Critical Review Form

Prognosis

Early Lactate Clearance Is Associated with Improved Outcome in Severe Sepsis & Septic Shock, Crit Care Med 2004; 32: 1637-1642

Objective: To examine the clinical utility of lactate clearance (or the percentage decrease in lactate) as early as six hours as an indicator of multiple system organ failure and death. Also to define a lactate clearance cutoff associated with improved outcome after six hours of ED intervention. (p. 1638)

Methods: Prospective, observational single center case series of adult patients presenting to Henry Ford Hospital (Detroit, MI) from February 1999 to February 2000 with severe sepsis or septic shock. Eligible if > 18 years old presenting between March 1997 and March 2000 to Henry Ford Hospital (Detroit, MI) without bleeding risk, complicated sepsis (such as concurrent acute coronary syndrome or cardiogenic shock), atypical immune system (HIV or cancer), or contra-indications to invasive procedures. Eligible subjects also had to possess a systolic blood pressure < 90 mm Hg (after a 20-30 cc/kg bolus over 30-minutes) OR lactate > 4mmol/L AND two out of five of the following: 36°C > T > 38°C, heart rate > 90, respiratory rate > 20, partial pressure of carbon dioxide < 32 mm Hg, 4 > WBC > 12 OR >10% Bands. Exclusion criteria included age < 18 years, myocardial infarction, pulmonary edema, hemorrhagic shock, trauma, seizure, pregnancy, DNR orders, or need for immediate surgery. All subjects were enrolled within one-hour of presentation (p. 1638). All patients received central venous and arterial lines in the ED with crystalloid and/or colloid volume resuscitation to achieve a CVP of 8-12 mm Hg with vasoactive agents utilized to attain MAP > 65 mm Hg. "The primary outcome variable was in-hospital mortality." The Acute Physiology and Chronic Health Evaluation (APACHE) II score was obtained at hours 0, 6, and then every 12 hours up to 72 hours post-ED presentation. Lactate clearance was defined as

$$[(\text{Lactate}^{\text{ED presentation}}) - (\text{Lactate}^{\text{Hour 6}})] * 100 \div (\text{Lactate}^{\text{ED presentation}})$$

Guide		Comments
I.	**Are the results valid?**	
A.	**Was the sample of patients representative?** *In other words, how were subjects selected and did they pass through some sort of "filtering" system which could bias your results based on a non-representative sample. Also, were objective criteria used to diagnose the patients with the disorder?*	Almost two-thirds of patients had pneumonia, urosepsis, or pancreatitis (Table 1, p. 1639) so may not be representative of those presenting with alternative source of sepsis (SBE, cellulitis, ascending cholangitis, etc.) which were represented in smaller numbers. Eligible patients were enrolled (in consecutive fashion?) with "the clinicians in the hospital blinded to the data collection process" and study investigators did not influence clinical decision making (p. 1638). No filtering process is apparent.

B.	**Were the patients sufficiently homogeneous with respect to prognostic risk?** *In other words, did all patients share a similar risk during the study period or was one group expected to begin with a higher morbidity or mortality risk?*	1) Comparing survivors to non-survivors (Table 2, p. 1640) non-survivors were more likely to have septic shock (70 versus 39%, p=0.001), lower platelets, coagulation parameters, and albumen, and higher bilirubin levels. Initial lactate was higher (8 versus 6%, p = 0.01) and lactate clearance lower (12 versus 38%, p = 0.005) among non-survivors compared with survivors. Baseline age, vital signs, APACHE score, WBC, and fluid resuscitation were similar between these two groups. 2) Comparing low lactate clearance (<10%) with high lactate clearance (>15%) on Table 4, p. 1641 there were statistically significant differences in that low lactate clearers were more likely to have low platelets, elevated PTT, vasopressor utilization, and elevated APACHE scores at 12, 24, and 36 hours. There is no discussion of confounding co-morbidities on Table 1.
C.	**Was follow-up sufficiently complete?** *In other words, were the investigators able to follow-up on subjects as planned or were a significant number lost to follow-up?*	No loss to follow-up at 72 hours in the ICU was reported. Data reported hospital length-of-stay and 60-day mortality rates, but methods do not discuss how this data was collected.
D.	**Were objective and unbiased outcome criteria used?** Investigators should clearly specify and define their target outcomes before the study and whenever possible they should base their criteria on objective measures.	Primary outcome was in-hospital mortality which is a clear and irrefutable measure.

<table>
<tr><td>II.</td><td>What are the results?</td><td></td></tr>
<tr><td>A.</td><td>How likely are the outcomes over time?</td><td>In-hospital mortality rate 42.3% with “an approximately 11% decreased likelihood of mortality for each 10% increase in lactate clearance” (p. 1638). After 6-hours of intervention a lactate clearance of <10% had sensitivity 44.7%, specificity 84.4%, and accuracy of 67.6% for predicting in-hospital mortality.
Accuracy Formula
Accuracy is the answer obtained by your test in the absence of random error or bias.
Disease<table><tr><th>Test</th><td>Present</td><td>Absent</td></tr><tr><td>Positive</td><td>a</td><td>b</td></tr><tr><td>Negative</td><td>c</td><td>d</td></tr></table>Accuracy = [a + d] ÷ [a + b + c + d]

Note that one can also calculate a positive Likelihood Ratio (2.8) and a negative LR (0.65) from the above sensitivity and specificity. Given these LR and a baseline mortality of 42% (the in-hospital mortality rate overall in this study), the astute clinician can then calculate a post-test probability of death if lactate clearance is less than 10% (67%) or greater than 15% (32%).</td></tr>
<tr><td>B.</td><td>How precise are the estimates of likelihood?
In other words, what are the confidence intervals for the given outcome likelihoods?</td><td>No Confidence Intervals are provided to assess precision.</td></tr>
<tr><td>III.</td><td>How can I apply the results to patient care?</td><td></td></tr>
<tr><td>A.</td><td>Were the study patients and their management similar to those in my practice?</td><td>Evaluating Table 1 (p. 1639) there is no mention of confounding co-morbidities, but expect urban tertiary care teaching hospital to see similar distribution of cases as BJH.</td></tr>
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B.	**Was the follow-up sufficiently long?**	Yes, 72-hours and 60-days are sufficient to assess a biomarker obtained during the "Golden (6) Hour(s)" of shock management.
C.	**Can I use the results in the management of patients in my practice?**	Yes, as per our BJH sepsis protocol, there is a reason to assess baseline lactate and 6-hour follow-up lactate to calculate lactate clearance for risk stratification purposes.

Limitations

1) Single center urban teaching hospital may lack external validity. In other words, results may not apply to dissimilar settings (rural, non-academic centers with different patient mix and hospital capabilities).
2) Limited spectrum of sepsis etiologies.
3) Little discussion of confounding co-morbidities.
4) Multiple comparisons in univariate analysis suggest the need for Bonferroni correction which could vastly alter the results.
5) No discussion is offered on the objective criteria used to make each specific diagnosis (pneumonia, urosepsis, etc.).

Bottom Line

Lactate clearance represents a useful, clinically obtainable surrogate marker of tissue hypoxia and disease severity which, independent of blood pressure, age, APACHE score, or other laboratory markers, can predict in-hospital mortality within the setting of an urban teaching hospital with a well-established early goal-directed therapy program. Serial lactate measurements are more important than a single lactate measurement as an outcome prognosticator. The minimization of "lactime" (the time during which lactate remains > 2 mmol/L) should be a goal of resuscitation.