Title: RESEARCH TITLE

Investigators: INSERT NAMES HERE

Question: Do elevated BMI individuals display altered lactate metabolism in the setting of culture-positive bacterial sepsis?

Hypothesis: Patients with elevated BMI's and bacterial sepsis may have different initial lactate levels when compared to non-elevated BMI patients with bacterial sepsis. Patients with elevated BMIs have higher lactate levels both in resting non-infected states and upon ED presentation in the setting of bacterial sepsis, reflecting differences in basal systemic metabolism and inflammatory response. Current sepsis guidelines use an initial lactate level >2 mmol/L as organ dysfunction criteria regardless of BMI. It is unknown if this initial lactate threshold of 2 mmol/L is equally applicable to patients with elevated BMIs.

Study rationale: The primary goal of this study is to determine if current lactate thresholds can be utilized to diagnose and prognosticate on severity of sepsis regardless of patient BMI or if new thresholds are required. As a secondary aim, we seek to determine if lactate clearance and mortality rates with resuscitation based on CMS-approved sepsis guidelines (SEP-1) vary between elevated BMI patients and non-elevated BMI patients. This work will specifically focus on patients who present to the ED with bacterial sepsis, a common problem seen in ED's across the United States that causes significant morbidity and mortality for patients and financial burden for the healthcare system as a whole. Given the high incidence of sepsis as well as the growing proportion of individuals with elevated BMIs in the country, the results of this study will have important implications for ED medical management. In general, individuals with elevated BMIs have decreased quality of life and poor outcomes in the healthcare setting given the high incidence of co-morbid diseases, general metabolic dysfunction and higher levels of baseline inflammation. Individuals with elevated BMIs have significantly increased mortality in the setting of viral sepsis but have also been shown in some studies to have decreased mortality in the setting of bacterial sepsis, a well known "paradox" that needs further exploration. Given this controversy in the field, it is important to determine if the same values of prognostic biomarkers can be used to determine disease severity between elevated and non-elevated BMI individuals.

Lactate levels are often used to identify septic patients and dictate sepsis management in addition to other SIRS criteria such as white blood cell count, respiratory rate, heart rate and temperature. Lactate is a metabolic end-product that is generated from pyruvate metabolism. In general, hyperlactatemia is either due to a Type A (hypoxic) or Type B (aerobic glycolytic) mechanism. Currently, our tools do not easily allow for us to determine the contribution of each of these mechanisms, yet lactate continues to be an important biomarker used in sepsis recognition and resuscitation. For example, a lactate greater than or equal to 2 in patients meeting at least 2 SIRS criteria indicates severe sepsis while a lactate greater than or equal to 4 may suggest septic shock, according to current SEP-1 guidelines. However, these threshold values are not universally agreed upon and other studies have suggested different values that correlate better with measures such as 30 day mortality. The CMS SEP-1 bundle guidelines also recommend standardized interventions such as 30 ml/kg of fluids (if BMI >30 then 30ml/kg of ideal body weight) for hypotensive patients or lactate ≥4 mmol/L who meet sepsis criteria to reduce mortality, but studies have not conclusively determined if elevated BMI patients have similar outcomes to non-elevated BMI patients with these interventions. Based on the existing deficits in the field of sepsis and obesity research, further exploration of the interaction between BMI and lactate levels and lactate clearance in the setting of sepsis may provide new, patient-specific guidelines. In addition, this work will open up the door for further mechanistic study of the pathophysiology of sepsis in elevated BMI individuals, specifically the interaction of intracellular and systemic metabolism with inflammation.

Background information: Sepsis is a major public health burden, affecting nearly 1.7 million Americans each year and leading to significant morbidity and mortality(1). Sepsis can be broadly defined as a state of systemic dysfunction in the setting of pathogenic infection that can lead to organ failure and death. Sepsis according to SEP-3 is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection(2). According to CMS SEP-2 definitions, there are several criteria that need to be met for a diagnosis of sepsis to be made, which can be further classified by severity into sepsis, severe sepsis and septic shock. The CMS accepted SEP-1 guidelines are the most widely accepted guidelines used for sepsis identification and management, though there is controversy regarding their utility and efficacy. CMS SEP-2 sepsis is defined as meeting at least 2 SIRS criteria along with a known or suspected infection while severe sepsis further includes evidence of organ dysfunction. Finally, septic shock, which is associated with the highest mortality, consists of the criteria for severe sepsis as well as a lactate level of at least 4 mmol/L or persistent hypotension despite fluid resuscitation.

Bacterial sepsis composes the majority of sepsis, characterized by positive blood cultures and strong inflammatory responses that often lead to hypotension, decreased organ perfusion and ultimately death. Other causes of sepsis include viral and fungal sepsis, which can display significantly different pathophysiology. Many septic patients initially present to the emergency department (ED), where early intervention can significantly alter patient outcomes, highlighting the need for highly sensitive and specific septic markers. The current mainstay of treatment involves antibiotic initiation, fluid resuscitation and pressure support as needed, with serial lactate measurements utilized to determine efficacy of resuscitation. Data suggests that delay of antibiotic initiation can lead to increased mortality of 2-7% per hour that antibiotics are not administered [3, 4]. Given the importance of timely intervention, hospitals often institute alert systems to identify providers of potential septic patients. Barnes-Jewish Hospital uses one such "critical illness alert" system, which identifies patients who meet at least 2 SIRS criteria and one sign of CMS organ dysfunction, to improve the time to intervention. The current lactate thresholds set by CMS-accepted guidelines to define severe sepsis (>2 mmol/L) and septic shock (≥4 mmol/L) may not apply to all patients, especially those with elevated BMIs or metabolic dysfunction.

Individuals with elevated BMIs compose a significant portion of the United States population and have poorer health outcomes compared to non-elevated BMI individuals in the setting of a spectrum of disease states. Obesity and obesity related diseases such as diabetes and cardiovascular disease reduce both lifespan and health span of individuals. However, at the intersection of obesity and sepsis, there exists an interesting "paradox". Obese and overweight individuals have been shown in several observational studies to have decreased mortality in the setting of bacterial sepsis(5, 6), though these patients are also more prone to infection and illness. Many hypotheses have been posited regarding the possible improved survival of obese patients in the setting of bacterial sepsis. Some of these include increased energy reserves, altered adipokine and cytokine signaling, differences in immune cell function and more. It is apparent that deeper understanding the pathophysiology of altered sepsis physiology in obese individuals can provide novel mechanistic insight, improved therapeutics and more accurate biomarkers.

Lactate is one of the primary biomarkers utilized in the treatment of sepsis, especially when following current sepsis management guidelines. Elevated lactate is often used as a surrogate for sepsis severity and resuscitation is regularly targeted towards a reduction in lactate, a measurement known as lactate clearance. It has been displayed repeatedly that hyperlactatemia is positively correlated with mortality in sepsis, suggesting that the factors that lead to generation of lactate may be correlated with disease pathophysiology. A 6 hour target lactate <3.5 and lactate clearance of >25% has been shown to be a viable resuscitation target in a recent 2021 clinical study with a reduction in 30 day mortality(7). However, the primary issue with utilizing lactate as a marker of disease severity and resuscitation success is that lactate is a "dirty" biomarker that can be generated from many sources in response to a variety of stressors.

Lactate is a product of glycolytic metabolism in which glucose is converted to pyruvate and then ultimately converted to lactate by the enzyme lactate dehydrogenase (LDH). This process is an inefficient method of energy production but is critical for cell survival during anaerobic conditions, and often takes place in the setting of reduced mitochondrial electron transport chain function. In these states, mitochondria cannot perform oxidative phosphorylation to generate ATP and there is a buildup of reduced electron transporters such as NADH, requiring lactate production to regenerate oxidized NAD+ and small amounts of ATP. Type A hyperlactatemia, caused by tissue hypoxia, can be treated effectively with improved oxygenation, fluid resuscitation and vasopressor support to improve oxygen delivery. However, lactate can also be elevated due to increased aerobic glycolysis, known as Type B hyperlactatemia, in which cells generate lactate even when oxygen is present for mitochondrial function. This is an adaptive response seen in many cell types during inflammatory states or in response to signaling mediators such as catecholamines or beta-agonists, as has been published by various groups. Furthermore, there is evidence that this metabolic shift leads to further inflammation, generating a vicious cycle in which inflammation and altered metabolism drive each other forward such as that seen with cytokine storm phenomena. This hyperlactatemia likely cannot be fixed directly with fluid resuscitation or oxygen delivery but instead requires antibiotics and therapeutics aimed at metabolic re-programming or anti-inflammatory management to intervene on pathologic inflammation. A greater understanding of lactate as a sepsis marker is required for patients with elevated BMIs, in addition to the development of novel biomarkers for augmenting sepsis diagnosis.

This study will address several deficits that exist in the field of obesity and sepsis research. Several studies have displayed that obese individuals may have elevated levels of circulating lactate at rest and in response to exercise, suggesting altered intracellular metabolism at baseline. However, it is unknown if this trend holds true in the setting of bacterial infection and sepsis. This work will contribute to the understanding of lactate utility in the workup and management of elevated BMI septic patients. In addition, it is unclear if current SEP-1 management guidelines are equally effective for elevated BMI patients compared to non-elevated BMI patients. This work will aim to answer these questions and lay the foundation for future work exploring the mechanism of septic progression in the setting of elevated BMI and metabolic dysfunction.

Methods:

Study design: A retrospective observational cohort study using electronic medical records of Barnes-Jewish Hospital (BJH) ED patients will be performed. This study will utilize existing patient records to identify outcomes and interventions, maintaining patient confidentiality by removing personal identifiers.
Study location: BJH is a quaternary center, teaching hospital and level 1 trauma center located in the city of St. Louis, Missouri. BJH is home to a high volume ED that sees approximately 90,000 patients annually, with a large Midwest catchment area. Importantly, BJH ED sees a significant proportion of overweight and obese individuals, with a recent report displaying that 61% of St. Louis city residents over the age of 16 are overweight or obese. Similarly, these individuals compose a significant proportion of ED visitors. The BJH ED also sees a significant volume of septic patients, with around 600 patients per year meeting CMS criteria for severe sepsis and septic shock. At the BJH ED, patients are flagged by an EMR Critical Illness Alert (CIA) as possibly septic based on meeting at least 2 SIRS criteria, as well as one sign of CMS organ dysfunction. If the provider confirms or suspects infection, the subsequent standard of care is to follow CMS SEP-1 bundle guidelines, which includes blood cultures, antibiotics, initial and repeat lactate levels, fluid and/or vasopressor resuscitation as indicated, and identification of possible sources through imaging and diagnostic modalities. Suspected septic patients are treated with broad spectrum antibiotics and fluid resuscitation is initiated at 30 ml/kg/hr in the setting of hypotension or lactate ≥4 mmol/L, unless contraindicated due to coexisting conditions. A CMS-bundle compliant order set is available and CMS-compliance is measured amongst physicians. Beyond the ED, BJH has ICU and inpatient levels of care, as well as extensive consulting services, such that patient diagnostics, interventions and outcomes over the course of admission from the ED can be accessed from EMR. **Outcomes**: The primary outcome is determining the sensitivity of lactate as a measure of sepsis-mediated mortality in elevated BMI vs non-elevated BMI patients. This will be determined by AUC analysis comparing initial lactate vs 30 day mortality between the two groups. There are several secondary outcomes that will be measured: correlation of initial lactate vs patient BMI between sepsis, severe sepsis and septic shock as determined by linear regression, and impact of CMS SEP-1 compliance on morality and lactate clearance in septic patients with elevated and non-elevated BMI's. Demographics will be compared to identify potential confounders and ensure matching of groups.
Data collection and inclusion/exclusion criteria: The Epic EMR system utilized at BJH and its partner hospitals will be interrogated to identify patients with sepsis, severe sepsis or septic shock (based on pre-determined SNOMED clinical terms utilized by Epic), as well as uncontaminated bacteria positive blood cultures. The diagnosis of sepsis, severe sepsis or septic shock will be provider-dependent and can occur

at any point along the hospital admission within 7 days of ED presentation. After query, records will be reviewed manually to verify query results. Variables to be collected from each patient chart are identified prior to the start of data collection to ensure uniformity. These variables include age, gender, race, BMI at ED presentation, presence of co-morbid diseases identified in "past medical history", initial lactate level, repeat lactate measure, time to repeat lactate, and blood culture results. Intervention measures will also be recorded from each chart including SEP-1 bundle compliant resuscitation, use of 30 mL/kg fluid resuscitation, time to antibiotic initiation, and need for vasopressors. Mortality data will be collected and will be defined as survival to discharge prior to 30 days or survival to 30 days from ED presentation if patient remains in the hospital. For studying the impact of CMS-compliance on patient outcomes, a subset of charts will be utilized. SEP-1 bundle compliance is measured at Barnes-Jewish Hospital and compliant patient charts are identified and available for data analysis of CMS-compliant vs non-compliant patient outcomes. Compliance with SEP-1 guidelines in this group will be verified by manual chart review. These patient charts will be utilized to determine if CMS-compliance has different efficacy on 30 day-mortality based on BMI sub-groups. BMI sub-groups will be defined based on existing WHO criteria, with BMI defined as the weight in kilograms divided by the square of height. These groups include healthy weight (18-25), overweight (25-30) and obese (>30). For analysis of elevated BMI vs non-elevated BMI groups, we will compare those with BMI >30 with those who have BMI <30 (but greater than 18) in order to simplify data analysis. In addition, SEP-1 bundle compliance requires repeat lactate measurement for patients who have an initial elevated lactate. This can be utilized to measure lactate clearance with SEP-1 compliance amongst BMI groups.

There will be stringent inclusion and exclusion criteria utilized to isolate the effect of BMI on sepsis and reduce effects of confounding factors on lactate levels and outcomes. Bacterial blood culture negative patients will be excluded to avoid grouping bacterial and viral sepsis patients, as well as those who meet SIRS criteria due to non-septic causes. Further exclusion criteria include factors that have been displayed in literature to elevate or reduce lactate levels in patients. Patients will be excluded if they have a history of hepatic failure (defined as active cirrhosis or hepatic failure), renal dysfunction (CKD stage 3 or greater), active cancer diagnosis, current alcohol abuse, thiamine deficiency or malnutrition, active diabetic ketoacidosis, seizure prior to presentation, cardiac arrest prior to presentation, active metformin use, active anti-retroviral use, active valproic acid use, oxygen saturation <94% in the one hour before lactate measurement, active beta-agonist or beta-blocker use, active vasopressor use, ejection fraction (EF) in past 6 months < 35%, and hemoglobin <7. When measuring repeat lactate levels to identify lactate clearance over time, patients that meet exclusion criteria in the interim period will be excluded from analysis of lactate clearance. Furthermore, repeat lactate will only be included in the analysis if measured within 6 hours of initial lactate after initiation of resuscitation. Presence of metabolic disease is not an exclusion factor as this is highly common amongst obese individuals and a likely part of the mechanism. Future work will determine the role of metabolic disease in lactate metabolism. Identifying patient information including names, DOB and medical registration number will be excluded after data extraction to protect patient confidentiality. Most data will be collected through electronic querying, though some will require manual chart review for extraction.

Statistical analysis: Statistical analysis will be performed using IBM SPSS software and R software. The patient demographics and characteristics will be represented as mean +/- standard deviation. The distribution of data and normality will be determined by histograms. For skewed characteristics, median value + IQR will be utilized instead of mean. Characteristics of elevated and non-elevated BMI patients who present with either sepsis, severe sepsis or septic shock will be compared by unpaired T-test or chi-square tests for quantitative vs qualitative values, respectively. To determine the sensitivity of lactate as a measure of sepsis severity and mortality outcomes between elevated BMI (>30) and non-elevated BMI (18<BMI<30) groups, ROC curves will be generated by graphing initial lactate vs 30-day mortality for patients at or above that lactate threshold. The AUC will then be compared between the two groups to identify sensitivity of lactate as well as to identify differences in lactate thresholds. For determining differences in initial lactate relative to BMI, patients will be analyzed separately based on if they present with sepsis, severe sepsis or septic shock. Linear regression analysis will be performed in each group comparing BMI to initial lactate to identify regression co-efficient for each group to identify if relationship exists between lactate and BMI. ANCOVA will be utilized to compare regression coefficients for patients presenting with sepsis, severe sepsis or septic shock in elevated or non-elevated BMI groups.

To determine the efficacy of CMS-bundle compliance for different weight groups in the setting of sepsis, rate of lactate clearance will be calculated for each CMS-compliant patient utilizing the formula ((initial lactate) - (repeat lactate))/(initial lactate)*(time between lactate measurement). CMS bundle requires repeat lactate, which has to be performed within 6 hours of initial lactate if >2 mmol/L. Quantitative lactate clearance will be compared to BMI within sepsis, severe sepsis and septic shock groups utilizing linear regression. ANCOVA will be utilized to compare regression coefficients for patients presenting with sepsis, severe sepsis or septic shock. 30 day-mortality will be compared between groups by sub-grouping patients by BMI into healthy weight (BMI 18-25), overweight (BMI 25-30) and obese (BMI>30) groups. Mortality measures will be compared by ANOVA if normally distributed or Kruskall Wallis if skewed.

The number of patients needed in the study will be determined based on assumed differences in outcomes. The number of patients required for the primary outcome in the study will be 1000, assuming a difference of 0.5 in lactate levels upon presentation with a power of 0.8 and beta of 0.95. This assumption is based on prior literature displaying that obese individuals at baseline can have increased lactate levels up to 20% higher. For determining the impact of CMS-bundle compliance on mortality between elevated and non-elevated BMI individuals, we will assume an absolute mortality difference of 5% to be significant. This will require 2000 patients to be statistically powered with a power of 0.8 and beta of 0.95. Post-hoc power analysis will be performed to confirm that appropriate initial assumptions were made, though this will be clearly stated if it is found that initial power was insufficient.

Budget: The estimated budget per year for this study will be $X,XXX. This money will be utilized for the purchase of statistical analysis software SPSS at a rate of $XXX per annum, as well as use of Emergency Care Research Core IT service to assist with EMR querying and data extraction given scope of project. The hourly rate is $XXX/hour with an estimated XX hours of usage required given the scope of the project. This was determined in assistance with XXXXXXX.

Summary of project: Overall, this project aims to determine if lactate serves as an appropriate marker of disease severity and resuscitation goal in ED septic patients with elevated BMIs. We will utilize existing patients charts to determine if lactate levels can tell us the severity of disease in elevated BMI patients with sepsis as well as if lactate levels can be used to tell us if patients are responding well to treatment. We predict this project will be completed within one year of grant submission.

Bibliography

1. Rhee C, Jones TM, Hamad Y, Pande A, Varon J, O'Brien C, et al. Prevalence, Underlying Causes, and Preventability of Sepsis-Associated Mortality in US Acute Care Hospitals. JAMA Netw Open. 2019;2(2):e187571.
2. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-10.
3. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34(6):1589-96.
4. Liu VX, Fielding-Singh V, Greene JD, Baker JM, Iwashyna TJ, Bhattacharya J, et al. The Timing of Early Antibiotics and Hospital Mortality in Sepsis. Am J Respir Crit Care Med. 2017;196(7):856-63.
5. Trivedi V, Bavishi C, Jean R. Impact of obesity on sepsis mortality: A systematic review. J Crit Care. 2015;30(3):518-24.
6. Robinson J, Swift-Scanlan T, Salyer J. Obesity and 1-Year Mortality in Adults After Sepsis: A Systematic Review. Biol Res Nurs. 2020;22(1):103-13.
7. Lee SG, Song J, Park DW, Moon S, Cho HJ, Kim JY, et al. Prognostic value of lactate levels and lactate clearance in sepsis and septic shock with initial hyperlactatemia: A retrospective cohort study according to the Sepsis-3 definitions. Medicine (Baltimore). 2021;100(7):e24835.