (SIRS) is an inflammatory state, which defines as the presence of 2 or more of the following criteria:

- 1) Temperature greater than 38°C or less than 36°C
- 2) Pulse rate greater than 90 beats/minutes
- 3) Respiratory rate greater than 20 breaths/min (or PaCO₂ less than 32 torr).
- 4) WBC count greater than 12,000/mm³ or less than 4,000/mm³, or greater than 10% immature band forms.

Sepsis is a fatal syndrome caused by severe infection. Severe sepsis is defined as the presence of one or more organ system dysfunction in the context of sepsis.

Organ dysfunction includes as pulmonary and hematologic abnormalities, neurologic disorder, renal dysfunction, liver or cardiac failure or hypo-perfusion with lactic acidosis. Septic shock is defined as the presence of sepsis and refractory hypotension in which intravenous fluid administration alone is insufficient to maintain the hemodynamic of the patient.

Bacteremia is found only in about 50% of cases of severe sepsis and septic shock, whereas 20% to 30% of patients will have no microbial causes identified from any source.

Epidemiology

Sepsis is now the 10th most common cause of death in the United States. A recent study defined severe sepsis as "infection" and "new-onset organ dysfunction. The incidence of sepsis and severe sepsis continues to increase exponentially with age. Severe sepsis occurs in 1-2% of all hospitalizations. It costs an estimated 16.7 \$ billion annually. Incidence and mortality of severe sepsis is always underestimated, however, overall hospital mortality rate was 28.6 % (10).

Pathogenesis

There are several pathogenic events, which are responsible for the transition from sepsis to severe sepsis/septic shock. These include a neurohumoral, generalized pro- and anti-inflammatory responses. The sepsis cascade begins with a cellular activation of monocytes, macrophages, neutrophils and activation of the complement that interacts with endothelial cells through numerous pathogen recognition receptors (11). The other mediators that may participate are

tumor necrosis factors (TNF)- α , interleukins, caspases, proteases, leukotrienes, kinins, reactive oxygen species, nitric oxide, arachidonic acid, platelet activating factor and eicosanoids. The vascular endothelium damage results in tissue ischemia and this diffuse endothelial disruption is responsible for the various organ dysfunctions and global tissue hypoxia that accompanies severe sepsis/septic shock.

Presentation and diagnosis

Sepsis is diagnosed by history and physical findings, corroborated by laboratory data such as circulating leukocyte count, body fluid examination and culture.

Detecting the syndrome in hospitalized patients is particularly important, as nosocomial sepsis is associated with longer lengths of stay and higher mortality rates compared with community-acquired sepsis (12). Most patients will meet at least three SIRS criteria at intensive care unit (ICU) admission (13). Fever occurs in approximately 60% of patients at admission but may be suppressed in those with advanced age, renal failure or patients taking anti-inflammatory medications (14). Hypothermia, although uncommon, is an ominous finding associated with mortality rates of up to 60%. The lethality of hypothermia likely is not a consequence of the temperature itself but rather the relationship of hypothermia with underlying chronic diseases, shock and an exaggerated inflammatory response. Tachypnea is present in up to 80% of ICU patients. Although possible, the diagnosis should be questioned in patients lacking tachypnea or gas exchange abnormalities. Hypoxia is common in septic patients; more than 90% of patients will develop sufficient hypoxemia that requires supplemental oxygen, generally correlating with a $\text{PaO}_2/\text{FiO}_2$ ratio less than 300. Tachycardia is a

cardinal sign of sepsis, unless patients have intrinsic cardiac disease or is taking nodal blocking medications, tachycardia is nearly universal. Abnormalities in circulating leukocyte count (more than 12,000 cells/ mm^3 or fewer than 4000 cells/ mm^3) are frequent enough to be considered important diagnostic criteria.

Several serum biomarkers are purported to have diagnostic and/or prognostic value, but none have demonstrated acceptable sensitivity and specificity for routine clinical use.

The serum lactate level is suggested to be a marker of global hypo-perfusion and tissue hypoxia in sepsis. According to the theory, even before patients develop frank hypotension, tissue perfusion is impaired by myocardial depression, relative hypovolemia from a leaky endothelium, increased metabolic demands and impaired vasoregulatory mechanisms. Consequently, oxygen demand exceeds supply and anaerobic production of lactate ensues. Not all agreed that lactate production was a reliable marker of global hypoxia in sepsis (15).

Animal models of polymicrobial sepsis suggested that certain organs, particularly the liver and small intestine, may be more sensitive to impaired oxygen delivery (16). Regardless of its exact mechanism of production, patients admitted with a sepsis-related diagnosis and elevated serum lactate levels (greater than 4 mmol/L) had an increased mortality rate (17). Furthermore, mortality rates have decreased in septic patients with higher lactate clearance rates after 6 hours of therapy (18). Serum lactate is a component of prognostic models in severe sepsis and septic shock and concentrations increased in these patients.

Procalcitonin and C-reactive protein (CRP), both markers of inflammation, have been studied as potential diagnostic tests in sepsis (19-21). The reported sensitivities

and specificities of these tests vary widely, hence neither has achieved widespread acceptance.

Scoring systems and ability to predict outcome

Most prognostic models evaluate survival using data collected at admission or within the first 24 hours in ED. There are two types including general models and disease-specific models.

The main categories of general prognostic models include:

1) The models for evaluating the severity of illness:

- APACHE II and III
- Simplified Acute Physiology Score (SAPS) II

2) The models for quantifying organ dysfunction and failure:

- Logistic Organ Dysfunction System
- Multiple Organ Dysfunction Score
- Organ System Failure (OSF)
- Sequential Organ Failure Assessment (SOFA).

Organ Dysfunction

The organ dysfunction that results from sepsis is central to the pathogenesis of the disease. A 3000-patient ED-based study demonstrated that organ dysfunction with septic shock portended increasingly worse outcomes. Patients with suspected infection alone had a mortality rate of 2.1%, while the presence of SIRS criteria and suspected infection had a mortality rate of only 1.3% (22). However, the mortality rate was 9% for those patients with severe sepsis (sepsis plus organ dysfunction) and 28% for those with septic shock (23).

1) Cardiovascular Insufficiency and global tissue hypoxia

The cardiovascular insufficiency is the most important events in severe

sepsis leading to morbidity and mortality characterized by global tissue hypoxia, decreased contractility and ventricular dilatation.

In recent studies, echocardiographic findings demonstrated that in 40-50% of patients with severe sepsis developed myocardial depression and changes in cardiac performances.

The responsible mechanisms for this organ dysfunction are probably mitochondrial dysfunction, myocardial cell death; however, the cardiac function is fully reversible in the survived patients.

2) Hematologic dysfunction

Hematologic manifestation of organ dysfunction is well-recognized in severe sepsis. The most common abnormalities include leukocytosis, anemia, abnormal PT and aPTT, DIC and thrombocytopenia.

3) Neurologic dysfunction

Patients with sepsis often display neurologic impairments manifested by altered mental status and lethargy, commonly referred as septic encephalopathy. The incidence has been reported between 10 and 70%. The mortality rate in patients with septic encephalopathy is higher than that in septic patients without significant neurologic involvement.

4) Pulmonary dysfunction

The lung is an early victim of the inflammatory response to sepsis. These effects are apparent irrespective of the primary infection that causes sepsis. Significant right-to-left shunting, arterial hypoxemia and intractable hypoxemia occur. The resulting morbidity is high and is a common endpoint to sepsis-related deaths. Sepsis produces a highly catabolic state and places significant demands on the respiratory system. At the same time, airway resistance increases and muscle function is impaired. Irrespective of whether pneumonia is the cause of sepsis,

the common pulmonary endpoint is acute respiratory distress syndrome (ARDS). The development of ARDS occurs 4 to 24 hours after radiographic abnormalities develop.

5) Endocrine dysfunction

An absolute or relative adrenal insufficiency is common in sepsis. Depending on the balance of circulating cytokines, augmentation or suppression of the hypothalamic-pituitary axis is possible. Interleukin (IL-1) and IL-6 both activate the hypothalamic-pituitary-adrenal axis. TNF- α and corticostatin depress pituitary function. Other factors contributed to adrenal insufficiency in sepsis include decreased blood flow to the adrenal cortex, decreased pituitary function and pituitary secretion of adrenocorticotrophic hormone due to severe stress.

Methods

Due to lack of high quality study, we decided to include all study types (randomized, controlled trials were prioritized, non-randomized trials, cohort and case-control studies). The case studies, studies with fewer than 40 patients and abstracts which full text articles that were not available were excluded. This review was restricted to English, Persian and French languages publications. Study characteristics were defined according to in the acute setting, which patients assessed in the emergency department or ICU.

Inclusion criteria

- 1) Blood lactate assessment in the acute setting: emergency department, or intensive care unit.
- 2) 65 years old > age > 18 years old
- 3) Serial lactate measured in arterial or venous.
- 4) Written in English and French language
- 5) Human studies

Exclusion criteria

- 1) Case study
- 2) Based on specific types of post-operative and chronic illnesses.

Data sources

Studies were identified by a systematic search using PubMed, Elsevier and SID up to 2013. The reference list was hand searched to identify any appropriate article that may be missed by the electronic search. The data of each extracted study included

- 1) Demographic characteristics of participants.
- 2) The serum lactate assessment.
- 3) Type of outcome.
- 4) Statistics supporting the main findings of the study.

To assess the quality of the included studies, methods validated for internal validity, precision and external validity. The methodological quality and clinical relevance of each study were graded as high, moderate, or low.

Results

The initial search included 83 abstracts, which were evaluated for its relationship. Twenty four articles were potentially associated and were assessed in full text and finally 15 articles were selected.

Sustained hyperlactatemia in patients hospitalized in ICU, demonstrated by serial measurements, has suggested to be predictive for in-hospital mortality (24-26).

Five of these studies had moderate quality and three with a low quality, showed that high lactate levels in serial measurements and prolonged time to normalize lactate, predicted a higher mortality rate. The cut off point of serum lactate level used in most studies was 2.0 mM. The findings of study by Nichol et al. pointed that a sustained lactate levels as low as 0.75-1.0 mM were associated with increasing the adverse outcomes (OR = 2.0, $p < 0.0001$) (27).

In 2004, Kliegel et al. examined patients resuscitated for cardiac arrest and survived at least 48 hours with sustained hyperlactatemia (> 2.0 mM after 48 hours) were associated with higher mortality as well as poor neurological outcome (28).

In a randomized controlled study by Jones et al. the patients with severe sepsis in contrast to other causes of hypoperfusion were treated by two different resuscitation protocols. The first group was guided by lactate levels and the other guided by SvO₂ (29). They found that there was no significant difference in mortality between two groups.

Two studies, suggested that the lactate level greater than or equal to 4.0 mmol/L was 36% sensitive (95% confidence interval [CI] 27% to 45%) and 92% specific (95% CI 90% to 93%) for any death (30,31).

Jansen et al. showed that the reduction of lactate level by 20% per 2 hours was correlated with reduced significant mortality in the intervention group (32).

Therefore, according to the reviewed articles, an interval between two and six hours seems reasonable.

Green et al. conducted an observational cohort study in all patients who were admitted to the ED with suspected infection during a 1-year period. Both CRP and lactate testing was done and it was shown that increased CRP level and hyperlactatemia had a higher mortality rate than patients with abnormalities of other laboratory tests in isolation (33).

Krishna et al. conducted a prospective non-interventional to ascertain the role of serum lactate as a predictor of sepsis and septic shock and showed that an increase in lactate values followed over a period of time was highly effective in predicting the impending complications or grave outcome in patients with sepsis (34).

Londono et al. aimed to determine the

usefulness of serum lactate as a prognostic factor of 28-day mortality in patients admitted to the ED with clinical diagnosis of sepsis without septic shock. They proved that mortality increased in a linear way with serum lactate from any detectable values (35).

Borthwick et al. showed in their study that there might be a role for monitoring the normalization of serum lactate level during goal directed therapy in the ICU (36).

Trzeciak et al. showed in a post-hoc analysis that serum lactate in patients with possible sepsis could affect assessment of mortality risk, especially with an initial lactate ≥ 4.0 , increased the probability of acute-phase death (37). In a single-center cohort study where an initial venous lactate categorized as low (<2), intermediate, or high (>4), Mikkelsen et al. showed that it was associated with high mortality without organ dysfunction and shock in patients with severe sepsis (38).

Discussion

In the population admitted to ED or ICU, it seems reasonable to have close monitoring and perform serial lactate measurements in all patients with severe sepsis. The serial lactate measurement are a useful approach to monitor the critically ill patient. In number of studies, the role of sustained hyperlactatemia for prediction of adverse outcomes has been shown to be undeniable.

Conclusion

We found that the serum lactate was a useful tool for risk-stratification of the patients with severe sepsis, especially the trend in serial lactate monitoring was valuable in predicting in-hospital mortality. The initial serum lactate greater than 4 was correlated with higher mortality.

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Conflict of Interest

The authors declare no conflict of interest.

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