

DISCOVERY TRACK SUMMER RESEARCH

FINAL PROGRESS REPORT

PROJECT TITLE: Prognostic Utility of Lactate Clearance Measurements After 24 Hours in Patients with SIRS, Sepsis, Severe Sepsis and Septic Shock

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BACKGROUND AND SIGNIFICANCE

Lactic acid is made by the body in response to tissue hypoperfusion, which is one of the main complications in sepsis. Intuitively, increased levels of lactate are present in many septic patients, as the body is not able to adequately circulate oxygen in these patients. This is the physiological premise for using lactate measurements as indicators of the degree of tissue hypoperfusion. Given the correlation between the adequacy of circulation in septic patients and their survival, early versions of the Surviving Sepsis Campaign recommended taking an initial lactate measurement in septic patients. (Dellinger, Trzeciak, Mikkelsen). Since these early recommendations, serial serum lactate measurements, and the use of lactate clearance have entered many clinicians' protocols in the treatment of sepsis. (Otero, Arnold, Nguyen 2010, Jansen, Jones). In particular, it has been proposed that lactate clearance should take the place of ScVO₂. This is based on evidence that within the initial 24 hours of treatment, targeting lactate clearance as a goal of treatment in the place of ScVO₂, is non-inferior (Nguyen 2010, Nguyen 2004, Arnold, Jones).

Often times, resuscitative efforts stretch well beyond 24 hours of initial presentation. Yet, only scattered, small studies have addressed the role of lactate clearance measurements late in the resuscitative protocol (Friedman, Bakker, Krishna, McNelis, Manikis). Furthermore, our literature review only revealed studies in the SICU (Husain et al), (Bakker et al), (Friedman et al), (Manikis et al, McNelis et al, Krishna et al). Given the potential benefit of post 24 hour lactate clearance as a prognostic indicator and guide to therapy, our group felt motivated to investigate the issue in a larger and more diverse clinical spectrum than that currently available in the literature.

HYPOTHESIS AND RATIONAL

Given the proven efficacy of lactate clearance measured early in treatment of patients with SIRS, sepsis, severe sepsis, or septic shock to predict morbidity and mortality, as well as its apparent viability as an effective treatment goal in protocol based therapy, our group hypothesized that lactate clearance measured after 24 hours of initiation of treatment will continue to be predictive of morbidity and mortality.

SPECIFIC AIMS

Our group sought to collect lactate clearance values as well as other clinical data from patients admitted to the hospital with SIRS, sepsis, severe sepsis or septic shock in order to elucidate any correlation between post 24 hour clearance values and select clinical outcomes. The primary outcome was mortality. Secondary outcomes were Length of ICU stay, ICU readmission, need for vasopressors, and need for intravenous bolus fluid resuscitation.

PROGRESS MADE TOWARD EACH SPECIFIC AIM

Post 24 hour lactate clearance and mortality

Our initial approach to analyzing the relationship between clearance and mortality was to divide our patients, (approximately 230), into two groups, those above the median clearance value and those below. These two groups were designated clearers and non-clearers, respectively.

	Survivors	Deceased
Clearers	80	25
Non-Clearers	61	44

Table 1: Survival and Mortality in clearers and non-clearers

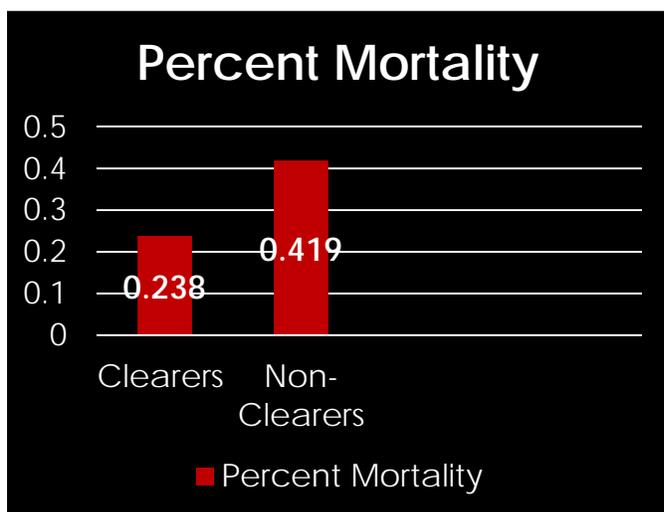


Figure 1: Percent mortality in clearers and non-clearers

Next, with the assistance of a graduate student in statistics, we performed a logistical regression of the effects of clearance on mortality in each group. The output was odds of mortality vs. survival. For

Clearers, odds of mortality was 0.24, for Non-Clearers, odds of mortality was 0.32. From this data, we derived an odds ratio. The odds ratio of odds of mortality in Non-Clearers over odds of mortality in Clearers was 1.305, indicating a 30.5% increase in the odds of mortality in the Non-Clearers group. A Wald's test indicated a P-value of less than 0.05, indicating significance. These results showed that clearers below the median indeed had increased mortality.

In order to best control for disease-severity, mortality analyses was also performed among all patients at once holding our measure of clinical severity, SOFA scores, constant. Our output was also modified to tell us the change in mortality that occurred for a 10% change in clearance. Logistical regression showed a 10% increase in clearance predicted a 5.5% decrease in the odds of mortality, (C.I. = 3.2-8.6%). This showed that the ability of lactate to predict mortality was independent of our measure of clinical severity.

Next, we used similar logistic regression models and outputs to investigate our secondary outcomes. SOFA scores were held constant for those outcomes which they proved to have a significant correlation to. For intravenous fluid resuscitation, logistical regression showed a 10% increase in clearance predicted a 5.3% decrease in the odds of a patient requiring fluid resuscitation, (C.I.= 3.3-8.1%). For vasopressors, logistical regression showed a 10% increase in clearance decreased the odds of a patient receiving vasopressors by 4.7%, (C.I. = 2.6-8.0%). For length of ICU stay, Poisson regression revealed length of stay decreased by 19.4% when clearance decreased by 100%, (C.I.=6.7-30.4%).

SUMMARY AND CONCLUSIONS

We began this investigation with the intent of uncovering whether lactate clearance maintained its prognostic utility later in the course of resuscitative therapy for SIRS, sepsis, severe sepsis, and septic shock patients. Through logistical regression we showed, even after controlling for clinical severity, lactate clearance values measured after 24 hours are predictive of mortality, length of ICU stay, (to a small extent), need for vasopressors and need for intravenous bolus fluid resuscitation. Based on our study, clinical studies investigating the efficacy of post 24 hour lactate clearance measurements as a therapeutic guide seem warranted.

LIST ANY ABSTRACTS OR PUBLICATIONS THAT MAY ARISE FROM THIS WORK:

An Abstract has been submitted for the DoM Celebration of Research Conference at The University of Florida College of Medicine
We anticipate submitting our work for publication.

REFERENCES:

Brown SD, Clark C, Gutierrez G. Pulmonary lactate release in patients with sepsis and the adult respiratory distress syndrome. (March 1996) *J Crit Care*. 11(1):2-8.
Retrieved from:
<http://www.ncbi.nlm.nih.gov/pubmed?cmd=historysearch&querykey=33>

Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM; Surviving Sepsis Campaign Management Guidelines Committee. (June 2004). Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med*, 32(6):1448. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/15090974>

Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL; International Surviving Sepsis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; World Federation of Societies of Intensive and Critical Care Medicine. (January 2008) [Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008](#). *Crit Care Med*. 36(1):296-327. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed?cmd=historysearch&querykey=11>

Friedman, Gilberto. Berlot, Giorgio. Kahn, Robert J.. Vincent, Jean-Louis. (January 1994). COMBINATION OF BLOOD LACTATE LEVELS AND pHi IN SEVERE SEPSIS. *Critical Care Medicine: Volume 22 - Issue 1 - ppg A113*. Retrieved from: http://journals.lww.com/ccmjournals/Citation/1994/01000/COMBINATION_OF_BLOOD_LACTATE_LEVELS_AND_pHi_IN.211.aspx

H Bryant Nguyen¹, Win Sen Kuan, Michael Batech, Pinak Shrikhande, Malcolm Mahadevan, Chih-Huang Li, Sumit Ray, Anna Dengel and the ATLAS (Asia Network to Regulate Sepsis care).(9/27/2011). Outcome effectiveness of the severe sepsis resuscitation bundle with addition of lactate clearance as a bundle item: a multi-national evaluation. *Critical Care*, 15(5). Retrieved from: <http://ccforum.com/content/15/5/R229>

James JH, Luchette FA, McCarter FD, Fischer JE. (August 7, 1999). Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. *Lancet*. 354(9177):505-8. Review. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/10465191>

Jan Bakker, Maarten WN Nijsten, and Tim C Jansen. (May 10, 2013). Clinical use of lactate monitoring in critically ill patients. *Ann Intensive Care*. 3: 12. Retrieved from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3654944/>

Jansen TC, van Bommel J, Schoonderbeek FJ, Sleswijk Visser SJ, van der Klooster JM, Lima AP, Willemsen SP, Bakker J; LACTATE study group. (September 15, 2010) Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. *Am J Respir Crit Care Med*. 182(6):752-61. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed?cmd=historysearch&querykey=19>

- Jesse D. Bolton. (March 2007). Clinical use of lactate testing in shock states. *Seminars in Anesthesia, Perioperative Medicine and Pain. Volume 26, Issue 1.* Retrieved from: <http://www.sciencedirect.com/science/article/pii/S0277032607000074>
- Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA; Emergency Medicine Shock Research Network (EMShockNet) Investigators. (February 24, 2010) [Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial.](#) *JAMA.* 303(8):739-46. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed?cmd=historysearch&querykey=17>
- Jones AE. (December 2011). Point: should lactate clearance be substituted for central venous oxygen saturation as goals of early severe sepsis and septic shock therapy? Yes. *Chest.* 140(6):1406-8. Retrieved from: <http://www.ncbi.nlm.nih.gov/sites/myncbi/collections/bibliography/42864605/>
- Krishna U, Joshi SP, Modh M. (2009 Apr-Jun;13) An evaluation of serial blood lactate measurement as an early predictor of shock and its outcome in patients of trauma or sepsis. *Indian J Crit Care Med.* (2):66-73. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed?cmd=historysearch&querykey=21>
- Levrant J, Ciebiera JP, Chave S, Rabary O, Jambou P, Carles M, Grimaud D. (April 1998). Mild hyperlactatemia in stable septic patients is due to impaired lactate clearance rather than overproduction. *Am J Respir Crit Care Med.* 157(4 Pt 1):1021-6. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed?cmd=historysearch&querykey=35>
- Manikis P, Jankowski S, Zhang H, Kahn RJ, Vincent JL. (1995) Correlation of serial blood lactate levels to organ failure and mortality after trauma. *Am J Emerg Med.* 13:619–622. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/7575797>
- McNelis J, Marini CP, Jurkiewicz A, Szomstein S, Simms HH, Ritter G, Nathan IM. (2001). Prolonged lactate clearance is associated with increased mortality in the surgical intensive care unit. *The American Journal of Surgery.* 182:481–485. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/11754855>