Early Metabolic Resuscitation: A Potential Solution to Multi-Organ Dysfunction Syndrome in Septic Shock

Protocol Number: 2018-0986

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SUMMARY TABLE

Title	*Early Metabolic Resuscitation: A Potential Solution to Multi-Organ Dysfunction Syndrome in Septic Shock*
Question	Is Early Metabolic Resuscitation the Solution to Multi-Organ Dysfunction Syndrome in Patients Diagnosed with Septic Shock?
Protocol Number	2018-0986
Study Size (# of patients)	The sample size will include 112 patients (56 patients randomly assigned to each study group).
Study Design	This is a prospective, single center, un-blinded, randomized controlled trial. Patients will be stratified by type of malignancy, and blocking will be used to ensure balance between study groups. Patients will be randomized to either Early Metabolic Resuscitation with Standard of Care (SC + EMR) or Standard of Care alone (SC). The randomization will be conducted through CORe.
Primary Objective	The primary objective of this study is to assess the efficacy of administering Early Metabolic Resuscitation with Standard of Care (SC + EMR) in patients diagnosed with septic shock for reducing 28-day mortality versus using the Standard of Care alone (SC).
Secondary Objective	1. To assess whether Early Metabolic Resuscitation with standard of care (SC + EMR) is an effective strategy to reduce ICU mortality, hospital mortality, and 90-day mortality relative to SC. ICU mortality is defined as mortality at ICU discharge. 2. To compare the time to death from any cause between patients administered SC + EMR versus SC after being diagnosed with septic shock. 3. To assess whether SC + EMR is an effective strategy to reduce complications of septic shock such as: i) acute kidney injury, ii) dialysis requirements, iii) need for cardiovascular support or days on vasopressors, iv) need for invasive ventilation, days on ventilator support, v) duration of ICU stay, and vi) duration of hospital stay versus SC.

	4. To describe the presence of any adverse effects between the two study groups (SC + EMR group vs SC group); thus, characterizing their safety.
Inclusion Criteria	1. Adult patients aged 18 years old or older 2. Admitted to the adult medical intensive care unit (MICU) 3. Diagnosis of Septic Shock within 12 hours of ICU admission, unless the patient is already admitted to the ICU, defined as meeting criteria for sepsis in addition to the following: a. Vasopressor therapy needed to elevate MAP ≥65 mmHg. o Lactate > 1 mmol/L (9 mg/dL) and/or Base excess <-2 after adequate fluid resuscitation 4. Sequential Organ Failure Assessment (SOFA) score meeting the following requirements a. Cardiovascular SOFA ≥ 2 b. Total SOFA score ≤12 5. Patients meeting the above and not able to tolerate enteral nutrition above 70% of their estimated daily caloric need
Study Details	
Primary Endpoint	The primary endpoint is 28-day mortality, defined during the time from the day SC+EMR or SC was first administered until a patient dies or is followed through 28 days (whichever comes first).
Sample Size Justification	The rate of 28 day mortality from septic shock at the UT MD Anderson Cancer Center was 70% in 2017. With the objective of decreasing this rate to 40%, a sample size of 112 patients (56 per group) provides 90% power to detect a 30% absolute reduction in the rate of 28-day mortality using a two-sided chi-square test at the 0.05 significance level. We plan to use stratified randomization in a 1:1 fashion to assign patients into two groups, and a fixed block size consisting of 4

	patients will be used. The randomization will be conducted in CORe.
Brief Analysis Plan	Descriptive statistics including the mean, standard deviation, median, and range will be used to summarize continuous variables. Frequency counts and percentages will be used to summarize categorical variables. Categorical variables, including 28-day mortality, will be compared between intervention groups using a chi-square test, or Fisher's exact tests if more appropriate. Continuous variables will be compared between intervention groups using an independent samples t-test, or Wilcoxon rank-sum test if more appropriate. Logistic regression will be used to assess relationships between patient characteristics and binary study outcomes of interest. Continuous variables, including the time on cardiovascular support and time on ventilator, will be compared using t-tests or Wilcoxon rank-sum tests. Time to event analyses will be conducted using Cox proportional hazards regression. For 28-day mortality, living patients will be censored at the end of 28 day follow-up after the treatment was given. For overall survival, patients will be followed until time of death or date of last follow-up (maximum 6 months). Kaplan-Meier plots will be used to visually compare time to death from any cause between intervention arms followed by a log-rank test to compare survival distributions.

1.0 STUDY OBJECTIVES

1.1 Primary Objective:

To assess the efficacy of administering Early Metabolic Resuscitation with Standard of Care (SC + EMR) in patients diagnosed with septic shock for reducing 28-day mortality versus using the Standard of Care alone (SC). Twenty-eight day mortality is defined during the time from the day SC+EMR or SC was first administered until a patient dies or is followed through 28 days (whichever comes first).

1.2 Secondary Objectives:

1. To assess whether Early Metabolic Resuscitation with standard of care (SC + EMR) is an effective strategy to reduce ICU mortality, hospital mortality, and 90-day mortality of septic shock patients relative to SC. ICU mortality is defined as mortality at ICU discharge relative to SC.

2. To compare the time to death from any cause between patients administered SC + EMR versus SC after being diagnosed with septic shock.

3. To assess whether SC + EMR is an effective strategy to reduce complications of septic shock such as: i) acute kidney injury, ii) dialysis requirements, iii) need for cardiovascular support or days on vasopressors, iv) need for invasive ventilation, days on ventilator support, v) duration of ICU stay, and vi) duration of hospital stay versus SC.

4. To describe the presence of any adverse effects between the two study groups (SC + EMR group vs SC group); thus, characterizing their safety.

2.0 BACKGROUND

2.1 Definitions

Sepsis is defined as a life-threatening condition, which is triggered by an exaggerated and unregulated response of the body to an infection. Septic shock consists of the state of sepsis where, in addition to the unregulated response, cellular, metabolic, and circulatory alterations lead to a marked increase in mortality(1). Previously the spectrum of the disease was divided into sepsis, severe sepsis and septic shock, where severe sepsis was defined as acute organ dysfunction secondary to documented or suspected infection(2). However, in the third international consensus for sepsis and septic shock (Sepsis -3) it was determined that the term severe sepsis was redundant and therefore it was decided only to use the diagnoses of sepsis and septic shock(1). Even so, today most retrospective epidemiological studies continue to use the term severe sepsis in their analysis, but this is expected to change over time.

2.2 Epidemiology

Worldwide, 19 million cases of sepsis are calculated each year, however, it is presumed that this value may be even higher due to under reporting, which is considered high in low- and middle-income countries (3,4). According to the report of the Center for Disease Control and Prevention (CDC) of 2017, sepsis annually affects 1.5 million individuals in the United States, of whom 250,000 die (5), which includes it among the top 10 causes of death in the US. This generates annual costs of over 24 billion dollars(6); which makes this condition a public health priority.

In a recent study not yet published performed by Nates et al. in 2017, a sample of 305 patients (154 with hematologic malignancies and 108 with solid tumors) with the diagnosis of septic shock hospitalized in the ICU of The University of Texas MD Anderson Cancer Center were assessed. It was found that the 28 day mortality was 70%. These values shed light on the emergent requirement of seeking treatment alternatives that may improve outcomes in these patients.

2.3 Pathophysiology

The normal response of the host to an infection is a complex process in which a microorganism is localized and controlled, while injured tissue repair processes are undergoing. When the inflammatory response is activated, proinflammatory mediators (tumor necrosis factor-alpha (TNFa), IL-1, IL-2, IL-6, among others) chemokines such as ICAM-1 and VCAM-1, and nitric oxide (NO) are released. The proinflammatory cytokines generate the activation and recruitment of cells of the immune system. Also the production of anti-inflammatory mediators such as IL-10 and IL-8 modulate the response and lead to homeostasis (8). Sepsis results when the response becomes generalized and uncontrolled, affecting normal tissue distant from the original site of infection. The mechanisms that lead to the unregulated response are not well known, however several studies have shown how the components of the causative organism may be involved in the way in which the immune system is stimulated (endotoxins, peptidoglycans, muramil dipeptidase and lipoteichoic acid, among others) (9,10). Likewise, studies have pointed out the possibility that there is a genetic susceptibility for the development of more severe responses, and worse outcomes (11).

The release of proinflammatory cytokines causes fever, hypotension, leukocytosis and the induction of other cytokines. In addition, there is an activation of the coagulation cascade and fibrinolysis. TNFa plays a key role in the disease and some studies have shown a significant increase in patients with septic shock (12). Nitric oxide is a biological molecule produced by a large number of cells. It is involved in several pathological processes and has been described as having both beneficial and harmful effects at the cellular and vascular level (13). At the cellular level NO generates nuclear damage, alterations of proteins and phospholipid membranes, and the inhibition of cellular respiration in several cell types. At the same time, it has been shown that NO can also reduce free oxygen radicals, generating a decrease in cell damage. Therefore its total inhibition as a therapeutic measure does not seem to be an adequate intervention and in fact it has been proven in clinical studies that the use of inhibitors of nitric oxide synthase (NOS) can increase mortality(14).

In the early septic phase, cellular metabolism is upregulated with systemic inflammation which leads the organism to enter into a hypermetabolic state (15). This is mainly caused by the requirement of supra physiological energy to deal with fever, amplified protein synthesis, tachycardia and tachypnea(16). It is estimated that basal energy requirements for a septic patient could reach up to 10,000 calories per day (17). This critical need for supplemental nutrients may not be met since it occurs under critical illness (thermodynamically closed system in which metabolic substrates are not administered to the patient) (16). This hypermetabolism also produces a large amount of toxic cellular by-products, such as hydrogen peroxide (H2O2), which under normal conditions, is well degraded by the enzyme glutathione peroxidase. In critically Ill patients, glutathione is commonly depleted and there is a significant increase in H2O2, cellular toxicity occurs, and a greater decrease in glutathione stores can be observed (18,19). In fact, low levels of glutathione have been indirectly related to increased mortality even after the subject survived the infectious insult(20).

After the above-mentioned process has been established, inflammatory products, such as nitric oxide and the reactive nitrogen species, can cause mitochondrial dysfunction due to the inhibition of the electron transport chain by direct blocking of respiratory enzymatic complexes, causing oxidative stress damage, and promoting mitochondrial DNA breakdown. All of these processes lead to a decrease in mitochondrial function in terms of the use and production of ATP, which triggers cytotoxicity and hypometabolism in the late phase of the disease. This has been described as a hibernation-like state where the organs reduce their metabolism in an attempt to survive the inflammation caused by sepsis (21).

The clinical relevance of mitochondrial dysfunction in septic shock has been studied extensively. In a study of 28 septic shock patients who underwent a skeletal muscle biopsy at 24 hours after ICU admission, the ATP concentrations in the muscle (a marker of mitochondrial oxidative phosphorylation) were significantly lower in the 12 patients who died compared to the 16 who survived. Additionally, there was an association between overproduction of NO, decrease of antioxidants and the severity of the clinical outcome

(22). This led to the conclusion that the cellular lesions were due to dysoxia, which is the inability to use the oxygen even under the presence of adequate concentrations. This is also known as oxygen limited energy depletion. Strikingly, in studies of patients who died from septic shock, both electron microscopy and immunohistochemical markers revealed that cell death was rare in septic patients with cardiac and renal dysfunction. The degree of cell injury or death was not related to the severity of the organ dysfunction. It was then considered that the presence of morphological changes in the mitochondria would explain the energetic crisis that results in organ dysfunction in the absence of cell death (23). This reinforces the theory that this hibernation-like response may initially start as a mechanism of cell survival, but ultimately ends in multi-organ dysfunction and death.

2.4 Clinical features

Sepsis clinical presentation is variable and depend to a great extent on the initial site of the infection, causal agent, colony count, the pattern of organ failure, patient's baseline health status, and the interval before initiation of treatment (3). Acute organ dysfunction most commonly affects the respiratory and cardiovascular systems; the first, usually manifested by tachypnea and acute respiratory distress syndrome and the second by hypotension and acute elevation of serum lactate. Hypotension may become refractory to volume expansion and may require the use of vasopressors and in addition, myocardial dysfunction may also occur (2,3,24). Likewise, the brain and kidneys can be affected; the clinical manifestations of central nervous system involvement may manifest with alterations in the state of consciousness. Neuroimaging generally shows no focal lesions, and the results of electroencephalography are usually consistent with non-focal encephalopathy. Polyneuropathy can also be evidenced in these patients(25). Acute kidney injury usually presents with a decrease in urinary output and an increase in serum creatinine, and these patients may require renal replacement therapies. It is important to highlight that acute kidney injury continues to have between 60% and 80% mortality. It is also important to note that a MAP <75 mmHg is associated with a higher incidence of renal failure(26). Finally, paralytic ileus, hepatic dysfunction, alterations in coagulation and glucose control are frequent in patients with sepsis and septic shock (3,27)

2.5 Diagnosis

Sepsis can be clinically diagnosed with an increase of 2 points in the baseline SOFA score of the patient (Table 1) in the context of an infectious process. Septic shock is the state of sepsis, where cellular, metabolic and circulatory alterations are also present, measured by the elevation of lactate levels above 2 mmol/L and the requirement of vasopressors to maintain a mean arterial pressure (MAP) greater than or equal to 65 mmHg (1). However, severe sepsis can be diagnosed with an increase of lactic acid above > 1 mmol/L (28).

Table 1 SOFA score(29)

SOFA score	**0**	**1**	**2**	**3**	**4**
Respiratory PaO2/FIO2 (mmHg) SaO2/FIO2	>400	<400 221-301	<300 142-220	<200 67-141	<100 <67
Coagulation Platelets $10^3/mm^3$	>150	<150	<100	<50	<20
Liver Bilirubin (mg/dl)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12
Cardiovascular Hypotension	NO	MAP<70	Dopamine <5 or Dobutamine	Dopamine >5 or Norepinephrine <=0.1 Epinephrine <=0.1	Dopamine >15 or Norepinephrine >0.1 Or epinephrine >0.1
Central Nervous System Glasgow Coma Scale	15	13-14	10-12	6-9	<6
Renal Creatinine mg/dl Urinary Output ml/d	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 <500	>5 <200

***SOFA= Sequential Organ Failure Assessment.**

2.6 Treatment

Different therapies have been studied to improve the treatment of sepsis and septic shock. There is no clear evidence that these can change the course of the disease, therefore the current treatment recommendations are based mainly on antibiotic and life support management(30). Due to the implications of the disease, it is necessary to develop new therapeutic interventions, which should be based on the pathophysiology of the disease and on the metabolic and cellular effects that lead to multi-organ failure.

The metabolic approach previously described by different authors is, in our opinion, the next step that should be considered in the management of the patient in septic shock. While this may bring therapeutic benefits and additionally reduce the economic burden of the disease, further investigation is required.

3.0 STUDY RATIONALE

Increasing ATP production before mitochondrial respiration slows down may prevent multi-organ dysfunction in sepsis(21,31). We hypothesize that providing large doses of glucose, protein, and essential metabolic cofactors early in the management of patients with sepsis can prevent this hibernation-like state (31).

The theory substantiating early metabolic resuscitation (EMR) is provided by a number of preliminary studies. In sepsis, there is known to be near universal dysfunction in mitochondria resulting in inefficient utilization of energy. This happens because the biochemical pathways of oxidative phosphorylation are inhibited in cells of septic patients (21,31,32). Complex I of the electron transport chain exists in both red blood cells and muscle tissue and the inhibition of the transport chain results in inefficient utilization of energy stores(32), which are often already deficient in critically ill patients(31,33,34).

Supporting our hypothesis regarding EMR involves the use of GIK (Glucose, Insulin and Potassium) therapy. This therapy has been studied extensively in the cardiac population, and has been of particular interest in cardiac surgery reviving stunned myocardium, although evidence remains limited. The theory is similar to the use of amino acids whereby substrates replenish the Krebs cycle (via anaplerosis). The recent IMMEDIATE trial in acute myocardial infarction patients showed no difference in 30 day mortality, but a reduction in hospital mortality and incidence of cardiac arrest(35).

Several case reports in septic shock patients have supported the use of GIK infusions, particularly in patients with low output shock where insulin-glucose infusions have led to improved hemodynamic parameters in cases unresponsive to inotropes (36–38). There remains a lack of well-designed large RCTs to support this intervention, although in a controlled environment such as an ICU, this does not represent a significant risk. In our protocol, we will be using some of the principles of GIK therapy to improve perfusion and oxygen metabolism to prevent organ dysfunction. This will be achieved through the use

of early infusion of glucose and a solution of free amino acids with additional essential metabolic cofactors and insulin.

Further evidence to support our hypothesis draws upon research done at Cambridge University. Nitric oxide (NO) and reactive nitrogen species inhibit mitochondrial complexes responsible for the production of ATP (39). Sepsis is a clinical situation where overproduction of reactive nitrogen species has been implicated in its pathophysiology (21). In this situation, glucose becomes critical to cell survival via glycolytic production of ATP at a time when mitochondrial production of ATP has been inhibited(39). Patients with septic shock demonstrated a strong association between decreased mitochondrial function, specifically loss of ATP synthase activity in peripheral blood mononuclear cells, and increased mortality (50, 51).

Differences with Total Parenteral Nutrition

To avoid any confusion, we must address the distinct nature of our approach from that of early total parenteral nutrition (TPN) in the ICU, given that this last intervention has caused great controversies(41). The EMR described in this protocol might be considered on a superficial level to be similar to early parenteral nutrition, given that both interventions share most of their components. Early metabolic resuscitation is distinct from early TPN for several reasons:

- Firstly, the acuity in time of EMR is much greater. This is an intervention that has to be started as soon as possible after the patient presents the first signs of septic shock and is considered to be in a hypermetabolic state. This contrasts to early TPN, which is often administered only within the first 48 hours and has the objective of supplying nutritional requirements (42).
- Secondly, the nutrients within EMR are specifically intended to best support cellular respiration in sepsis. For example, glucose is considered to be an essential substrate as in the absence of glucose, moderate levels of NO are known to cause necrosis simply by respiratory inhibition. Adequate levels of glucose are known to

prevent necrosis in vitro (39). Typical TPN solutions do not provide large quantities of glucose.

- Thirdly, in the EMR protocol, we are not using lipids, which are a common component of TPN. The rationale of the exclusion of this component is due to the fact that studies have shown an increase in lung injury due to the administration of lipids. In the initial phase of septic shock, it is well known that tissues become hypoxic, preventing adequate beta-oxidation of fatty acids. We consider that the inclusion of lipids may cause more risk than benefit in the early phase of septic shock.
- The use of carbohydrates in hypoxic states is based on the Pasteur Effect which states that the consumption of carbohydrates is inversely proportional to the availability of oxygen.
- Glucose provides a P/O ratio (number of molecules of ATP synthesized by each pair of electrons travelling down the electron transport chain) of 3, as opposed to a P/O ratio of 2 provided by lipids.

As mentioned before, timing is crucial. Studies in animal models suggest that mitochondrial respiration may be initially increased and eventually declines after a prolonged (>12-16 hours) septic insult(43). Of note, these animal models are typically performed in rodents (specifically rats) in whom, according to P Hochachka, their biological time must be multiplied by a factor of 5 if we are to translate it into human biological time. The crux of the metabolic intervention lies in the timing of the initiation, which should occur only during the hypermetabolic phase marked by the typical clinical and hemodynamic findings (tachypnea, hyperthermia, tachycardia, increased cardiac Index).

This goes along with the novel concept that patients suffering from septic shock (Ken Mattox) should be treated under the light of Chaos Theory. The basic concept of Chaos Theory, as stated by James Gleick, refers to the “sensitive dependence on the initial conditions”, meaning that as time goes by, the introduction of any additional variable into

a complex system (i.e. biological system), may have exponential results. Once septic shock is established, we are on a clock. We hypothesize that multi-organ dysfunction is caused by bioenergetic failure. The law of mass action states that “the rate of reaction is directly proportional to the concentration of the participating molecules”. The crux of the matter may lie in the timely delivery of critical mass (energy), before mitochondrial respiration slows down, with the ultimate goal of achieving cellular homeostasis.

The following components are pivotal for the EMR intervention.

Free Amino Acids – Anaplerosis

During sepsis and cardiac ischemia, it has been shown that mitochondria are not as readily able to create ATP through oxidative phosphorylation and beta-oxidation and as such, must rely on other substrates(32,44). This can be achieved through anaplerosis via carboxylation of pyruvate and with the replenishment of the tricyclic acid cycle (Krebs cycle), accessed through the induction of intermediary metabolites provided by glucose and free amino acids(44). This is the rationale for the inclusion of free amino acids infusion as part of the protocol. The shift of metabolism to primary utilization of protein is well documented in the critically ill patient population(45). In fact, the amount of protein metabolized by a septic patient is limited only by the rate at which it can be liberated from the skeletal muscle(45). This argument supports a protocol in which we provide early calories and high amounts of free amino acids to the septic shock patient to support underlying organ function before catastrophic metabolic failure occurs.

Insulin

Insulin has many potential actions which may be beneficial in sepsis.

1. Insulin may benefit patients by facilitating glucose transportation into certain tissues such as striated muscle and adipose tissue.
2. Insulin also replenishes the depleted tricyclic acid cycle by anaplerosis.

3. Insulin suppresses the production of macrophage inhibitory factor (MIF), TNF-alpha, IL-1, IL-6, and free radicals, enhances endothelial NO generation, and enhances the production of anti-inflammatory cytokines IL-4, and IL-10(46).
4. Insulin increases metabolic rate, in turn increasing turnover of ATP, with this being the most important goal of intermediary metabolism.
5. Insulin has an indirect inotropic effect on the heart due to its metabolic effects (46,47).
6. Insulin decreases fatty acid levels. Furthermore, fatty acids are less efficiently oxidized when compared to glucose(47).
7. Insulin stimulates the pentose phosphate pathway, pivotal to nucleotide regulation, synthesis of glutathione, and availability of cytochrome p450, amongst others.

Thiamine

With regard to the vitamins included in the intervention proposed, thiamine is an essential vitamin for aerobic metabolism, acting as a key juncture for the Krebs cycle as well as in the pentose-phosphate pathway. Thiamine is a cofactor for pyruvate dehydrogenase, which converts pyruvate into acetyl co-enzyme A for use in the Krebs cycle. Deficiency of thiamine leads to lactate generation and a relative deficiency may exist in the context of the hypermetabolic state of sepsis. A small study has demonstrated that the administration of thiamine leads to decreased lactate levels in those who were thiamine deficient – a surprisingly high level of 35% of septic patients within the study (47). In addition, thiamine also exerts action via alpha-ketoglutarate (one of two factors regulating substrate oxidation, with the other being the electron transfer chain). Thiamine has a positive effect on the pentose phosphate pathway via transketolase, which feeds F-6P and G3P back to the glycolytic pathway. The pentose phosphate pathway plays a part in the regulation of thyroid, adrenal, liver, erythrocyte, leukocyte, and adipose tissue intermediary metabolism, as well as in the synthesis of nucleotides (NAD, and NADP vital for catabolic and biosynthetic pathways respectively) and the synthesis of glutathione and

P-450. Thiamine may therefore help to resolve derangements in thyroid and adrenal function that are often implicated in sepsis pathophysiology(21).

Studies have shown a decrease in requirement of renal replacement therapy in patients with septic shock that received thiamine (p=0.04) (48). In another RCT in which thiamine was used as a metabolic resuscitator in patients with septic shock, it was noted that in those patients with a baseline deficiency, the administration of thiamine was associated with a significantly lower lactate level at 24 hours (p=0.03) and a decrease in mortality over time (p=0.047)(49).

Ascorbic Acid (Vitamin C)

Vitamin C is a potent antioxidant that directly scavenges oxygen free radicals, restore cellular antioxidants, and is an essential cofactor for iron and copper containing enzymes(50). Patients with sepsis may have low Vitamin C levels, which can only be corrected with intravenous Vitamin C. In a recent pharmacokinetic study, it was described that 2 g/d dose was associated with normal plasma concentrations, and that 10 g/d dose was associated with supranormal plasma concentrations, increased oxalate excretion, and metabolic alkalosis (51). In a before-and-after study, there was a statistically significant mortality decrease after the administration of a combination of vitamin C (6g day), thiamine and hydrocortisone, from 40.4% to 8.5%(52), although these were striking results, the study had several limitations and has caused criticism with regard to the Hawthorne effect. However, this important observation needs further randomized studies. Our EMR protocol does not include corticosteroids, since the most recent large RCT performed did not show any improvement with the use of this medication in septic shock patients(53).

Other vitamins,

Finally, it is worth noting that there are several vitamins and minerals included which would be excessive to individually explain in detail. These vitamins and minerals are essential factors in normal human metabolism. By providing these nutrients, septic shock

patients may more efficiently utilize the substrates provided, increasing their metabolic rate to overcome the septic insult.

The imminent need to identify novel therapies, improve survival, and decrease the economic burden generated by the patients suffering from septic shock is a top priority. If our therapeutic approach proves to be effective in demonstrating a significant reduction in mortality, the clinical and social impact could be highly relevant. A decrease in mortality and incidence of multi-organ dysfunction syndrome has the potential to reduce the disability associated with septic shock.

The rationale of selecting 28-day mortality as the primary endpoint of the study is that in our population the ICU length of stay and Hospital length of stay have wide variability (ICU LOS = Mean 9.45days ± 13.06 min: 0 days max: 104 days, and Hospital LOS = Mean 26.4 days ± SD 26.4 min:1 day, max: 242 days). This variability increases the risk of biases at the moment of the analysis, therefore selecting a more objective point in time will allow us to perform a better analysis. Additionally the Food and Drug Administration and other licensing authorities consider the 28-day timeframe better for assessing drug efficacy, this because shorter periods may not be sufficient to determine the effect of the treatment and longer time spans may make difficult to differentiate causes of mortality(54). This last point is particularly important in our oncologic population where the comorbidities and prognosis may reduce long term survival.

4.0 STUDY DESIGN

This is a prospective, single center, un-blinded, randomized controlled trial. Patients will be stratified by type of malignancy, and blocking will be used to ensure balance between study groups. Patients will be randomized to either Early Metabolic Resuscitation with Standard of Care (SC + EMR) or Standard of Care alone (SC).

Patients will be recruited from the Intensive Care Unit at The University of Texas MD Anderson Cancer Center with the intention of assessing the impact of (SC + EMR) on mortality: i) 28-day ii) during hospitalization, iii) in the ICU, and iv) at 90 days along with other known complications of septic shock relative to SC.

5.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

5.1 Inclusion Criteria

- Adult patients aged 18 years old or older
- Admitted to the adult medical intensive care unit (MICU)
- Diagnosis of Septic Shock within 12 hours of ICU admission , unless the patient is already admitted to the ICU, defined as meeting criteria for sepsis in addition to the following:
    - Vasopressor therapy needed to elevate MAP ≥65 mmg Hg.
    - Lactate > 1 mmol/L (9 mg/dL) and/or Base excess <-2 after adequate fluid resuscitation.
- Sequential Organ Failure Assessment (SOFA) score meeting the following requirements
    - Cardiovascular SOFA ≥ 2
    - Total SOFA score ≤12
- Patients meeting the mentioned inclusion criteria and not able to tolerate enteral nutrition above 70% of their estimated daily caloric need

5.2 Exclusion Criteria

- Do Not Resuscitate (DNR),
- Comfort Care and end-of-life patients
- Patients with SOFA score greater than 12
- Pregnant women
- Jehovah witnesses that do not accept albumin.
- Active bleeding (e.g., gastrointestinal bleeding)
- Acute neurological syndromes (e.g., stroke, hemorrhage, etc)
- End-stage Renal Disease (ESRD)
- Transaminitis

- Renal replacement therapy
- Chronic Liver Disease
    - Childs-Pugh Class C *or*
    - Diagnosis of Cirrhosis
- Heart rate less than 50 bpm,
- Respiratory rate less than 8 rpm,
- Temperature less than 95`F or 35`C
- Tumor Lysis Syndrome
- Myasthenia gravis
- Sulfite Allergy: amino acids administration are contraindicated. It is more common in steroid dependent asthmatics. (Please note that this is NOT sulfa allergy and is NOT contraindicated patients with sulfa allergy). Sulfites are present in dried fruits, beer, wines, sausages, jams, maple syrup, and many other food products.
- Serum sodium concentration < 130 mEq/L or >150 mEq/L (Note: Once serum sodium levels are ≥ 130 or ≤ 150 mEq/L within 12 hours after meeting inclusion criteria, the patient can then be considered for the study. This is only a temporary restriction.
- Serum Creatinine level: SCr ≥ 3 mg/dL(Note: Once serum creatinine levels are ≤ 2.5 mg/dL within 12 hours after meeting inclusion criteria, the patient can then be considered for the study. This is only a temporary restriction).
- Urine output < 400 cc/24hrs(Note: Once urine output levels are ≥ 400 cc within 12 hours after meeting inclusion criteria, the patient can then be considered for the study. This is only a temporary restriction).
- Hyperkalemia K > 5.5 mEq/L (Note: Once potassium levels are ≤ 5.5 mEq/L within 12 hours after meeting inclusion criteria, the patient can then be considered for the study. This is only a temporary restriction).
- Hyperglycemia: Glucose > 250 mg/dL (Note: Once glucose is below 250 mg/dL within 12 hours after meeting inclusion criteria, the patient can then be considered for the study. This is only a temporary restriction.)

- Hypophosphatemia: Serum Phosphorous < 1.5 mg/dL (Note: Once phosphorus is above 1.5 mg/dL within 12 hours after meeting inclusion criteria, the patient can then be considered for the study. This is only a temporary restriction.)
- Hyperphosphatemia: Serum Phosphorous > 6.5 md/dL(Note: Once phosphorus is below 6.5 mg/dL within 12 hours after meeting inclusion criteria, the patient can then be considered for the study. This is only a temporary restriction.)
- Patient with a history of metabolic abnormality in any one of the following amino acids: Alanine, Arginine, Cysteine hydrochloride, Glycine, Histidine, Isoleucine, Leucine, Lysine acetate, Methionine, Phenylalanine, Phosphoric acid, Proline, Serine, Threonine, Tryptophan, and Valine

  Any other condition in which the ICU clinical team feels the patient should not be a candidate for the protocol.

5.3 Study Enrollment Procedures

A. Upon admission to the Emergency room or MICU, patients diagnosed with septic shock will be referred by the ICU attending to the designated study personnel who will then screen the patient for inclusion and exclusion criteria. The Basic Metabolic Panel (BMP) and patient medical chart history will be reviewed. If patient meets inclusion criteria (and no exclusion criteria) the patient's primary attending will be contacted for permission to enroll patient into the study. If the attending physician agrees, the patient (or if patient unable to consent, the patient's Legal Representative Power of Attorney or Next of Kin) will be approached.

B. A discussion will be held with the next of kin and/or patient as appropriate to discuss the study procedures, possible adverse effects and research rationale. Informed consent will be mandatory and we will provide ample time to answer any questions or concerns about the protocol. A fully informed consent will be recorded in writing as per local guidance. It will be made clear to the participant and relatives that they are under no obligation to participate in the study and are free to withdraw

at any time, without giving a reason. Please see appendix for consenting material. If there is a possibility of pregnancy (defined as women <60 who have not been postmenopausal for at least one year or have not had a hysterectomy) then a serum or urine B-HCG test will be taken (with consent) prior to enrollment into the study. Refusal of pregnancy test will be considered grounds for exclusion.

The research coordinator will track all the potential candidates (patients meeting inclusion criteria) not included in the study in parallel due to logistical limitations (e.g. lack of research staff on weekends).

C. Screening will be within 12 hours of patient being admitted to the ICU. Recruitment and initiation of study solution (where applicable) must occur both within twelve hours of the recorded onset of septic shock and admission to the MICU.

6.0 STUDY INTERVENTIONS

6.1 Description of study groups

There will be two arms or groups in this study

1. **(Standard of Care: SC)** - follow institutional ICU management algorithm for septic shock
2. **(Early metabolic resuscitation with Standard of Care: SC + EMR)** - infusion of EMR solution with Standard of Care

6.2 Description of EMR protocol group

The combined EMR solution will be infused at a set rate (<12hours or > 12 hours) as the main metabolic resuscitation strategy. Additional volume may be required to achieve euvolemia. This will be in the form of either albumin (if serum albumin < 3 as mentioned below) or crystalloids depending on the clinical situation and the serum sodium content. The early metabolic support components include the following:

Table 2 show the components of the EMR solutions per liter

Table 2. EMR Solution

EMR SOLUTION WILL BE PREPARED IN A BAG WITH THE FOLLOWING COMPONENTS	
EMR I (with potassium)	**EMR II * (without potassium)**
Dextrose 50% with Potassium Phosphate 30 mmol	Dextrose 50% with Sodium Phosphate 30 mmol
Sodium Acetate 75 mEq	Sodium Acetate 55 mEq
Sodium Chloride 75 mEq	Sodium Chloride 55 mEq
Thiamine 500 mg	Thiamine 500 mg
Folic Acid 1 mg	Folic Acid 1 mg
Zinc Sulfate 5 mg	Zinc Sulfate 5 mg
Selenium 60 mcg	Selenium 60 mcg
Copper 1.2 mg	Copper 1.2 mg
Chromium 12 mcg	Chromium 12 mcg
Magnesium Sulfate 16 mEq	Magnesium Sulfate 16 mEq
Multivitamin for Injection 10 ml	Multivitamin for Injection 10 ml

Insulin 25 units (actrapid)	Insulin 25 units (actrapid)
SPECIFICATIONS OF THE TREATMENT AND ADJUVANTS	
A. **EMR solutions**: will be infused at 0.5 ml/kg/h by CVC. If serum glucose is greater than 180mg/dL-250mg/dL, EMR solution will be infused at 0.25 ml/kg/h. Prior to starting EMR infusion, a bolus of 500mg IV of thiamine should be administered to all patients on SC+EMR arm of treatment. B. Clinisol 15% AA. Infusion rate (IV) will be 0.25 ml/kg/hr for the first 12 hours, then 0.5 ml/kg/h for the remainder of the intervention – this must be infused via a dedicated Central Venous Catheter. C. If serum albumin is lower than 3 g/dL, then use Albumin 25% 100ml IV Q 8 hours until serum albumin level ≥ 3 g/dL – this can be infused peripherally or centrally. Once albumin >3g/dL this can be stopped, but should resume whenever albumin falls <3g/dL D. **Vitamin C** 1g q 8h IV **(100 ml per gram of Vitamin C)**	

**If the level of K is ≥ 5.0mmol/L the patient will receive EMR II. Any conditions, which the K^+ trend is rising, clinicians could opt to switch EMR solution to prevent hyperkalemia. This solution does not contains potassium phosphate, but contains sodium phosphate. Sodium content is consequently adjusted to have a compatible concentration*

Total amount of administered fluids on day one.

EMR I or II formula during first 12 hours: **EMR** 0.5 ml/kg/h + Clinisol 0.25 ml/kg/h + **Vitamin C** 100 ml q8. **EMR + Clinisol**: 0.75 ml/kg/h in a 70 kg individual will be 630 mL/12 hr + (100 ml VitC x 1 times).

TOTAL= 730 mL within the first 12h of treatment

EMR I or II formula after 12 hours: **EMR** 0.5 ml/kg/h + **Clinisol** 0.5 ml/kg/h + **Vitamin C** 100ml q8. **EMR + Clinisol** = 1ml/kg/h in a 70 kg individual will be 840 mL/12hr + (100ml VitC x 3 times)

TOTAL = 1.98 L/24h

For SC+ EMR Arm – Serum targets:

a. Target serum Albumin > 3 g/dl
b. Target serum Magnesium of 3mg/dl

Sodium management

a. <130 meq/L use Sodium Chloride 0.90% and call the PI
b. 130-134 meq/L use Plasmalyte
c. 135-140 meq/L Ringer's Lactate
d. >140 meq/L use Sodium Chloride 0.45%

6.3 Duration of intervention

The above infusions will be started and continued for seven days unless the patient dies or is discharged from the ICU. Infusions have to be continuously maintained and not stopped for any routine investigations. If the patient is tolerating enteral tube feeds at ≥70% of goal for a full 24 hours as determined by the ICU dietician, the intervention will be stopped (established weaning process to avoid precipitation of hypoglycemia).

6.4 Adherence Assessment

Adherence will be defined as continuous infusion of study solutions 90% of the time from onset of study until cessation. This will be assessed via the electronic patient record, which will record infusion stop/start times.

Patients who have requested to be withdrawn from the study or achieve Comfort Care status during ICU stay will be removed from the study. Those who die or begin renal replacement will be followed up but the interventions will be stopped.

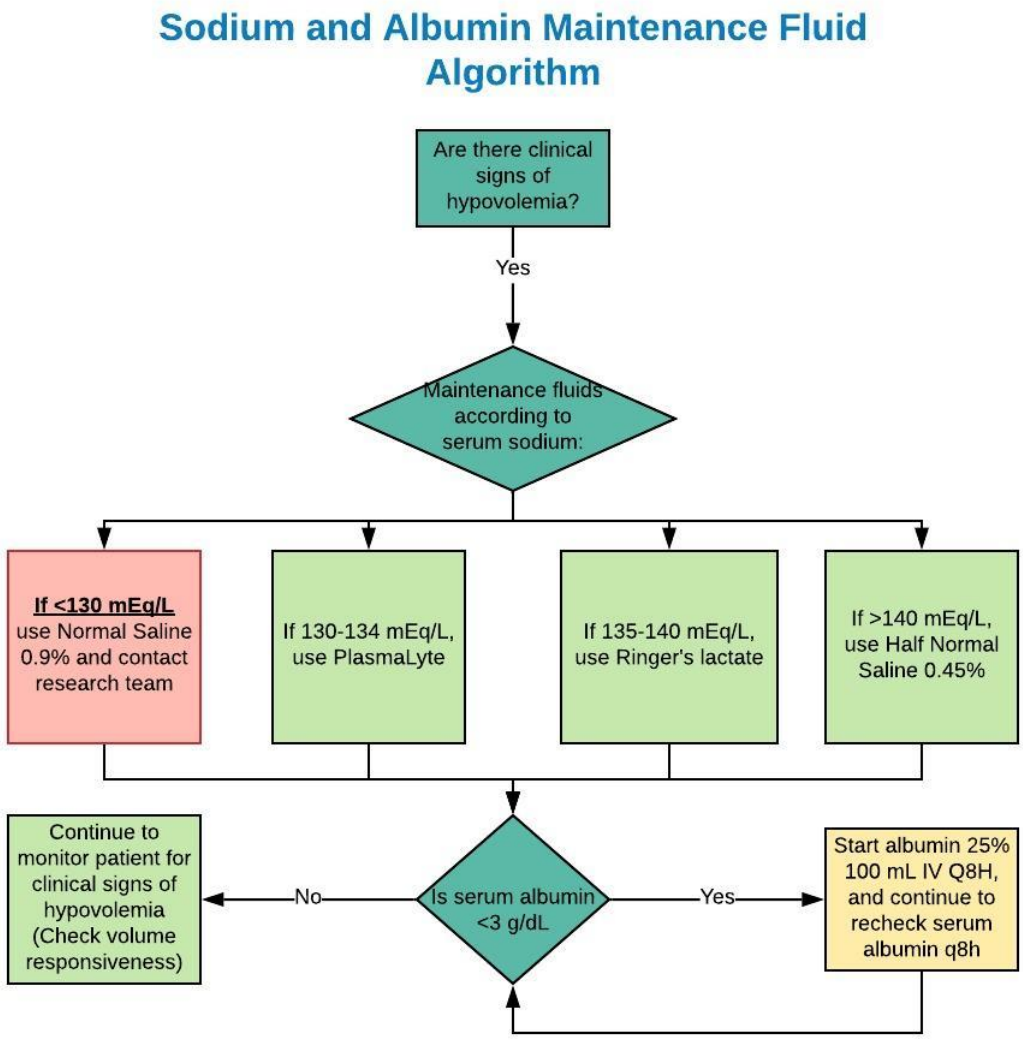
6.5 Required interventions

If the patient does not have a central venous access or arterial line, then this patient cannot be included in the study. All patients treated for septic shock must have central venous and arterial access as standard of care. All participants must have both a central venous catheter and arterial line inserted. As this represents standard of care in septic shock, this is likely to be universal and will not be an impediment to enroll patients.

6.6 Additional fluids to maintain euvolemia

Additional fluids following sodium algorithm may be required in order to achieve euvolemia. This should be according to the attending physician's clinical judgement after assessment of the overall hemodynamic parameters and resuscitation status, including pressure (macrocirculation), flow (microcirculation), and function (metabolism). If function is compromised (e.g., rising creatinine, decrease in urine output, rising liver function tests) consider optimizing the coronary and systemic pressure gradient.

Figure 1. Sodium and Albumin to maintain euvolemia



6.7 Weaning procedure for EMR solution

To wean EMR, decrease rate of both solutions, EMR I or II and Clinisol to half the current rate for 4 hours, and then discontinue. Check serum glucose within 30 minutes of discontinuation of EMR. Further decisions regarding management of IVF, amino acid infusions or parental nutrition will be at the discretion of the ICU team or the primary team.

7.0 STUDY PROCEDURES

7.1 Data to be collected prior to start of intervention

1. Patient demographics at time of ICU admission (age, gender, weight, height, BMI, race, ethnicity, date of birth)

2. Past medical and surgical history as recorded in the latest admission on the electronic patient record (EPR)

3. Date and reason for hospital admission, and source of admission.

4. Date, time and reason for ICU admission including any concomitant problems

5. Date and time of septic shock onset (start time defined by criteria for septic shock, vital information that should be carefully determined, since “Timely delivery of EMR before Mitochondrial Respiration slows down” is the crux of the study)

6. Suspected source of sepsis

7. Presence or absence of oncologic disease, state and diagnosis of metastatic disease at time of ICU admission if known

8. Nutritional status based on the assessment by the dietitian in the ICU (this may be recorded after onset of intervention if not available initially) including any history of weight loss or signs of malnutrition

9. Patient vital signs and hemodynamic status

10. Supplementary oxygen and NIV/intubation status

11. Baseline CBC, blood chemistry panel, coagulation screen and ABG (baseline defined as within 12 hours of randomization for venous tests and 4 hours for ABG – if these have not been done we will send additional baseline investigations)

12. Any relevant microbiology results (blood, urine cultures, wound cultures, serum microbiological tests) and pertinent imaging results (radiology reports only – images not to be recorded)

13. Admission Sequential Organ Failure Assessment (SOFA) score

14. Pregnancy status - women of child bearing potential (defined as women <60 who have not been postmenopausal for at least one year or have not had a hysterectomy) will have either a serum or urine B-HCG test to exclude pregnancy. A positive pregnancy test is grounds for exclusion from the study. This will have already been undertaken as a part of screening if the above criteria are met.

7.2 Data to be collected prospectively

Vital signs including blood pressure, heart rate, respiratory rate, pulse oximetry, co-oximetry will be measured, as well as cardiac assessment by 2D echocardiogram. The following information will be collected prospectively if available. The order sets describe the timing and frequency of the lab draws. If clinical condition indicates, blood tests may occur more frequently at discretion of primary team. Additional tests may not necessarily be recorded. The below order sets indicate minimum frequency. *Day 0 is day of recruitment.*

Daily SOFA scores - will be generated automatically by the electronic health record if this option exists in the institution or manually with table 1 once daily.

Laboratory Data:

1. Complete Blood Count and Coagulation profile
    a. First 24hrs after start of intervention: every 8 hours ± 120 minutes
    b. After 24hrs of intervention: every 12 hours ± 120 minutes

2. Cultures (as ordered by primary team – *we will not specify culture requirements though at least one set of blood cultures should be taken as required by sepsis management algorithm*)

3. Liver function tests and lipase
    a. First 24hrs after start of intervention: every 12 hours ± 120 minutes
    b. After 24hrs of intervention: every 24 hours ± 120 minutes

4. Serum cholesterol (to be collected once daily only days 1, 3, 5)

5. Thyroid test: Thyroid function tests (to be collected once daily only days 1, 3, 5)

6. Blood chemistry panel
    a. Includes: Albumin, BUN, Ca^{2+}, Na^{+}, K^{+}, Cl^{-}, CO_2, Creatinine, Glucose, Phosphorus, and Gama-Glutamyl transpeptidase
    b. First 24-hrs after start of intervention: every 4 hours ± 120 minutes (Will require VAMP System or similar blood sparing device to avoid wasting blood)
    c. After 24-hrs of intervention: every 8 hours ± 120 minutes

7. Arterial blood gas and venous blood gas (via central venous catheter)

a. First 24hrs after start of intervention: every 4 hours ± 120 minutes
b. After 24hrs of intervention: every 8 hours ± 120 minutes

8. Lactic acid
    a. First 24-hrs after start of intervention: every 4 hours ± 120 minutes
    b. After 24-hrs of intervention: every 8 hours ± 120 minutes

9. Serum Cortisol once daily (morning)

10. Uric acid once daily (morning)

11. Inflammatory markers (ESR, Procalcitonin) to be collected once daily.

12. Creatinine phosphokinase (to be collected once daily only on day 1, 3, 5)

Outcome data:

1. Length of stay (LOS)
    a. Time from hospital admission to admission to the ICU (Length of stay before admission to the ICU)
    b. Length of the stay in the ICU
    c. Length of hospital stay
2. Mortality
    a. Hospital mortality
    b. ICU mortality
    c. 28 day mortality
    d. 90 day mortality

3. Ventilator days – ventilator free days, duration of intubation (days)
4. Any newly documented hospital acquired infection(s)
5. Any acute kidney injury as defined by acute kidney injury network criteria:
    a. An acute (within 48h) rise in serum creatinine of 0.3g/dl or more

b. A percentage increase of serum creatinine of 50% or more
c. Documented oliguria <0.5 ml/kg/hr for >6 hours
d. Need for dialysis
e. Dialysis free days

6. Inotropic free days and duration of inotropic support (hours or days)
7. Vital signs and any hemodynamic monitoring (cardiac index, CVP, ScvO2) implemented will be recorded – there is no specific requirement for hemodynamic monitoring beyond arterial-line recorded MAP/BP/HR.
8. All patients will be followed up for up to 90 days.

8.0 SAFETY ASSESSMENTS

8.1 Theoretical and potential adverse events

The study intervention is assessing an infusion containing products, which are normal components of the diet and are not toxic in themselves. Although this trial is expected to be very safe there are four main etiologies by which harm may occur in any of the groups:

1. **Fluid overload**
2. **Electrolyte disturbances**
3. **Hyper/hypoglycemia**
4. **Hypersensitivity reactions**

Such events are frequent in an ICU, and medical personnel are well trained and experienced to deal with these situations. This, combined with the very close monitoring provided by ICU means that a serious adverse reaction is thought to be exceedingly unlikely. All of the described scenarios already have ICU management protocols.

As the study is unblinded, attending physicians and care team members will be aware of the contents of the solutions being infused. Thus, if the study team is not available to advise, the care team should be able to make a decision based on clinical factors and may use their discretion to discontinue the intervention where necessary.

8.2 Management of anticipated adverse events

1. Fluid overload

This is considered to be very unlikely as sepsis and particularly septic shock are conditions where aggressive fluid resuscitation is recommended (30). The amount of fluid administered daily is considered to be relatively conservative. Furthermore, patients requiring renal replacement therapy will be excluded for further intervention, so harm from this intervention is highly unlikely.

There is no consensus or standard definition of fluid overload. We ask physicians to discontinue other fluids in preference to the EMR investigation fluids when possible. If there is severe fluid overload whereby the primary team finds it necessary to discontinue the fluid, then the patient will be withdrawn. It is not considered acceptable to slow the rate of the study solution – if this is felt to be essential, then the study solutions will be weaned and fluid management left to the care of the primary team.

2. Electrolyte abnormalities

a. Hyperkalemia (see appendix)
   i. Once potassium reaches ≥5 mmol/L EMR solution I (with potassium) has to be substituted with EMR solution II (without potassium) – EMR II has to continue despite hyperkalemia. EMR I has to replace EMR II once potassium levels reach ≤4 mmol/L
   ii. Potassium levels over ≥5.5mmol/L have to be treated with standard ICU protocol. If EMR I is infused this has to be recorded as an adverse event and EMR I must be immediately replaced with EMR II

b. Hypokalemia (K ≤3) (see appendix)

The ICU patients typically demonstrate low serum potassium level between 3 and 3.5, which are typically treated using the standard ICU electrolyte replacement protocol. Only serum potassium level of ≤ 3 will be reported as an adverse event.

c. Hypernatremia (Na >150)
    i. Discuss with study team – this may be criteria for cessation of intervention. Record as adverse event. If study team not immediately available (i.e. weekends, nights) wean infusion at discretion of attending responsible.
        - Caution with glucose once EMR is stopped – glucose management algorithm must continue to be followed.

d. Hyponatremia (Na <130)
    i. Additional sodium replacement (or diuresis) at discretion of primary team
    ii. If SIADH suspected and for fluid restriction – intervention has to be weaned. Caution with glucose once EMR is stopped(weaned) – glucose management algorithm must continue to be followed.

e. Severe Hypermagnesemia (Mg >4 mg/dl)
    i. Study intervention is to be stopped. Record as adverse event. Manage as per ICU protocol

f. Hypomagnesemia (Mg <1.5mg/dl)
    i. Replace as per ICU guidelines – N.B. target magnesium is ≥3mg/dl in intervention group

g. Aluminum toxicity
    i. Aluminum toxicity is seen in neonates; however, this population is excluded in our study.

ii. Patients in renal failure are at risk of bio-accumulating aluminum when solutions contain >50 micrograms/L. In this study, patients with renal failure are excluded and free amino acids only contains <25 micrograms/L.
iii. Currently, to measure blood aluminum levels is not standard of care in a) patients not at risk of bio-cumulating the metal, b) patients receiving solutions that contain aluminum below 50 micrograms/L.
iv. Aluminum toxicity is not an expected adverse event in this study patient population.

h. Hypophosphatemia (PO4 <1mg/dl)
    i. Additional replacement as per standard ICU guidelines

i. Hyperphosphatemia (PO4 >6.5mg/dL)
    i. Check renal function and calcium. Discuss with principal investigator. Hyperphosphatemia is not usually symptomatic and does not usually cause direct toxicity. The product of calcium x phosphate should be less or equal to 60. Record as adverse event

3. Hyper/hypoglycemia (see appendix)

For the very likely event of hyper/hypoglycemia in the EMR group we have developed an algorithm, which is a slight modification of standard ICU glucose management protocols and itself refers to ICU sliding scale insulin protocols. As glucose management is anticipated as a potential issue, monitoring of glucose is to occur at least hourly in the treatment arm. Please see appendix for detailed information on glucose management. Target glucose is 140-180mg/dl.

4. **Allergic reactions (related to study components or suspected relation)**

- Urticarial reaction
    - Begin antihistamine. Record as possible adverse event. Monitor patient – if EMR components suspected as the causative AND worsening reaction consider stopping solution and replace with D50 IV solution and exclude the patient from the protocol. At the same time treat the patient until reaction resolves. (Frequent glucose monitoring once solution discontinued). Contact principal investigator and follow hypersensitivity institutional protocol.

- Anaphylaxis
    - As mentioned above, if EMR causes an anaphylaxis reaction, begin emergency anaphylaxis management as per ICU protocol. Record serious adverse event and inform research team immediately. Stop solution and replace by D50 IV solution until a decision is made to exclude the patient from the protocol. At the same time treat the patient until reaction resolves. Caution with glucose once EMR is stopped – glucose management algorithm must continue to be followed. Contact study lead.

8.3 Adverse Events and Serious Adverse Events

- **An adverse event (AE)** is generally defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events have to be recorded regardless of their relationship to the study intervention.

- **A serious adverse event (SAE)** is generally defined as any untoward medical occurrence that results in death or that is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or in a congenital anomaly.

As discussed in 8.1, the study solution is not a novel pharmaceutical product and is unlikely to cause any significant adverse event. Theoretical complications of the solution are common problems in critical care units. Vigilance and close monitoring, together with high staffing levels in ICU reduce the potential for harm. Bearing these facts in mind, there are only three scenarios, which will be reported as serious adverse events in the EMR group:

1) **Anaphylaxis (to study components)**
2) **Arrhythmia secondary to electrolyte disturbance**
3) **Hypoglycemia (<70mg/dL)**

These will be monitored for via electronic medical records. All suspected adverse reactions and above adverse events must be reported by unit staff or research team to the principle investigator who will provide within 1 week such reports to the Institutional Review Board. We estimate that adverse reactions are not very likely, as this study lacks novel pharmaceutical agents. Patient safety has been thoroughly considered by the study chairs.

Only the adverse events and serious adverse events that happen within the 7 days of enrollment will be logged and reported to the IRB.

9.0 CRITERIA FOR INTERVENTION DISCONTINUATION

These include:

- Patient's consent withdrawn
- Patient's discharge from the ICU
- Allergy to any of the components of EMR
- Patient requiring renal replacement therapy
- Patient's death
- Patient changed to Comfort Care status
- Patients receiving greater than 70% of their nutritional needs via enteral nutrition
- Unable to undergo placement of CVC for any technical reasons or withdrawal of CVC
- Severe fluid overload or electrolyte abnormality requiring discontinuation (as described in Chapter 7)
- Jehovah's Witness who decides not to accept albumin.
- If patient develops a known contraindication, or an unspecified condition where the clinician thinks the patient should be taken off the protocol, then there should be a discussion and treatment should be weaned according to safety protocol.

In case of discontinuation, please follow weaning procedure detailed in section 6.7.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Endpoint and Outcomes

The primary objective of this study is to assess the efficacy of administering Early Metabolic Resuscitation with Standard of Care (SC + EMR) in patients diagnosed with septic shock for reducing 28 day mortality versus using the Standard of Care alone (SC).

The primary endpoint of the study is 28-day mortality. The rationale for selecting the 28-day timeframe as the primary endpoint for comparison is that the MDACC ICU length of stay and the hospital length of stay in patients diagnosed with septic shock have wide variability (ICU LOS = Mean 9.45 ± 13.06 min: 0 max: 104, and Hospital LOS = Mean 26.4 ± SD 26.4 min:1, max: 242). This variability is incurred from sources that cannot be controlled. For this reason, measures such as 28-day and 90-day mortality provide more objectivity and align with outcomes described in the literature.

Secondary outcomes include ICU mortality, hospital mortality, 90-day morality, incidence of acute kidney injury (dichotomous variable), time on cardiovascular support (continuous variable), time on ventilator (continuous variable) and length of ICU and hospital stays (continuous variables).

10.2 Sample Size Justification and Randomization

The rate of 28 day mortality from septic shock at the UT MD Anderson Cancer Center was 70% in 2017. With the objective of decreasing this rate to 40%, a sample size of 112 patients (56 per group) provides 90% power to detect a 30% absolute reduction in the rate of 28 day mortality using a two-sided chi-square test at the 0.05 significance level. We plan to use stratified randomization in a 1:1 fashion to assign patients into two groups, and a fixed block size consisting of 4 patients will be applied for this purpose. The randomization will be conducted in CORe (Figure 2).

Tables 3 displays effect sizes that correspond with conducting a test of equal proportions after randomizing 56 patients to each study arm. The first scenario in Table 3 is what we have currently provided in the protocol. Subsequent scenarios in Table 3 illustrate the change the in the effect size as the Type I error increases. Table 4 is provided to illustrate effect size results if the power is reduced to 80%. Smaller effect sizes are detectable if you increase Type I error or reduce power.

Table 3. Effect size with varying Type I error with Sample Size and Power controlled at 56 patients per study arm and 90%, respectively

Sample Size Per Study Group	Effect Size (percentage point change from $\hat{\pi}_0$ = 70%)	Type I error
N = 56	-30% (0.70 vs 0.40)	0.05
N = 56	-27% (0.70 vs 0.43)	0.10
N = 56	-25% (0.70 vs 0.45)	0.15
N = 56	-24% (0.70 vs 0.46)	0.20

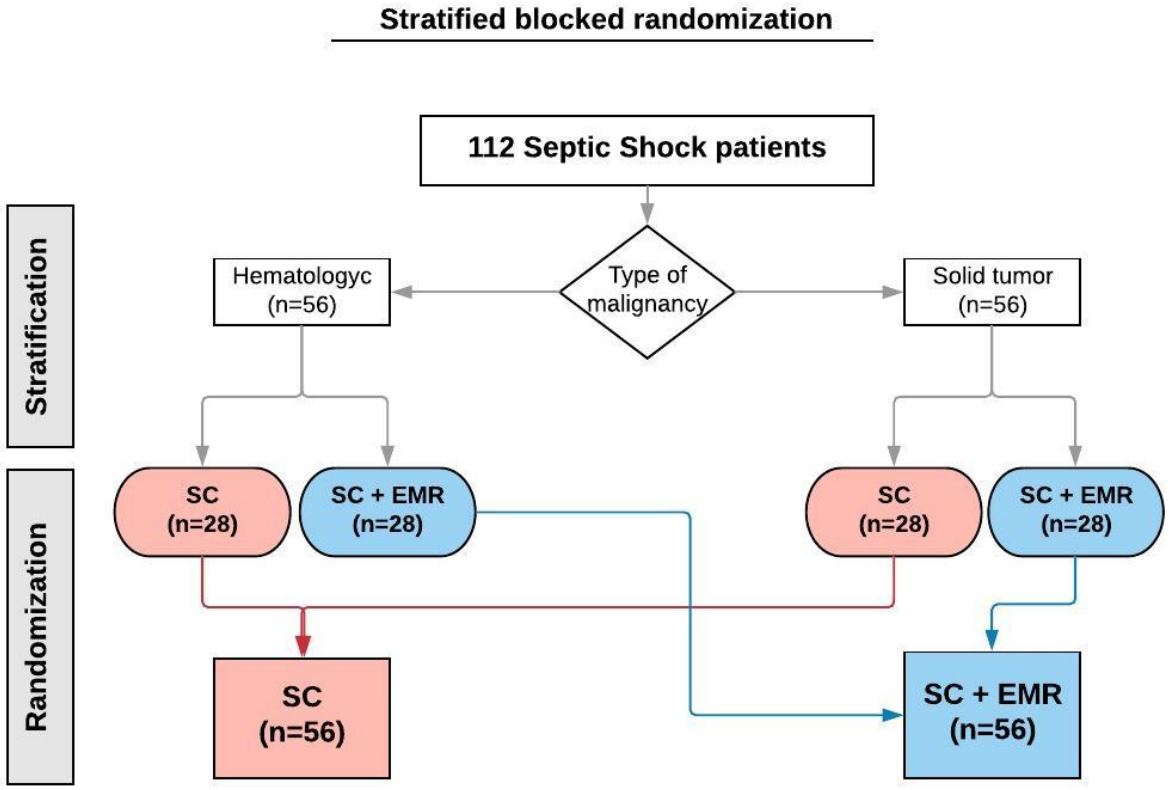
Estimates provided by (nQuery Advisor v7.0) for the difference between two proportions using a two-sided chi-square test.

Table 4. Effect size with varying Type I error with Sample Size and Power controlled at 56 patients per study arm and 80%, respectively

Sample Size Per Study Group	Effect Size (percentage point change from $\hat{\pi}_0$ = 70%)	Type I error
N = 56	-26% (0.70 vs 0.44)	0.05
N = 56	-23% (0.70 vs 0.47)	0.10
N = 56	-21% (0.70 vs 0.49)	0.15
N = 56	-20% (0.70 vs 0.50)	0.20

Estimates provided by (nQuery Advisor v7.0) for the difference between two proportions using a two-sided chi-square test

Figure 2. Sample size and randomization

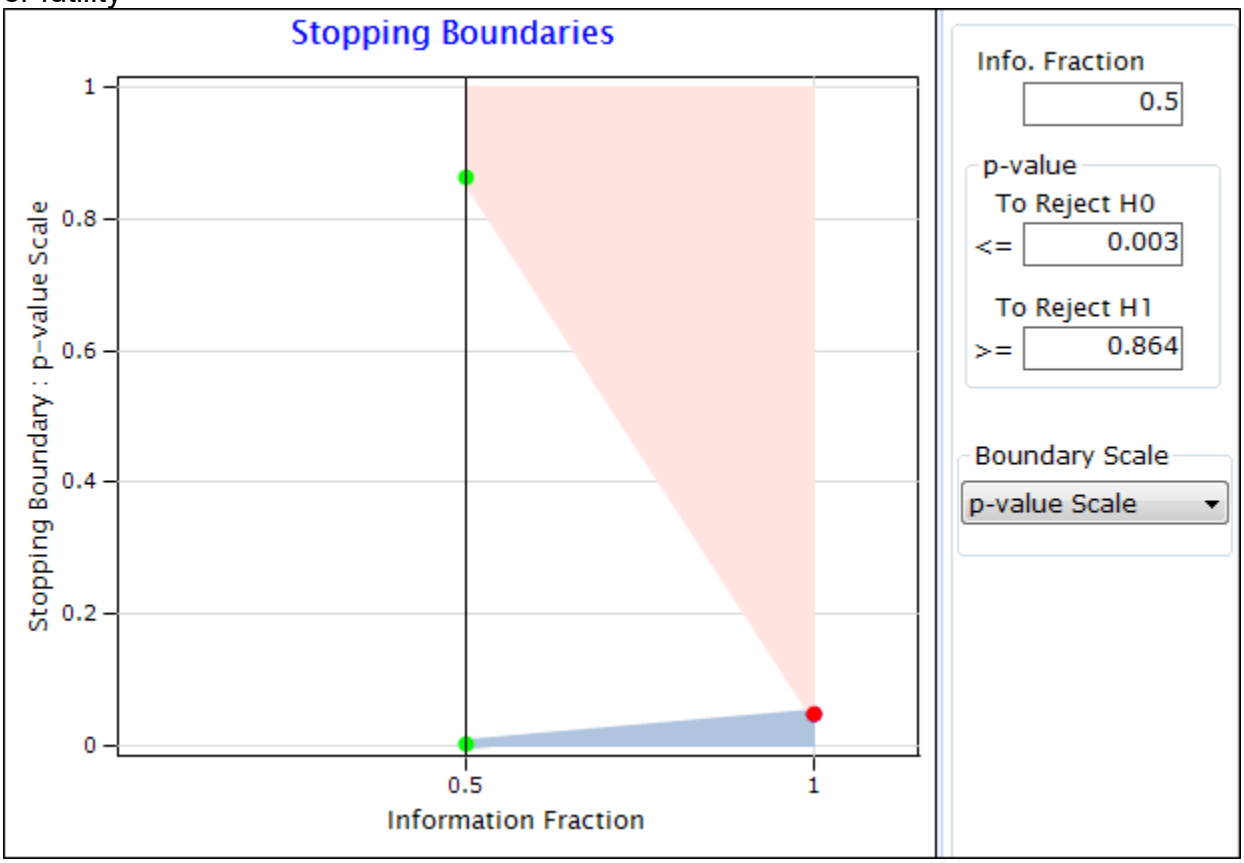


The septic shock patients will be stratified by type of malignancy given that hematologic patients may be more morbid than solid tumor patients. SC + EMR: Early Metabolic Resuscitation plus Standard of Care SC: Standard of Care. Blue boxes represent the group of patients that will receive EMR plus Standard of Care intervention and the pink boxes represent the group that will receive Standard of Care alone.

10.3 Interim Analysis

The parameters indicated in the full analysis set comprised of 112 patient for detecting an effect size of -30% (.70 vs .40) with a 2-sided test and Type I error of 5% conferring > 90% power were used to develop interim stopping boundaries based on the method of Lan-DeMets with an O'Brien Flemming type spending function. An interim analysis will be conducted when the first 56 patients (28 patients randomized per treatment arm) have been evaluated for the primary endpoint. Figure 1 provides the stopping boundaries for early termination on a p-value scale for both superiority and futility (East Version 6.3.1). At the interim analysis, a p-value < 0.003 or a p-value > 0.864 elicits early stopping for superiority or futility, respectively. The PI will make the final determination whether to terminate or continue with the trial after evaluating the study results. Accrual will not be suspended while this analysis is being conducted.

Figure 1. Stopping boundaries (on a P-value scale) for early termination due to superiority or futility



10.4 Data Monitoring

During the course of the study, safety and data quality monitoring will be performed on an ongoing basis by the Research Coordinator and the Principal Investigator. The clinical research coordinator will be responsible for collecting and recording all clinical data. This includes ensuring that all source documents exist for the data on the case report forms, ensuring all fields are completed appropriately, and all corrections are done according to Good Clinical Practice (GCP's). Any inconsistencies/deviations will be documented. The P.I. will review the obtained data for each patient on an ongoing basis.

10.5 Data Analyses

Descriptive statistics including the mean, standard deviation, median, and range will be used to summarize continuous variables. Frequency counts and percentages will be used to summarize categorical variables. Categorical variables, including 28 day mortality, will be compared between intervention groups using a chi-square test, or Fisher's exact tests if more appropriate. Continuous variables will be compared between intervention groups using an independent samples t-test, or Wilcoxon rank-sum test if more appropriate.

Logistic regression will be used to assess relationships between patient characteristics and binary study outcomes of interest. Continuous variables, including the time on cardiovascular support and time on ventilator, will be compared using t-tests or Wilcoxon rank-sum tests.

Time to event analyses will be conducted using Cox proportional hazards regression. For 28-day mortality, living patients will be censored after one month after the treatment was given. For overall survival, patients will be followed until time of death or date of last follow-up (maximum 6 months). Kaplan-Meier plots will be used to visually compare time to death from any cause between intervention arms followed by a log-rank test to compare survival distributions.

10.6 Safety monitoring for Patients assigned to (SC + EMR)

Patient safety will be monitored group sequentially for the first 50 patients in (SC + EMR) group. The monitoring rule will be applied in cohorts of size 10 during the 7 days of treatment.

Patient safety will be monitored to ensure that the rate of select AEs described in Section 8.2 (which include: severe fluid overload, untreatable electrolyte abnormalities, severe hyper/hypoglycemia, allergic reactions) does not exceed 25%. If the AE rate exceeds 25%, then the novel treatment approach of (SC + EMR) exceeds an acceptable rate and the trial will suspend accrual, while at the same time, protecting patients from the burden of being exposed to an untoward therapy.

We will employ Bayesian stopping boundaries derived using a beta-binomial distribution. We will consider the treatment as acceptable if the AE rate during the first seven days post administration of (SC + EMR) is below 25%. The following prior probability for the AE rate will be modeled with a beta distribution (1, 1). Allowing θ_T to denote the true rate of AEs, the trial will suspend accrual if the Prob($\theta_T > 0.25 \mid$ data) > 0.80. Patients will be monitored in cohorts of size 10 according to the following stopping boundaries displayed in Table 3.

Table 4 illustrates the operating characteristics associated with the Bayesian stopping rule. The probability of stopping accrual early is 61% if the true AE rate is 30%.

Table 3. Stopping Boundaries assuming prior θ_T ~ beta (1, 1)

Number of Patients Evaluated	Recommended stopping accrual if ≥ AEs are observed
10	4-10
20	7-20
30	10-30
40	13-40
50	15-50

*stopping boundaries and operating characteristics supplied using (https://ibl.mdanderson.org/BTM/)

Table 4: Operating Characteristics for the Bayesian Sequential Design

True AE Rate	Probability of Stopping Accrual Early	Average Sample Size
0.1	0.014	49.5
0.2	0.180	43.7
0.3	0.610	29.9
0.4	0.928	17.7
0.5	0.996	12.3

11.0 DATA COLLECTION AND QUALITY ASSURANCE

11.1 Records to Be Kept

All patient-reported outcomes, laboratory, and clinical data gathered in this protocol will be stored in a password-protected database. A digital data collection form will be used to record data relating to outcomes described (to be included in appendix). All patient information will be handled using anonymous identifiers. Linkage to patient identity is only possible after accessing a password-protected database. Access to the database is only available to individuals directly involved in the study. Information gathered for this study will not be reused or disclosed to any other person or entity, or for other research. Once the research has been completed, identifiers will be retained for as long as is required by law and by institutional regulations, and at that point will be destroyed.

11.2 REDCap Summary

Study data will be collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at MD Anderson. REDCap (www.project-redcap.org) is a secure, web-based application with controlled access designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless downloads to common statistical packages; and 4) procedures for importing data from external sources. In the case of multi-center studies REDCap uses Data Access Groups (DAGs) to ensure that personnel at each institution are blinded to the data from other institutions. REDCap (https://redcap.mdanderson.org) is hosted on a secure server by MD Anderson Cancer Center's Department of Research Information Systems & Technology Services. REDCap has undergone a Governance Risk & Compliance Assessment (May 2014) by MD Anderson's Information Security Office and found to be compliant with HIPAA, Texas Administrative Codes 202-203, University of Texas Policy 165, federal regulations outlined in 21CFR Part 11, and UTMDACC Institutional Policy #ADM0335.

Those having access to the data include the study PI and research team personnel. Users are authenticated against MDACC's Active Directory system. External collaborators are given access to the database once approved by the PI, with their access expiring in 6 months but renewable in 6 month increments at the request of the PI. The application is accessed through Secure Socket Layer (SSL). All protected health information (PHI) will be removed from the data when it is exported from REDCap for analysis. All dates for a given patient will be shifted by a randomly generated number between 0 and 364, thus preserving the distance between dates. Dates for each patient will be shifted by a different randomly generated number.

Following publication, study data will be archived in REDCap. Since study data may be useful for future research studies performed under separate IRB approved protocols, study data will be archived indefinitely in REDCap. Since REDCap is a secure electronic database with controlled access, and because patient identifiers may be needed to link study data to data from other sources under future IRB approved protocols, patient identifying information will be retained in the archived database.

11.3 Data Management

The PI will oversee the day-to-day operation of the project along with the Project Coordinator. The PI is responsible for reporting on trial progress to the IRB and he will take responsibility for the conduct of the research team, including, in general, optimal research ethics, adherence to protocol, and commitment to study completion. Specifically, site start-up and maintenance, protocol refinement, assurance of data quality, and trial success are the responsibility of both co-applicants and collaborators.

11.4 Quality Assurance

11.4.1 Training

Prior to the undertaking of the study, several educational sessions will be provided to ICU physicians (faculty and trainees), nurses, and advanced nurse practitioners (where present). These will be provided by the study chair Dr. Joseph Nates or their designees. These sessions will focus on training ICU staff with the protocol with particular focus on:

- *New definitions of sepsis and septic shock*
- *Rationale and purpose of study*
- *The interventions given*
- *Possible adverse reactions and how to manage them (particular focus on electrolytes & glucose)*
- *Criteria for intervention discontinuation*
- *Study team composition and contact information*
- *Adverse event reporting*

11.4.2 Quality Control

Integrity of data is ensured by oversight from MD Anderson's Data Monitoring and Safety Board. As well as adverse event reporting and annual reports will be provided to the DSMB with the help of the trial statisticians in order to ensure integrity of the data. Along with planned recording for protocol deviations, we feel this will ensure the integrity and quality of the data recorded

11.4.3 Protocol Deviations

Deviations from protocol, whether or not they may lead to harm or risk of harm, will be recorded by investigators and provided to the principle investigator who may share these

with the DSMB. Protocol deviations, if felt to be significant, will be shared with statisticians and included in potential analyses where possible.

11.4.4 Monitoring

Protocol compliance will be assessed by review of records, including inpatient electronic records, by the research team during the collection of study outcomes. All consent documents and any other information collected non-electronically will be reviewed by the principle investigator. The MD Anderson Data and Safety Monitoring Board (DSMB) may decide to audit the research at any stage and review the progress of the research at the frequency they so desire.

12.0 PARTICIPANT RIGHTS AND CONFIDENTIALITY

12.1 Institutional Review Board (IRB) evaluation

This study and any amendments to it are subject to review by the MD Anderson Institutional Review Board before the commencement of any research activities. The MD Anderson IRB is registered with the Office for Human Research Protections and is compliant with all international, national and local guidelines pertaining to the conduct of research using human subjects.

12.2 Informed Consent

A signed IRB approved consent form will be obtained from the subject or, if the subject's lacks decision-making capacity, the subject's legally authorized representative will sign the consent form on their behalf. The consent form describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject or to the subject's legally authorized representative, and this fact will be documented in the subject's record.

12.3 Subject Confidentiality

Study confidentiality standards will be followed handling the data. No patient identifiable data will be shared outside of the research team. All computer entry for data analysis will be done using study identification numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, or the OHRP.

12.4 Study Modification/Discontinuation

The study may be modified or discontinued at any time by the IRB, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

13.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by MD Anderson. Any publications or presentations must be agreed with the co-principle investigators prior to publication.

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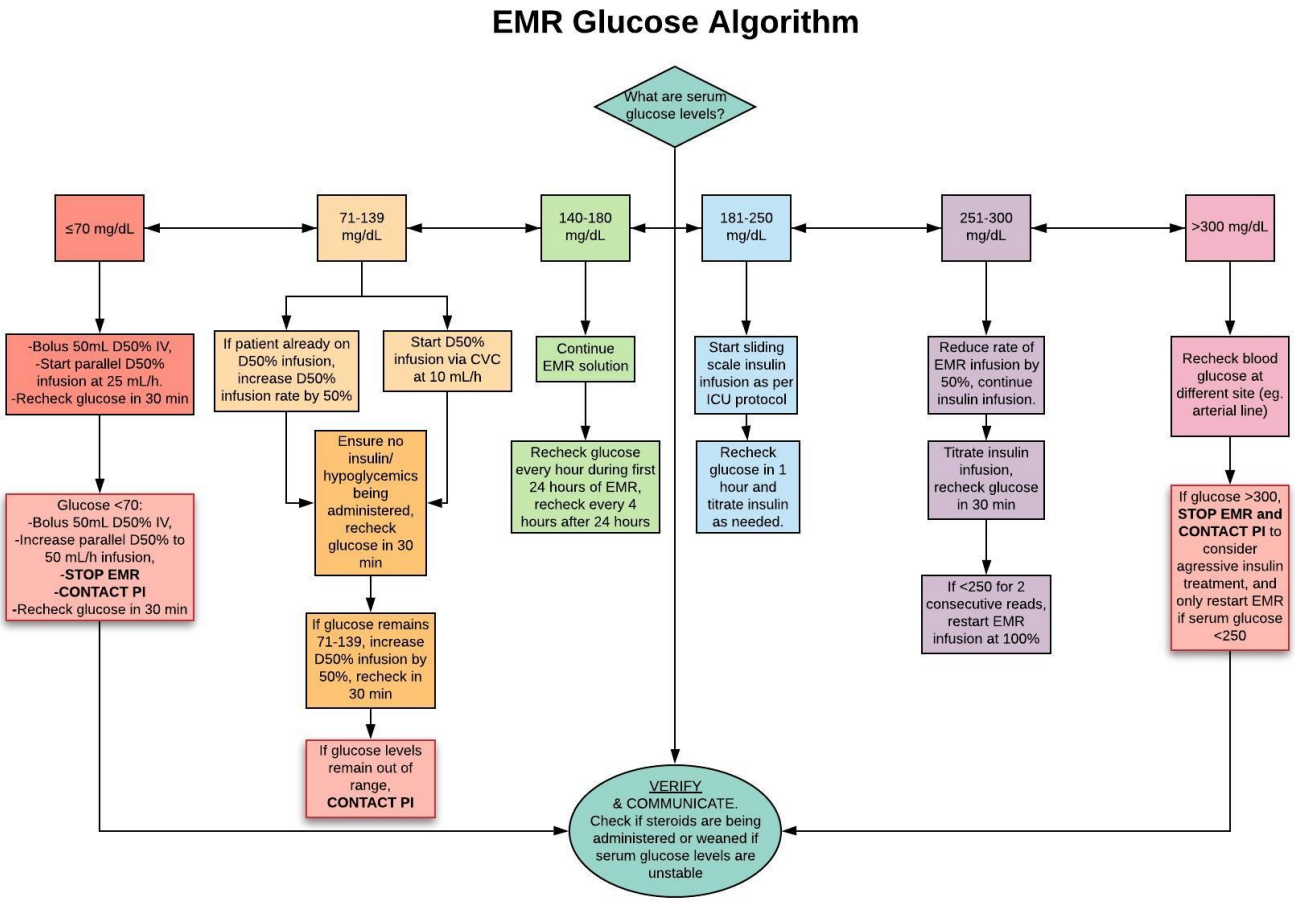
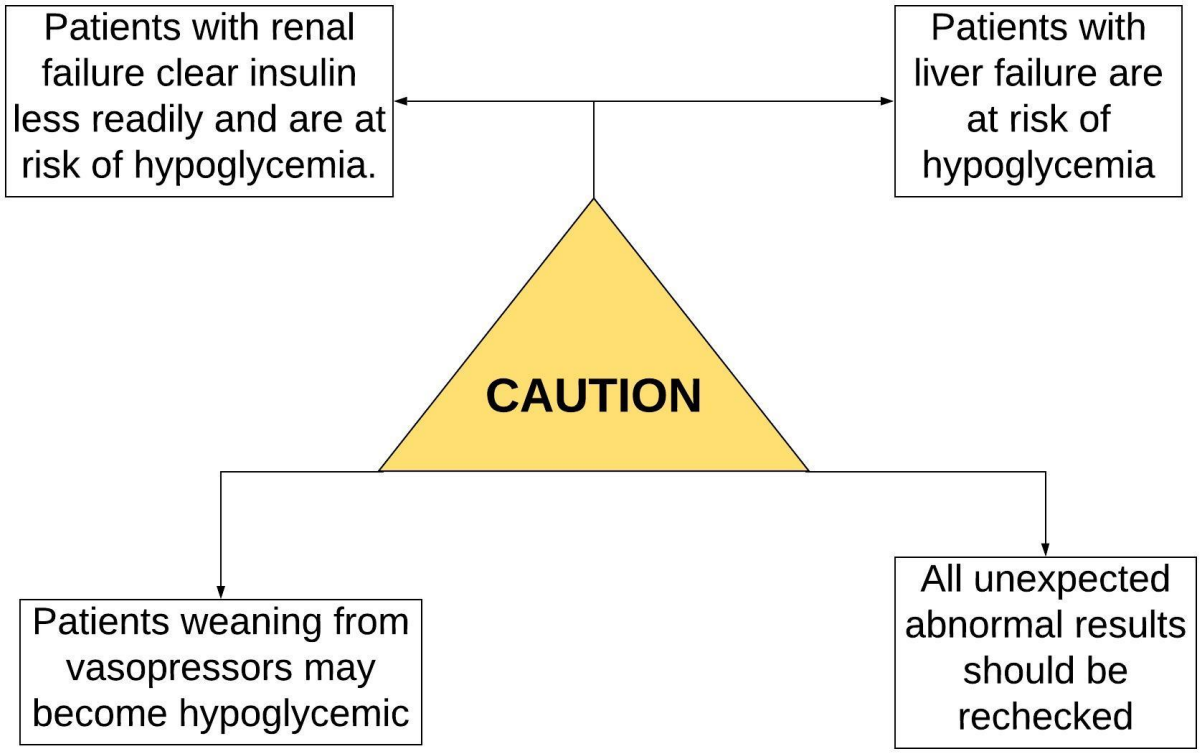
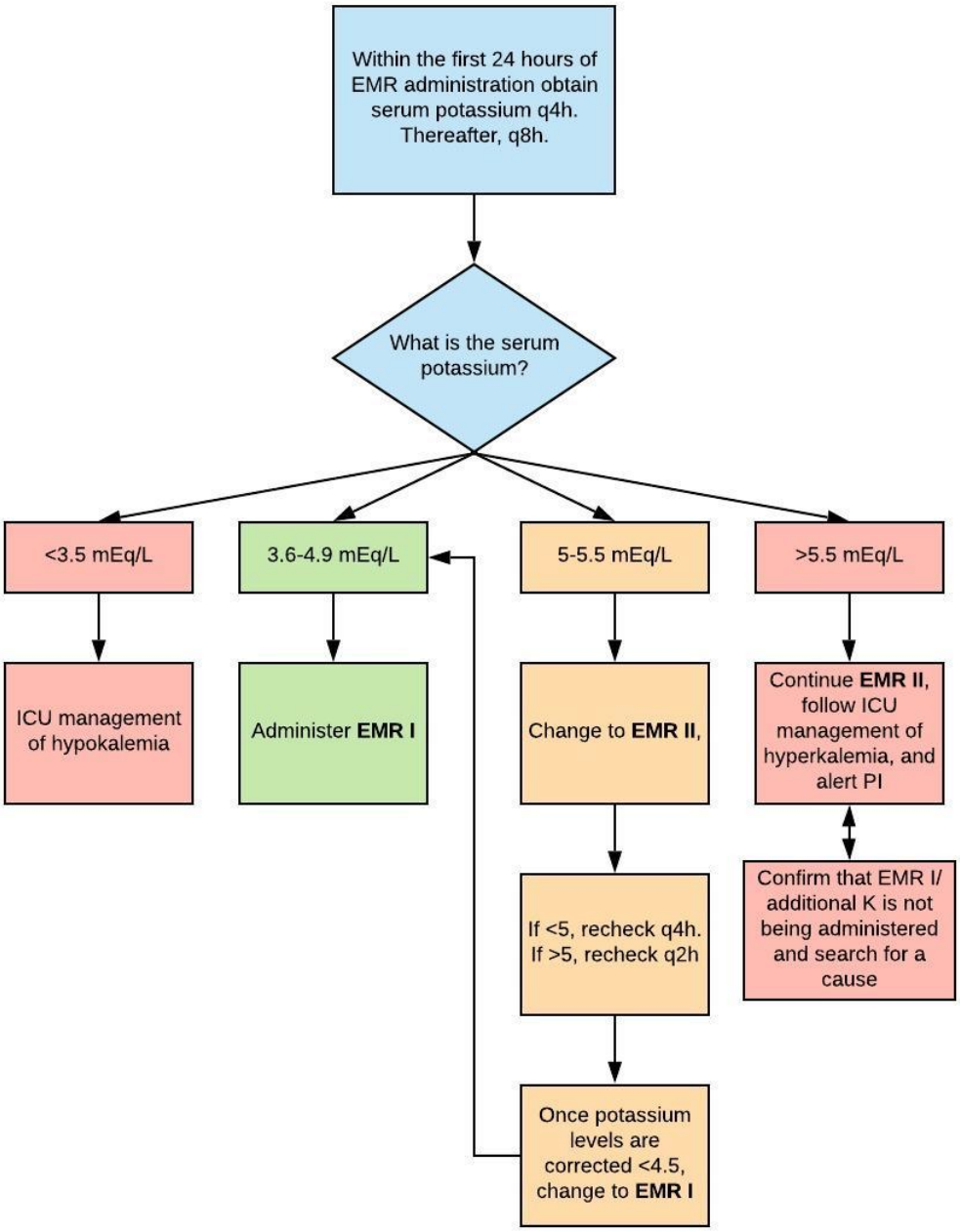
15. APPENDIX

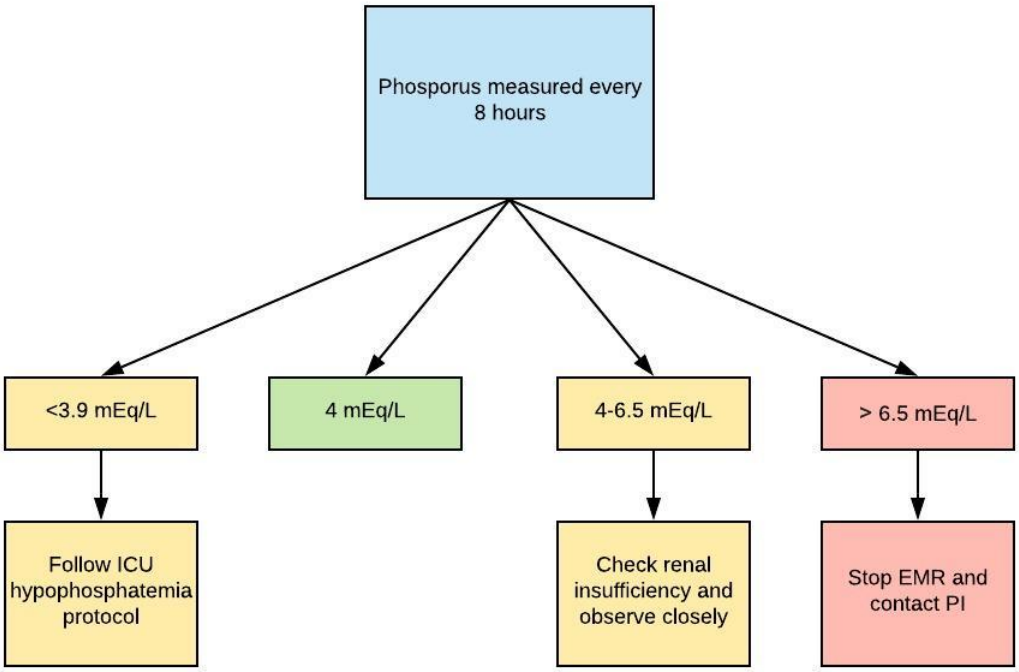

EMR Glucose Algorithm
What are serum glucose levels?
≤70 mg/dL
71-139 mg/dL
140-180 mg/dL
181-250 mg/dL
251-300 mg/dL
>300 mg/dL
-Bolus 50mL D50% IV, -Start parallel D50% infusion at 25 mL/h. -Recheck glucose in 30 min
If patient already on D50% infusion, increase D50% infusion rate by 50%
Start D50% infusion via CVC at 10 mL/h
Continue EMR solution
Start sliding scale insulin infusion as per ICU protocol
Reduce rate of EMR infusion by 50%, continue insulin infusion.
Recheck blood glucose at different site (eg. arterial line)
Glucose <70: -Bolus 50mL D50% IV, -Increase parallel D50% to 50 mL/h infusion, -STOP EMR -CONTACT PI -Recheck glucose in 30 min
Ensure no insulin/ hypoglycemics being administered, recheck glucose in 30 min
Recheck glucose every hour during first 24 hours of EMR, recheck every 4 hours after 24 hours
Recheck glucose in 1 hour and titrate insulin as needed.
Titrate insulin infusion, recheck glucose in 30 min
If glucose >300, STOP EMR and CONTACT PI to consider agressive insulin treatment, and only restart EMR if serum glucose <250
If glucose remains 71-139, increase D50% infusion by 50%, recheck in 30 min
If <250 for 2 consecutive reads, restart EMR infusion at 100%
If glucose levels remain out of range, CONTACT PI
VERIFY & COMMUNICATE. Check if steroids are being administered or weaned if serum glucose levels are unstable


Patients with renal failure clear insulin less readily and are at risk of hypoglycemia.
Patients with liver failure are at risk of hypoglycemia
CAUTION
Patients weaning from vasopressors may become hypoglycemic
All unexpected abnormal results should be rechecked

EMR Potassium Algorithm



EMR Phosphorus Algorithm



Sodium and Albumin Maintenance Fluid Algorithm