Unique Protocol ID:
PRO17010532

Brief Title:
Study of Early Enteral Dextrose in Sepsis (SEEDS)

Official Title:
Study of Early Enteral Dextrose in Sepsis

Secondary IDs:
5K23GM122069 [U.S. NIH Grant/Contract Award Number]

NCT03454087

Study of Early Enteral Dextrose in Sepsis (SEEDS): A Randomized-Controlled Clinical Trial

Principal Investigator:

Faraaz Ali Shah, MD
Assistant Professor of Medicine
University of Pittsburgh School of Medicine
Division of Pulmonary, Allergy, and Critical Care Medicine
UPMC Montefiore NW 628
3459 Fifth Avenue
Pittsburgh, PA 15213

Sub-Investigator:

Bryan McVerry, MD
Associate Professor of Medicine
University of Pittsburgh School of Medicine
Division of Pulmonary, Allergy, and Critical Care Medicine
UPMC Montefiore NW 628
3459 Fifth Avenue
Pittsburgh, PA 15213

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1.0 SYNOPSIS

Design	The study is a prospective randomized double-blinded placebo-controlled clinical trial to test the effects of early enteral dextrose as a therapeutic agent in critically ill patients with sepsis. Primary outcomes are differences in circulating plasma levels of the pro-inflammatory cytokine IL-6 to be tested 24 hours after randomization. Secondary outcomes include differences in circulating incretin hormone levels, differences in other pro-inflammatory cytokines including IL-1β and TNF-α, changes in intestinal microbial composition and function after intervention, glycemic control and variability as assessed by capillary blood glucose measurements and exogenous insulin dosing during the intervention period, and clinical outcomes including intensive care unit (ICU) and hospital stay and in-hospital mortality.
Duration	Study participants will be randomized within 48 hours of meeting sepsis criteria, undergo a 24 hour intervention and data collection period, and will be followed for clinical outcomes.
Sample Size	72 participants (36 patients in each arm)
Population	Men and women older than 18 years of age with evidence of sepsis admitted to the intensive care unit with an existing enteral feeding tube (or with imminent plans to place one).
Regimen	Participants will be randomized to either receive early low level enteral infusion of dextrose (intervention) or enteral free water (placebo control).

2.0 GLOSSARY

Cytokine: a cell-signaling protein released by immune cells in response to infection or injury

Enteral Nutrition: feeding or nutrients that are provided directly into the stomach or intestines

Glucagon-like peptide 1 (GLP-1): an incretin hormone released in the distal intestines and colon

Glucose-dependent insulinotropic peptide (GIP): an incretin hormone released in the proximal small intestine

Interleukin-1 beta (IL-1β): a pro-inflammatory cytokine involved in the pathogenesis of sepsis

Interleukin-6 (IL-6): a pro-inflammatory cytokine involved in the pathogenesis of sepsis

Incretin: an intestine-derived hormone released in response to enteral nutrients with a primary function of potentiating insulin release from the pancreas

Microbiome: the community of micro-organisms including all bacteria, viruses, and fungi that reside within animals and humans

Parenteral Nutrition: feeding or nutrients that is provided intravenously

Sepsis: a syndrome characterized by a pro-inflammatory response to infection

Tumor Necrosis Factor alpha (TNF-α): a pro-inflammatory cytokine involved in the pathogenesis of sepsis

3.0 HYPOTHESIS AND OBJECTIVES

3.1 Hypothesis

- Early enteral dextrose decreases inflammation, increases incretin hormones, prevents hyperglycemia, and preserves a healthy gut microbiome in critically ill septic patients

3.2 Primary objective

- To test the effects of early enteral dextrose on inflammation in critically ill septic patients as measured by the pro-inflammatory cytokine interleukin-6 (IL-6)

3.3 Secondary objectives

- To determine the effect of early enteral dextrose on glucose metabolism in critically ill septic patients
- To determine the effects of early enteral dextrose on the gut microbiome in critically ill septic patients.
- To determine the effects of early enteral dextrose on clinical outcomes in septic patients.

4.0 BACKGROUND AND SIGNIFICANCE

4.1 Background

4.1.1 The clinical problem of sepsis

Sepsis, a complex syndrome characterized by an overwhelming inflammatory response to infection, affects over 1 million Americans annually and is associated with substantial health care costs, in-hospital mortality or 20-30%, and significant long-term functional and neurocognitive deficits in survivors.[1-4] Exaggerated pro-inflammatory responses early in the course of sepsis have been associated with increased organ dysfunction and lower survival.[5]

Despite advances in our understanding of sepsis pathophysiology including inflammatory responses, endothelial dysfunction, and coagulation abnormalities, no specific therapies targeting the underlying mechanisms of sepsis have been successfully developed (ex- anti-IL-1 therapy, activated protein C).[6,7] Instead, the therapies that have demonstrated the greatest benefit in survival from sepsis have been the early use of broad spectrum antibiotics and resuscitative intravenous fluids. Sepsis management guidelines focus primarily on reducing delay to these life-saving therapies and providing additional supportive therapies including vasoactive medications and mechanical ventilation as necessary since late implementation is associated with worse outcomes.[8-10]

4.1.2 Hyperglycemia and inflammation in sepsis

Approximately 40% of patients in the intensive care unit develop hyperglycemia, and, of those, one third do not have pre-existing diabetes.[11] The development of hyperglycemia in previously non-diabetic patients with sepsis (referred to as stress hyperglycemia) is associated with increased organ dysfunction and mortality.[12-16] Stress hyperglycemia shares many characteristics with diabetes mellitus type 2: disrupted glucose homeostasis, impaired insulin sensitivity, inflammation, and counter-regulatory hormone imbalance. Once hyperglycemia develops, it further increases production of pro-inflammatory cytokines, suppresses neutrophil activity, and increases leukocyte adhesion and migration.[20-22] While

initial clinical trials in critically ill patients demonstrated mortality benefits with tight glycemic control using intravenous insulin,[17] subsequent trials have failed to replicate the same benefits with the use of insulin alone.[18,19] Better understanding of the mechanisms contributing to hyperglycemia during sepsis and newer strategies to prevent its development, as proposed in our study, rather than respond once hyperglycemia has occurred are needed to improve patient outcomes.

4.1.3 Nutritional support in sepsis

The provision of nutrition is a cornerstone of supportive therapy in critically-ill patients, yet uncertainty remains regarding the optimal timing, dose, and route of administration.[23-25] Sepsis represents a catabolic stress state and patients are frequently unable to consume any calories of their own volition due to their clinical condition and associated care. Nutritional support in the intensive care unit can be provided to septic patients by either the parenteral or enteral route. Recent clinical trials have highlighted potential harm with the early initiation of parenteral nutrition in critically ill patients, and, as such, current guidelines favor the provision of nutrition support via enteral route. The optimal timing and dose of enteral nutritional support during sepsis remains uncertain.[26,27] Current guidelines state[28]:

- "nutrition support therapy in the form of early enteral nutrition should be initiated within 24–48 hours in the critically ill patient" (Quality of Evidence: Very Low)
- "in the setting of hemodynamic compromise or instability, EN should be withheld until the patient is fully resuscitated and/or stable. Initiation/re-initiation of EN may be considered with caution in patients undergoing withdrawal of vasopressor support." (Expert consensus)

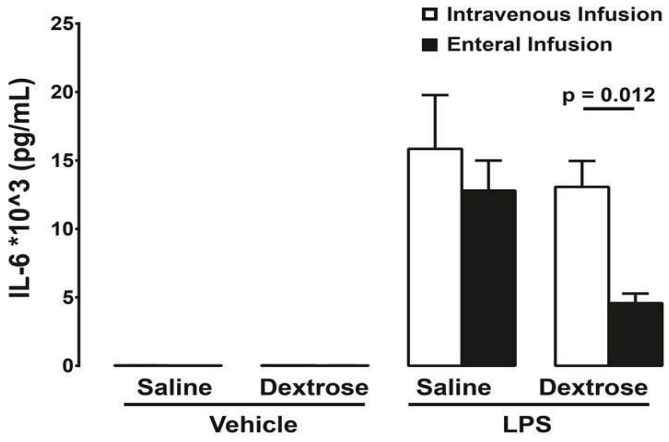
Nutrition is provided to septic patients with the goals of preserving lean body mass, preventing malnutrition, and facilitating recovery. Providing nutrition via enteral route is also believed to maintain the integrity of intestinal epithelium, prevent bacterial translocation, and even potentially modulate inflammatory responses.[28-31] Importantly the benefits of enteral nutrition are noted at low (so-called "trophic") levels of support.[32] As described in this proposed protocol, the benefits of low-level enteral support in the acute phase of sepsis may include activation of endogenous endocrine pathways to regulate glucose metabolism, modulation of the acute systemic inflammatory response, and preservation of the healthy intestinal microbiome. However, clinical evidence for the dose and timing of enteral nutrition is limited and guidelines are based largely on studies of low quality or expert consensus. Although current guidelines recommend early nutrition, within the first 24 to 48 hours in critically ill patients, clinical studies specifically in septic patients are lacking and the effects of early nutrition therapy on mechanistic pathways underlying illness and recovery remain unknown.

Despite the guideline recommendations for early initiation of enteral nutrition, clinical observations from the Acute Lung Injury Registry at UPMC Presbyterian Hospital show more than half of septic patients receive no enteral nutrition within the first 48 hours perhaps due the expert consensus recommendation to avoid enteral nutrition during periods of hemodynamic compromise. The SCCM guidelines base this recommendation in part on the theoretical risk of bowel ischemia, but this is a rare clinical condition that occurs in less than 1% of patients receiving enteral nutrition.[33] Furthermore, a retrospective propensity score based analysis of critically ill patients demonstrated that patients with hemodynamic instability requiring vasopressors not only tolerated enteral support but had a reduction in mortality compared to similar patients who did not receive enteral support.[34] The potential benefit of enteral nutrition in this retrospective study of critically ill patients highlights the need for further prospective clinical trials to better characterize the effects of early enteral support with a focus on understanding underlying physiology and mechanisms of disease.

4.1.4 Enteral glucose as an anti-inflammatory intervention in sepsis

Simple carbohydrates, such as dextrose, are readily digested and absorbed in the intestinal tract. Recent data from our lab suggest that low level enteral dextrose provision (~10% daily caloric requirements) early in the course of sepsis attenuates the systemic inflammatory response and improves glucose disposal in mice.

Figure 1: Enteral dextrose infusion in mice exposed to endotoxin (LPS) decreases circulating levels of pro-inflammatory cytokines such as IL-6

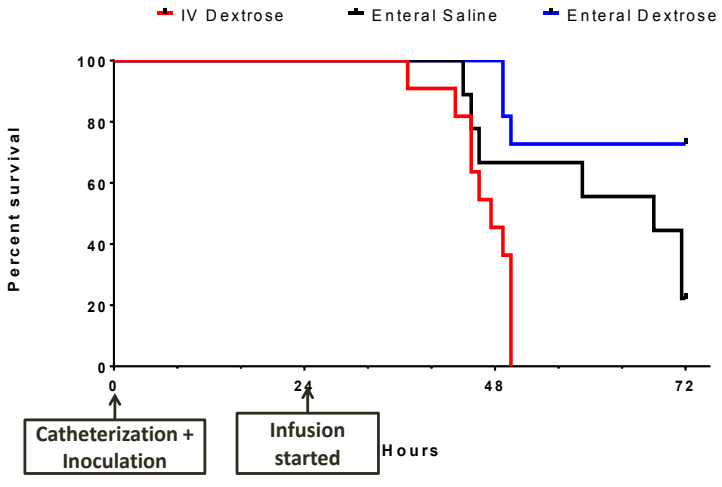


In our first set of experiments, we used intravascular endotoxin (LPS), a component of the cell wall of gram negative bacteria, administered to 10 week old C57BL/6J male mice to test the effects of intravenous (IV, parenteral) and intragastric (enteral) dextrose in the acute phase of sepsis.

Infusion of a low level of IV dextrose in endotoxemic mice significantly impaired glucose tolerance compared to either IV dextrose or LPS alone. Enteral dextrose infusion at an equivalent level of support, however, increased insulin secretion and preserved glucose disposal in endotoxemic mice. Furthermore, infusion of early enteral dextrose in endotoxemic mice was associated with improvement in mean arterial blood pressure and attenuated the systemic inflammatory response, evidenced by reduced levels of the pro-inflammatory cytokine IL-6 by 35-50% (Figure 1) compared to endotoxemic mice receiving saline infusion or intravenous (IV) dextrose. Similar trends were noted for the pro-inflammatory cytokines IL-1β and TNF-α. Thus, early enteral dextrose infusion in endotoxemic mice had beneficial effects on the systemic inflammatory response as well as glucose metabolism.

In a second set of experiments, we examined the effects of IV and enteral dextrose in a pneumonia model of sepsis. Mice were infected with *Klebsiella pneumoniae* and 24 hours after septic insult were randomized to receive (1) IV dextrose, (2) enteral dextrose, or (3) enteral saline. Infusion of IV dextrose in septic mice was associated with hyperglycemia and decreased survival. Mice receiving IV dextrose exhibited 100% mortality at 36 hr whereas 25% of septic mice receiving enteral saline survived to 72 hours. In contrast, infusion of enteral dextrose increased survival to ~70% at 72 hours (Figure 2). Mice receiving enteral dextrose also

Figure 2: Enteral dextrose improved survival at 72 hours in a Klebsiella pneumoniae septic mouse model. In contrast, intravenous dextrose infusion in this pneumonia model markedly worsened survival.



demonstrated improved systemic inflammation, blood pressure, and glucose control compared to mice receiving enteral saline.

Taken together, our data suggest that early enteral dextrose administration at low levels of caloric support attenuates systemic cytokine release, improves glucose tolerance, improves hemodynamics, and prevents mortality in the acute phase of sepsis in mice. Consequently, early enteral glucose provision could constitute a method to regulate the inflammatory response and metabolic function in patients with sepsis. However, this approach has not yet been explored in humans.

4.1.5 Activation of the incretin hormone axis in sepsis

Improvements in glucose homeostasis with provision of enteral dextrose in our model appear to be mediated through the incretin hormone pathway. The incretin hormones glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1) are secreted by intestinal cells in response to enteral administration of carbohydrates, proteins, and lipids, and improve glucose disposal by increasing insulin secretion and sensitivity and suppressing glucagon activity.[35,36] Relevant to our study, incretin hormones also demonstrate immunomodulatory effects in addition to effects on glycemic control. In animal studies, incretin hormones decrease systemic inflammation and cytokine release in chronic inflammatory models.[37-42] Incretin hormone receptors are present on macrophages in both mice and humans[43,44] and thus increased incretin release may have direct effects modulating acute inflammation in sepsis. Therapies targeting increased incretin activity, including incretin analogues and inhibitors of the dipeptidyl peptidase IV (DPP IV) protease, are FDA approved and widely used for the treatment of type 2 diabetes,[36,45,46] and clinical trials have studied the effect of GLP-1 analogues in critically ill patients.[47,48]

Our data suggest that activation of incretin hormone pathways plays a vital role in mediating the beneficial effects of enteral dextrose in endotoxemic mice.[49,50] Infusion of low-level continuous enteral dextrose in our model increases circulating levels of the incretin hormone GIP. When incretin signaling is blocked with pharmacologic agents, the beneficial effects of enteral dextrose on glucose tolerance, insulin secretion, and inflammation are lost. Blocking GIP, which is released more proximally in the intestine, appears to be more detrimental than blocking GLP-1 in our model. Further supporting the therapeutic potential of incretin hormones, exogenous infusions of GLP-1 and GIP were able to rescue glucose tolerance, improve insulin release, and decrease inflammation in endotoxemic mice receiving intravenous dextrose, the group of mice that had previously demonstrated the worst glucose tolerance. Thus, targeting the endogenous incretin hormone pathway in septic patients with the use of enteral dextrose infusion may provide a novel means of maintaining euglycemia and modulating the systemic inflammatory response while preventing the hypoglycemia that is often associated with exogenous insulin administration.

4.1.6 Host-microbiome interactions as a therapeutic target in sepsis

Recent research has highlighted the importance of understanding the complex interactions between the critically ill host and the endogenous micro-organisms in the human intestinal tract in the development and evolution of sepsis.[51,52] The advent of culture-independent techniques for the study of microbes with next-generation sequencing has revealed that humans harbor in their gastrointestinal tracts up to ~ 4 trillion bacteria, which collectively with viruses and fungi are referred to as the human microbiome.[53] In healthy individuals, the gastrointestinal microbiome plays important commensal homeostatic roles, including nutrient metabolism, hormone and vitamin biosynthesis, immune response modulation, preservation of mucosal integrity and colonization resistance against invasive pathogens.[54] Dysbiosis or disruption of a “healthy” gut microbiome is associated with a loss of commensal microbiota resulting in increased susceptibility to pathogens and dysregulated immune responses.[55]

The gut microbiome in sepsis is severely disturbed by effects of the pathophysiologic processes of sepsis (e.g. gut hypoperfusion, endogenous catecholamines, systemic hyperglycemia etc.) but also from critical care interventions, including systemic antibiotics, gastric acid suppression, and nutrition delivery interruptions.[51,52] The dysbiotic gut microbiome is now considered a central orchestrator in sepsis (*gut-origin sepsis*), both in triggering pathogen invasion (*microbial translocation*) and in mediating distal end-organ damage by inflammatory mediators (*gut-lymph hypothesis*).[56,57] Interactions at the interface between the intestinal mucosal layer and the indigenous microbiome result in barrier integrity failure on the epithelial side, and in pathogen expansion on the micro-organism end that dominate their respective microbial communities.[58] Restoration of a healthy gut microbiome through early enteral nutrition is emerging as an appealing therapeutic goal in sepsis,[51,52] but the effects of different types of enteral nutrition on the gut microbiome have not been well-defined. Given that commensal microbiota depend on host nutrition for their survival,[59] early enteral dextrose in septic patients may assist may promote maintenance of a healthy gut microbiome in sepsis.

At the same time, dextrose administered in the stomach or duodenum is expected to be completely absorbed in the jejunum, and thus, we do not anticipate that our experimental arm intervention will have measurable effects in the colonic microbiota. However, little is known about the composition and evolution of gastric/proximal intestinal microbiome in sepsis, and gastric acid suppression and dysmotility from sedatives are well known to promote bacterial growth in critically-ill patients.[51] Given that the stomach forms a reservoir for bacterial aspiration in the upper and lower airways of critically-ill patients with downstream infectious complications, we will comprehensively examine the microbiome profiles of different parts of the upper aerodigestive tract (oral swabs, tracheal aspirates and gastric aspirates) to assess for a potential impact of enteral dextrose on host microbial communities. We will also examine stool samples or rectal swabs as proxies for the assessment of the colonic microbiome to examine its relatedness to the aerodigestive tract microbiota and possible impact of our intervention.

4.2 Significance

4.2.1 The significance of an interventional trial of early enteral dextrose

Current clinical guidelines suggest the early initiation of enteral tube feed formulations within the first 24-48 hours of intensive care unit admission, but evidence is lacking on the physiologic and mechanistic effects of these interventions in the acute phase of sepsis. Results from our animal models suggest that early administration of enteral dextrose at low levels has potential benefits on the systemic inflammatory response and on glucose metabolism while also providing some caloric support. With this study, we propose an interventional trial to test the effects of early enteral dextrose on inflammation and glycemic control in septic patients. Our study utilizes a low-cost intervention during the most acute phase of illness, a time when most patients are not receiving any support by the enteral route. Our study will provide important information on the effects of early enteral nutrients on inflammatory and endocrine pathways as well as on the gut microbiome. Our study has important implications for clinical care. Results consistent with our animal models that demonstrate enteral dextrose improves inflammation and glycemic control in septic patients would support a larger interventional trial testing the effect of very early enteral nutrition, similar to early antibiotics or resuscitative fluids, in septic patients. Thus, the results of this clinical trial will be vital in informing future studies of the effects of enteral nutrients in critically ill patients.

5.0 RESEARCH DESIGN AND METHODS

This study is a single-center, prospective, double-blinded, randomized placebo-controlled clinical trial to determine the therapeutic effects of early enteral dextrose in critically ill patients admitted with sepsis. This trial will have an interventional arm in which participants receive a low level enteral dextrose infusion and a placebo control arm in which participants will receive an enteral free water infusion. The primary outcome of this study is the extent of systemic inflammation as determined by circulating levels of the pro-inflammatory cytokines IL-6 measured at the end of the intervention. Secondary outcomes include measures of glycemic control by capillary blood glucose; measures of insulin, C-peptide, and the incretin hormones glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1); measures of other pro-inflammatory cytokines including IL-1β and TNF-α; determination of the composition and function of the aerodigestive tract and colonic microbiome; and clinical measures (including incidence of emesis, ICU length of stay, hospital length of stay, mortality).

5.1 General characteristics

We will include patients 18 years or older diagnosed with sepsis at the time of admission to an intensive care unit (ICU) at UPMC Presbyterian, UPMC Montefiore, UPMC Shadyside, or UPMC McKeesport hospitals. Etiology of sepsis can include any organ system (e.g. pneumonia, urinary tract infection, severe soft tissue infection, etc.) as long as the type of infection does not preclude use of the gastrointestinal tract for nutrition and medication administration (e.g. peritonitis).

5.1.1 Inclusion criteria

1. Adults aged 18 years and older admitted to an ICU at UPMC Presbyterian, UPMC Montefiore, UPMC Shadyside, or UPMC McKeesport.
2. New presentation of sepsis characterized by a confirmed or suspected infection, with an acute increase from baseline in a modified Sepsis-Related Organ Failure Assessment (SOFA) score of greater than or equal to 2 points (Appendix 11.1). If baseline values are unknown, baseline SOFA score of 0 will be assumed.
3. Available enteral access defined by: (1) an existing nasogastric or orogastric tube, (2) plans to place a nasogastric or orogastric tube, or (3) an existing percutaneous endoscopic gastrostomy (PEG) tube.
4. Less than 48 hours since meeting criteria for sepsis.
5. Expected to stay at least 24 hours in the ICU.

5.1.2 Exclusion Criteria

1. Pre-existing continuous enteral tube feed use prior to study entry.
2. Diabetic ketoacidosis or diabetic hyperosmolar hyperglycemic syndrome.
3. Previously enrolled in this study within the same hospital admission.
4. ICU physician request to exclude patient based on clinical assessment or contraindication to enteral feeding.

5.2 Recruitment and screening procedures

This is a single center RCT with recruitment to be performed in the ICUs of UPMC Presbyterian, UPMC Montefiore, UPMC Shadyside, and UPMC McKeesport hospitals.

5.2.1 Initial screening (pre-consent):

The principal investigators will introduce the study to ICU physicians in the In-Service Session before the start of the study and in ongoing staff meetings, grand rounds, and in any other ICU meetings. The study procedures, eligibility criteria, and study window will be explained. With this knowledge, the clinicians in the ICU will be able to assist in identifying potential subjects and communicate this to the study team for possible enrollment.

Screening evaluations to determine eligibility will be conducted daily by the study team based on chart review of documentation for new patients being admitted to the ICU with a diagnosis of sepsis/septic shock. Initial assessment will rely on review of admitting diagnoses as recorded by treating physicians, admitting medical documentation, and lab and imaging results to assess possible sources of infection, presence or absence of organ dysfunction, and use of invasive mechanical ventilation. Initial screen for inclusion/exclusion will based on chart review. For those individuals meeting criteria for enrollment, the subject or his/her legally authorized representative (LAR) will be contacted by a member of the clinical ICU team and offered the opportunity to participate in the clinical trial. This will avoid "cold calling" coercion that could occur if direct contact by research team members was the initial method of assessing willingness to enroll. If that agreement is obtained, a member of the research team will preliminarily introduce the study to the subject or LAR. At that time, a member of the study team will review other inclusion and exclusion criteria with the LAR to assess eligibility.

5.2.2 Consenting process:

The PI or a designated physician co-investigator will follow-up the preliminary discussion to answer any additional questions and obtain written authorization and consent for participation from subjects or their LAR. The investigator or a co-investigator will discuss the nature of the research study and study procedures with the participant or LAR inclusive of the risks and potential benefits of study participation. In cases where the LAR is not present in the hospital, the study will be discussed over the telephone. If the LAR agrees, the consent form (ICF) will be e-mailed or faxed to the number provided by the LAR. No research activities can start before the signed document is received from the LAR. The PI or any physician investigator who discussed the study by phone must sign, date, and time the consent form when it is received (date/time of receipt, not the date of discussion).

Pennsylvania law defines no specific surrogate decision maker for health care. However, if consent is obtained from a surrogate decision maker, the basis for establishing his/her identity should be one of the following: Durable Power of Attorney for Health Care, next of kin, or following lines of sanguinity in order of relationship (i.e., court appointed guardian, spouse, natural or adoptive parent, adult child, adult sibling, any other available adult relative related through blood or marriage known and documented to have made decisions for the subject in prior health care settings).

Rights as a research subject will be explained and ample time for the participant or LAR to review the consent document prior to obtaining written signature of informed consent will be given. After this detailed discussion of the study and conclusion of any questions, the study investigator and/or co-investigator will obtain informed consent with documentation of the consenting process, prior to beginning any research activities. All participants and LARs will be informed of their right to withdraw the patients from study participation at any time. Additionally, enrolled patients will have the right to withdraw from the study once decision-making capacity is regained if the patients recover quickly from their acute illness (e.g. with early liberation from the ventilator while the patient is still in the study).

After consent, the pre-entry procedures include those listed in Section 5.4.2. Pre-entry evaluations must be completed within 12 hours prior to study entry.

5.2.3 Baseline evaluation and randomization:

If pre-entry evaluation is acceptable, the participant will be enrolled in the study and undergo baseline testing included in Section 5.4.3. At that point, the participants will be randomized to interventional and placebo control arms. Enrollment into interventional and placebo arms will be stratified at one level by the presence or absence of pre-existing self-reported diabetes mellitus utilizing separate randomization tables. The University of Pittsburgh Medical Center Investigational Drug Service (UPMC-IDS) will be responsible for randomization, blinding, and providing the study infusion at the bedside to the clinical team.

5.2.4 Blinding:

The UPMC-IDS will dispense investigational infusions that conceal infusion contents with an opaque cover, thus the treating ICU clinicians, nursing staff, and study investigators will be blinded to group allocation. Group allocation will remain concealed until blinding is broken after final data analysis is completed.

5.3 Study treatment

5.3.1 Treatment arms

At study entry, the participant will be randomized into an interventional arm that will receive an enteral dextrose infusion or a control arm that will receive enteral free water placebo.

1a: Enteral dextrose infusion: A standard solution of 50% Dextrose (0.85 kcal/mL) will be initiated within 48 hours of meeting sepsis criteria and will be infused at 10 mL per hour for 24 hours. For a participant that would have an expected daily caloric requirement of 2000 kcal per day, enteral dextrose infusion would deliver approximately 20% of the daily caloric need. As a reference, the enteral tube formulation Jevity 1.2 provides 1.2 kcal/mL and is often infused at 10 mL per hour upon initiation of enteral tube feeding. Thus the volume and level of delivered calories in the study group will be similar to the amount delivered in low level enteral tube feed formulations.

1b. Placebo control: Patients in the placebo control arm will receive enteral free water at a rate of 10 mL per hour following randomization to control for the effects of an enteral infusion. Although these participants will not receive any enteral calories, a retrospective review of critically ill patients admitted to the Acute Lung Injury Registry at the University of Pittsburgh with a patient population similar to the patients we will enroll to this study revealed that (1) less than 10% of patients receive any enteral infusions in the first 48 hours of ICU admission, (2) greater than 50% of calories are delivered in intravenous infusions rather than the enteral route, and (3) total level of caloric support in the absence of enteral feeding is approximately 10-15% of daily caloric needs.

5.3.2 Study drug

Dextrose infusion: 50% Dextrose solution will be infused via an oro/nasogastric tube by ICU nursing personnel per standard practices. The solution will be prepared and provided by the IDS and will be infused at a rate of 10 mL per hour for 24hr through a standard enteral nutrition pump. No additional water flushing will be necessary. Interruption/discontinuation of the infusion will be at the discretion of the treating physicians. Symptoms/signs of intolerance including vomiting or aspiration will be considered an adverse event. Gastric residuals will not be checked monitored in this study as they are not required per current critical care guidelines.[28]

5.3.3 Study duration

Study treatment will be administered for a total of 24 hrs. Subsequent decisions for type/rate of enteral nutrition following the 24hrs will be at the discretion of the medical ICU team.

5.3.4 Study product formulation and storage

50% Dextrose solution and free water solution will be stored at room temperature in a dry place

5.3.5 Pharmacy role

The UPMC-IDS will be responsible for (1) preparation of 50% Dextrose and free water solutions, (2) randomization of participants into intervention and placebo groups, and (3) distribution of intervention solutions such that clinical team and investigators are blinded to group allocation.

5.4 Study exams and procedures

Study exams are described below and in Table 5.1.

5.4.1 Initial screening (pre-consent)

- Review of admission documentation in ICU and assessment of eligibility.

5.4.2 Pre-entry evaluation and consent

- Clinical assessment
- Medical history
- Informed consent

5.4.3 Baseline testing and randomization

- Baseline clinical variable recording
- Pre-intervention capillary blood glucose measurement
- Initial research blood draw (up to 4 hours prior to the start of infusion)
- Aerodigestive tract samples for microbiome analyses (up to 4 hours prior to the start of infusion):
    - Oral swab
    - Tracheal aspirate (if the patient is on mechanical ventilation)
    - Gastric aspirate
- Colonic tract samples for microbiome analyses (up to 4 hours prior to the start of infusion)
    - Rectal swab
    - Stool sample (if available)

5.4.4 Study period

- Initiation of study interventions as per protocol for 24 hrs
- Hemodynamic monitoring per ICU protocol
- Capillary blood glucose approximately every 6 hours

5.4.5 Mid-intervention assessment

- Clinical assessment by study team member to monitor status and tolerance to infusion to be performed 12 hours after the start of infusion +/- 4 hours

5.4.6 Intervention conclusion – End of infusion period

- Second research blood draw (up to 2 hours prior to the end of infusion or ½ hour after)
- Repeat aerodigestive tract samples for microbiome analyses (+/- 2 hours to the end of infusion):
    - Oral swab
    - Tracheal aspirate (if the patient is on mechanical ventilation)
    - Gastric aspirate
- Repeat colonic tract samples for microbiome analyses (+/- 2 hours to the end of infusion)
    - Rectal swab
    - Stool sample (if available)

5.4.7 Day 7 testing and procedures

- Review of electronic medical record for length of stay and in hospital mortality
- For patients still within the hospital, repeat aerodigestive and colonic tract samples for microbiome analyses (+/- 1 day)
    - Oral swab
    - Tracheal aspirate (if the patient is on mechanical ventilation)
    - Gastric aspirate (if a gastric/enteric tube remains in place)
    - Rectal swab
    - Stool sample (if available)

5.4.8 Day 30 testing and procedures

- Review of electronic medical record for clinical variables including length of stay and in hospital mortality

Table 5-1. Schedule of Procedures

	Pre-Entry	Screen	Baseline	Study Period	12 hrs	24 hrs	Day 7	Day 30
Documentation of Sepsis	X							
Medical Review for Inclusion/Exclusion	X	X						
Informed Consent		X						
Baseline Characteristic Measurement		X	X					
Clinical Assessment			X		X	X		
Blood Glucose Measurement			X	X				
Research Infusion				X				
Research Blood Draw			X			X		
Microbiome sampling			X			X	X	
Review of Electronic Medical Record			X			X	X	X

6.0 EXPERIMENTAL PROCEDURES

6.1 Screening

The screening form will be completed by study personnel. Diagnosis of sepsis will be based on review of medical chart by criteria in 5.1.1.

6.2 Clinical assessment

A clinical assessment will be performed at enrollment by a study physician and subsequently by study personnel at designated time points, to include review of clinical diagnoses, physical exam findings, microbiological, clinical, and physiological and laboratory information.

6.3 Study procedures

6.3.1 Capillary blood glucose measurement

Blood glucose will be monitored by capillary blood measurement for the 24 hour intervention period no less frequently than every six hours starting at the time of randomization in both usual care and intervention arms. Capillary blood glucose measurements in the ICU are obtained by fingerstick utilizing less than 10 microliters of blood and do not require an additional blood draw. Current sepsis guidelines recommend preventing hyperglycemia as part of best care practices but variability remains in glycemic monitoring among critically ill patients.[10] We will ensure blood glucose is checked routinely at least every 6 hours in patients enrolled in our study. If capillary blood glucoses are already ordered as part of the medical care in the ICU, these glucose checks will be utilized for study purposes. More frequent glycemic monitoring may be utilized as part of the care dictated by the medical ICU team and will not disqualify patient from the study.

6.3.2 Research blood draws

Blood will be drawn for plasma and serum at two time points (a) at the time of randomization and (b) after the completion of the intervention period. Approximately 10 mL of blood will be drawn each time either by venipuncture or by drawing blood from existing indwelling catheters (central venous lines or arterial lines) by the patient's bedside nurse. Blood will be drawn into several tubes including serum, EDTA, and BD P800 collection tubes.

6.3.3 Microbiome sampling

Aerodigestive and colonic tract samples will be collected as follows at baseline, at the end of the infusion period, and at day 7:

Oral swabs: A swab will be gently rubbed on the tongue dorsum, the hard palate, the buccal mucosa, and the gingiva. Specimens will be secured in a sterile tube and stored in a locked freezer until bacterial nucleic acid extraction procedures. The procedure will be performed twice in order to obtain samples for both bacterial DNA and RNA extractions.

Tracheal aspirates: Five to 10 ml of tracheal aspirates will be collected using a sterile catheter during endotracheal tube suctioning if the patient remains on mechanical ventilation for the study period. Samples are collected according to standardized protocols by trained respiratory therapists. Such samples are typically collected as part of routine clinical care, but are usually discarded. Samples will be transported immediately in wet ice. Sample aliquots are stored at -80^{o}C in a locked freezer until bacterial nucleic extraction procedures.

Gastric aspirates: Ten to 20 ml of gastric aspirates will be collected through the existing feeding tube. A first sample of gastric aspirate will be collected prior to initiation of experimental infusions. If no gastric aspirate obtained, then instillation of approximately 20 mL of water through the feeding tube will be performed for suctioning an adequate amount of gastric aspirate, which will be placed in a sterile specimen cup and then stored at -80^{o}C in a locked freezer until bacterial nucleic acid extraction procedures. At 24 hr, we will obtain a gastric aspirate of 10-20 mL, again stored in similar fashion. At day 7, we will obtain a similar specimen if a feeding tube is still in place and the patient remains in the ICU.

Stool samples: If stool is available, a portion of the sample will be taken and stored in a sterile specimen cup, as above.

Rectal swabs: A swab will be gently advanced through the anal sphincter in the anal vault and gently rubbed on the rectal mucosa. Specimens will be secured in a sterile tube and stored at -80^{o}C in a locked freezer until bacterial nucleic acid extraction procedures. The procedure will be performed twice in order to obtain samples for both bacterial DNA and RNA extractions.

7.0 CLINICAL MANAGEMENT ISSUES

7.1 Definition of adverse events

An adverse event will be defined as any unintended and unfavorable symptom or outcome during the 24 hour intervention period.

7.1.1 Vomiting

Vomiting in study and use of anti-emetic agents in participants will be recorded and incidence will be compared in intervention and placebo groups. In the event of emesis, enteral study infusion will be temporarily discontinued and will be restarted per ICU management guidelines for enteral infusions. Gastric residuals will not be monitored in this study.

7.1.2 Diabetic ketoacidosis and hyperglycemia hyperosmolar syndrome (HHS)

The development of either diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome during the intervention period of this study will prompt cessation of enteral infusion to allow for the strict control of caloric delivery required in the treatment of these syndromes.

7.1.3 Ischemic bowel

Ischemic bowel is a rare and potentially serious complication associated with enteral feeding occurring in less than 1% of patients.[33] Ischemic bowel presents with intolerance to enteral feedings manifested by emesis, abdominal pain, or bloating and is characterized by ischemia or necrosis of the intestinal tissue thought to be related to diversion of blood flow to intestinal blood vessels in response to

enteral nutrients during periods of hypotension and shock. By utilizing only dextrose this risk is expected to be minimal.

7.2 Reportable severe adverse events

Critically ill septic patients represent a population in whom life-threatening multi-organ dysfunction and a high rate of untoward medical events are commonly seen routinely during their clinical course as part of their presenting medical condition. In an effort to document only clinically-relevant untoward medical events that have a greater likelihood of being study related, study endpoints (including level of glycemic control, incidence of emesis, incidence of hypotension) and certain pre-specified expected events for critically ill septic patients (see Appendix 11.3) will not be reported as serious adverse events if they occur during the 24-hour intervention period. Reportable serious adverse events (defined as fatal or immediately life-threatening or those that are permanently disabling) that are unexpected and are suspected to be related to study interventions will be disclosed within 24 hours to the IRB.

7.3 Monitoring for adverse events

Participants will be assessed for adverse events by both the study investigators and by the treating ICU team during 24 hours of study intervention. Record of adverse events in the usual care and intervention arms will be made available to the DSMB.

7.4 Indications for study discontinuation

The following indications will be criteria for study discontinuation:

- Request by participant.
- Serious adverse event related to intervention.
- Medical need to hold further enteral infusions including impending intra-abdominal surgery.
- Clinical evaluation by either the investigator or ICU physician that continuation of the intervention would be unsafe including blood glucose greater than 500 mg/dL, severe ileus, or development of severe abdominal pain or emesis related to study intervention.
- Discretion of the investigator.
- Decision by data safety and monitoring board to discontinue enrollment.

7.5 Protocol adherence

Participants in both the placebo and intervention group will be assessed to determine the (1) the number of interruptions in enteral study infusion and (2) total amount of time that enteral study infusion was successfully administered during the 24 hour intervention period.

7.6 Clinical nutrition management

The clinical ICU team will be encouraged by study investigators to avoid the use of dextrose-containing intravenous infusions and enteral tube feed formulations during the 24 hour intervention period. Study infusions will not be given concomitantly with enteral tube feeds. If enteral tube feeds are started during the intervention period, the study infusion will be stopped and the total time the study infusion was delivered will be recorded. Research specimens will still be collected for these participants. After the 24 hour intervention period, further nutrition support (if any) will be at the discretion of the clinical ICU team.

7.7 Data Safety and Monitoring Plan (DSMP)

The data safety and monitoring plan for this research study will be conducted by a local Data Safety and Monitoring Board (DSMB) that will be created to review this study. The individuals to be chosen for the DSMB will be free from financial and academic conflicts, will not include study investigators, and will have the expertise required to understand and identify any issues that would arise with the conduct of a clinical trial in critically ill patients.

The DSMB will meet every six months to review: (1) trial performance with a focus on recruitment, (2) protocol adherence, (3) completeness of data management, and (4) trial safety.

Furthermore, monthly meetings for the monitoring of individual case review will be conducted by the Principal Investigators and research team with review of the following items: recruitment, enrollment, retention, all adverse events, unanticipated problems, withdrawals and any breaches of confidentiality. A regular review of accrued data will be done to ensure data integrity and validity and to ensure that there is no change in the risk to benefit ratio of the study. Any serious or unexpected adverse events, unexpected problems that involve risk to the participants or others, or breaches of confidentiality will be reported to the Institute Review Board (IRB) in compliance with IRB Policies and Procedures. Reporting to the NIH will be the responsibility of the Principal Investigator and the research team.

All Serious Adverse Event reporting to the IRB will occur within 24 hours of notification to the Principal Investigator and or research team for appropriate action and file reporting in accordance with the IRB's stated policy for reporting adverse events. If an unexpected adverse event occurs, the investigators will re-assess the risk/benefit ratio of the study and submit any modifications deemed necessary to the IRB for approval. At the time of the IRB renewal the PI will submit in writing the information about the frequency of the monitoring, the dates that the monthly meetings took place, any external factors or relevant information that might have an impact on the safety or ethics of the study, and final recommendations related to the continuation, changing, or termination of the study.

7.7.1 Required education in the protection of human research participants

Most participants are expected to have cognitive impairment at some time during the study given that study population was specifically selected to be high risk for delirium and long-term cognitive impairment due to sepsis. This vulnerable population cannot be substituted since these forms of cognitive impairment are the focus of our investigation.

All participants who are enrolled when cognitively impaired will be given the opportunity to consent to further participation (or to withdraw) once they regain decision making capacity. Both participants and their authorized representatives can choose to withdraw the participant from the study at any time.

All principal and co-investigators listed on Institutional Review Board-approved protocols at University of Pittsburgh are required to participate in a course entitled "The Education and Certification Program in Research & Practice Fundamentals (RPF)". This web-based tutorial is a requirement of the IRB for protocol submission.

The University of Pittsburgh requires registration of all principal and co-investigators on the Pitt CITI Access Portal. The Collaborative Institutional Training Initiative (CITI) is an organization whose goal is to develop and distribute high quality, peer reviewed educational resources for the research investigators. CITI training programs have become the de facto standard to meet Responsible Conduct of Research (RCR) and Human Subjects Research training requirements at most institutions in the United States. Certifications in Responsible Conduct of Research and Human Subjects Research (either biomedical or social/behavioral) are required for individuals conducting research projects involving human subjects. Further information on training required at the University of Pittsburgh may be found at the following website: http://www.rcco.pitt.edu/ResearchTrainingRequirements.htm.

8.0 DATA MANAGEMENT AND TRACKING

Data collected during this randomized clinical trial will be stored on an electronic database on the password-protected UPMC network. Any printed documents containing relevant data from the clinical trial will be stored in a locked cabinet in the office of Dr. Shah in UPMC Montefiore Hospital. Dr. Shah will be responsible for monitoring the security and confidentiality of the database and associated protected health information including participant name, date of birth, and medical record number on a monthly basis. Quality control for the database will be performed with range checks and inspection of any outlier values by Dr. Shah or Dr. McVerry.

The electronic medical record of participants will be accessed to obtain patient demographics, hemodynamic parameters, and laboratory and imaging results relevant to determining the severity of illness. The only individuals who will access identifiable medical record information are those who already have (or will have been given) access to the identifiable medical records, granted by the privacy office, by means of their job responsibilities. Dr. Shah and Dr. McVerry have legitimate access to these medical records as part of their clinical responsibilities.

9.0 DATA COLLECTION AND STATISTICAL CONSIDERATIONS

9.1 Sample size and power calculation

Prior published estimates of cytokine levels in septic patients at 24 hours,[61] suggest that recruitment of 7 patients in each group will provide 90% power to detect a 15% difference in IL-6 with an alpha error of 0.05 (Table 9.1). However, we will need to consider the risk of unbalanced baseline characteristics in our sample and allow for dropouts as well. Therefore, 36 patients will be enrolled in each group, which will provide greater than 90% power to detect 15% difference in IL-6.[62] In our septic mouse model, early initiation of enteral dextrose reduced levels of IL-6 by a much larger amount (~40%) than we are currently powering our clinical trial.

Table 9.1: Per Group Estimates for Detecting Differences in Circulating Cytokines

Difference	Power	IL-6
15%	80%	6
15%	90%	7
20%	80%	4
20%	90%	5

9.2 Proposed statistical analysis

Primary statistical analysis comparing levels of pro-inflammatory cytokines will be determined by t-test (or non-parametric test if indicated) by intention-to-treat analysis. Differences in secondary continuous outcome variables between intervention and control groups will be determined by t-test or non-parametric test as appropriate. Differences in dichotomous secondary outcomes (development of

hyperglycemia, in-hospital mortality, etc.) will be determined by chi-squared analysis or Fisher's exact test as appropriate.

10.0 COSTS AND PAYMENTS

10.1 Research study payments

No research payment will be provided to participants or health care proxys in this study. When principal investigators are unavailable, study co-investigators will aide in screening, consenting, and enrolling participants and will be compensated $20 for research activities. Principal investigators will not be reimbursed for research activities.

11.0 APPENDIX

11.1 Modified Sepsis-Related Organ Failure Assessment (SOFA) score

Adapted from Singer et al,[62] modified to exclude assessments of liver function

	Score				
Organ System	**0**	**1**	**2**	**3**	**4**
Respiratory					
PaO2/FiO2	Greater than or equal to 400	Less than 400 but greater than or equal to 300	Less than 300 but greater than or equal to 200	Less than 200 but greater than 100, with respiratory support	Less than 100, with respiratory support
Coagulation					
Platelet count	Greater than or equal to 150,0000	Less than 150,000 but greater than or equal to 100,000	Less than 100,000 but greater than or equal to 50,000	Less than 50,000 but greater than or equal to 20,000	Less than 20,000
Cardiovascular					
Blood pressure	Mean arterial pressure greater than or equal to 70 mmHg	Mean arterial pressure less than 70 mmHg but not requiring vasopressor therapy	Requiring vasopressor therapy with dopamine less than 5 µg/kg/min for at least 1 hour or dobutamine at any dose	Requiring vasopressor therapy with either dopamine 5.1-15 µg/kg/min or epinephrine less than or equal to 0.1 µg/kg/min or norepinephrine 0.1 µg/kg/min for at least 1 hour	Requiring vasopressor therapy with either dopamine greater than 15 µg/kg/min or epinephrine greater than 0.1 µg/kg/min or norepinephrine 0.1 µg/kg/min for at least 1 hour
Central nervous system					
Glasgow Coma Scale	15	13-14	10-12	6-9	Less than 6
Renal					
Creatinine (mg/dL)	Less than 1.2	1.2-1.9	2.0-3.4	3.5-4.9	Greater than or equal to 5
Urine output (mL/day)				Less than 500 but greater than or equal to 200	Less than 200

Note: If the PaO2 is unavailable, this trial will allow for the substitution with the oxygen saturation (SpO2) for calculation of the SOFA score as per the table in Appendix 11.2.

11.2 Estimation of PaO2/FiO2 from SpO2/FiO2

Adapted from Huang et al[63]

SpO2	FiO2														
	0.3	0.35	0.4	0.45	0.5	0.55	0.6	0.65	0.7	0.75	0.8	0.85	0.9	0.95	1
80%	141	127	111	98	89	81	74	68	63	59	55	52	49	47	44
81%	151	129	113	101	91	82	76	70	65	60	57	53	50	48	45
82%	155	132	116	103	93	84	77	71	66	62	58	55	52	49	46
83%	158	136	119	106	95	86	79	73	68	63	59	56	53	50	47
84%	162	139	122	108	97	89	81	75	70	65	61	57	54	51	49
85%	167	143	125	111	100	91	83	77	71	67	63	59	56	53	50
86%	171	147	129	114	103	94	86	79	73	69	64	61	57	54	51
87%	177	151	132	118	106	96	88	81	76	71	66	62	59	56	53
88%	182	156	137	121	109	99	91	84	78	73	68	64	61	58	55
89%	189	162	141	126	113	103	94	87	81	75	71	67	63	60	57
90%	196	168	147	130	117	107	98	90	84	78	73	69	65	62	59
91%	203	174	153	136	122	111	102	94	87	81	76	72	68	64	61
92%	213	182	159	142	128	116	106	98	91	85	80	75	71	67	64
93%	223	191	168	149	134	122	112	103	96	89	84	79	74	71	67
94%	236	202	177	157	142	129	118	109	101	94	89	83	79	75	71
95%	252	216	189	168	151	138	126	116	108	101	95	89	84	80	76
96%	273	234	205	182	164	149	136	126	117	109	102	96	91	86	82

11.3 Expected Adverse Effects of Sepsis

The following events are expected to occur with a reasonable frequency in the typical course of a critically ill patient with sepsis:

Constitutional: Fever, malaise, hypothermia, chills, rigors

Cardiovascular: Hypotension, arrhythmias (atrial fibrillation, atrial flutter, ventricular fibrillation, ventricular tachycardia), tachycardia, bradycardia, myocardial ischemia, syncope, shock

Pulmonary: Acute lung injury, dyspnea, hypoxemia, aspiration, atelectasis, mucus plugging, pneumothorax, pleural effusion, pulmonary embolism

Gastrointestinal: Nausea, vomiting, abdominal pain, paralytic ileus, ischemic bowel, gastritis, gastrointestinal bleeding, acute liver failure, pancreatitis

Renal: Dysuria, urinary retention, urinary frequency, incontinence, acute kidney injury, acute tubular necrosis, oliguria, acute interstitial nephritis, acidosis or alkalosis, hypokalemia or hyperkalemia, hyponatremia or hypernatremia

Hematology: Anemia, thrombocytopenia, abnormal coagulation, disseminated intravascular coagulation, hematoma, hemorrhage, venous thrombosis, pancytopenia

Neurology: Headache, confusion, delirium, hallucinations, agitation, anxiety, critical illness neuropathy

Musculoskeletal: Leg cramps, hemiparesis, quadriparesis, neuromuscular weakness, critical illness myopathy

Dermatology: Rash, bruising, cellulitis, Steven-Johnson syndrome, decubitus ulcer

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13.0 PROTOCOL AMENDMENT LOG

- Version 1.0
    - Initial IRB submission: November 22, 2017.
    - Approved by Scientific Reviewer: January 4, 2018.
    - Changes requested by IRB: January 25, 2018.

- Version 2.0
    - Changes in this version
        - Mid-Intervention Assessment added in section 5.4.5.
        - Indications for Study Discontinuation updated in section 7.4 to include clinical evaluation that continuation of the intervention is unsafe due to elevated blood sugar, severe ileus, or severe abdominal pain or emesis as criteria for discontinuation.
        - Required Education in the Protection of Human Research Participants updated in section 7.7.1 to reflect that participants are at high risk for delirium and cognitive impairment at the time of consent.
    - Protocol updated February 8, 2018
    - Informed Consent forms updated February 18, 2018

- Version 3.0
    - Changes in this version
        - Exclusion Criteria (Section 5.1.2) updated to include ICU physician request to exclude patient based on contraindication to enteral feeding.
        - Study Exam and Procedures (Section 5.4) updated to include time frames for sample collection at pre-infusion, 24-hour, and day 7 time points.
        - Day 28 Testing and Procedures (Section 5.4.8) changed to Day 30 Testing and Procedures.
        - Baseline Evaluation and Randomization (Section 5.2.3) updated to reflect that enrollment into intervention and placebo arms will be stratified at one level by the presence or absence of pre-existing diabetes mellitus.
        - Research Payments (Section 10.1) updated to include payment for co-investigators for screening, consenting, and enrollment activities.

- Version 3.1
    - Changes in this version
        - Modified to reflect expansion of recruitment to the ICUs at UPMC Shadyside and UPMC McKeesport Hospitals in Section 5.1, Section 5.11, and Section 5.2.