

OPEN

# A Pilot Double-Blind Placebo-Controlled Randomized Clinical Trial to Investigate the Effects of Early Enteral Nutrients in Sepsis

**OBJECTIVES:** Preclinical studies from our laboratory demonstrated therapeutic effects of enteral dextrose administration in the acute phase of sepsis, mediated by the intestine-derived incretin hormone glucose-dependent insulinotropic peptide. The current study investigated the effects of an early enteral dextrose infusion on systemic inflammation and glucose metabolism in critically ill septic patients.

**DESIGN:** Single-center, double-blind, placebo-controlled randomized pilot clinical trial (NCT03454087).

**SETTING:** Tertiary-care medical center in Pittsburgh, PA.

**PATIENTS:** Critically ill adult patients within 48 hours of sepsis diagnosis and with established enteral access.

**INTERVENTIONS:** Participants were randomized 1:1 to receive a continuous water (placebo) or enteral dextrose infusion (50% dextrose; 0.5 g/mL) at 10 mL per hour for 24 hours.

**MEASUREMENTS AND MAIN RESULTS:** We randomized 58 participants between June 2018 and January 2020 (placebo:  $n = 29$ , dextrose:  $n = 29$ ). Protocol adherence was high with similar duration of study infusion in the placebo (median duration, 24 hr [interquartile range, 20.9–24 hr]) and dextrose (23.9 hr [23–24 hr]) groups ( $p = 0.59$ ). The primary outcome of circulating interleukin-6 at end-infusion did not differ between the dextrose (median, 32 pg/mL [19–79 pg/mL]) and placebo groups (24 pg/mL [9–59 pg/mL];  $p = 0.13$ ) with similar results in other measures of the systemic host immune response. Enteral dextrose increased circulating glucose-dependent insulinotropic peptide (76% increase; 95% CI [35–119];  $p < 0.01$ ) and insulin (53% [17–88];  $p < 0.01$ ) compared with placebo consistent with preclinical studies, but also increased blood glucose during the 24-hour infusion period (153 mg/dL [119–223] vs 116 mg/dL [91–140];  $p < 0.01$ ). Occurrence of emesis, ICU and hospital length of stay, and 30-day mortality did not differ between the placebo and enteral dextrose groups.

**CONCLUSIONS:** Early infusion of low-level enteral dextrose in critically ill septic patients increased circulating levels of insulin and the incretin hormone glucose-dependent insulinotropic peptide without decreasing systemic inflammation.

**KEY WORDS:** dextrose; enteral nutrition; incretins; inflammation; sepsis

Current guidelines recommend initiation of early enteral nutrition for critically ill patients, but the mechanisms through which early enteral nutrition may improve outcomes in these patients remain unclear (1, 2). Proposed beneficial effects of enteral nutrition include preservation of mucosal integrity of the intestinal tract, prevention of bacterial translocation, and reduction in critical illness-induced catabolism (3, 4), but the effects of enteral nutrition on metabolic and inflammatory pathways specifically in septic populations are not well established.

Faraaz Ali Shah, MD, MPH<sup>1-3</sup>  
 Georgios D. Kitsios, MD, PhD<sup>1,3,4</sup>  
 Sachin Yende, MD, MS<sup>5,6</sup>  
 Daniel G. Dunlap, MD<sup>1,3,4</sup>  
 Denise Scholl, CRC<sup>6</sup>  
 Byron Chuan, MS<sup>1</sup>  
 Nameer Al-Yousif, MD<sup>7</sup>  
 Yingze Zhang, PhD<sup>1,3</sup>  
 Seyed Mehdi Nouraie, MD, PhD<sup>1,3</sup>  
 Alison Morris, MD, MS<sup>1,3,4</sup>  
 David T. Huang, MD, MPH<sup>6</sup>  
 Christopher P. O'Donnell, PhD<sup>1</sup>  
 Bryan J. McVerry, MD<sup>1,3,4</sup>

Copyright © 2021 The Authors. Published by Wolters Kluwer Health, Inc. on behalf of the Society of Critical Care Medicine. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1097/CCE.0000000000000550

A potential mechanism by which enteral nutrition may improve outcomes is through its effects on incretins (5,6). The intestine-derived incretin hormones glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1) are released in response to enteral nutrients and increase insulin release in a glucose-dependent manner, thereby preventing hyperglycemia with a theoretical lower risk of hypoglycemia compared with exogenous insulin (7, 8). Incretins also exert pleiotropic anti-inflammatory effects and, in preclinical sepsis studies, incretin analogs attenuate systemic inflammation, decrease organ injury, and improve survival (6, 9–11). Exogenous incretin analogs have been tested in critically ill patients in trials of glycemic control but have not translated into clinical practice (12, 13). Promotion of the incretin axis by enteral nutrients in sepsis may exert similar therapeutic effects.

In prior preclinical studies, we demonstrated that low-level enteral dextrose infusion in mice exposed to endotoxin improved glucose disposal, increased insulin release, decreased insulin resistance, and decreased systemic inflammation dependent on endogenous increases in the incretin hormone GIP (14). Similarly, enteral dextrose promoted euglycemia and improved survival in a murine model of *Klebsiella pneumoniae* (15). We conducted the Study of Early Enteral Dextrose in Sepsis (SEEDS) to translate our preclinical findings to the bedside and test the effects of an early low-level enteral dextrose infusion in critically ill septic patients. We hypothesized that enteral dextrose would increase incretin hormones, promote euglycemia, and decrease systemic inflammation compared with a placebo control.

## MATERIALS AND METHODS

### Trial Design and Oversight

SEEDS was a pilot single-center randomized placebo-controlled clinical trial testing an early enteral dextrose infusion in critically ill patients with sepsis (ClinicalTrials.gov registration number NCT03454087). Details of the design and rationale have been previously published (16). The trial protocol was approved by the University of Pittsburgh Institutional Review Board (PRO17010532, STUDY19080314) and funding was provided by the National Institutes of Health (K23GM122069). SEEDS was coordinated through the Multidisciplinary Acute Care Research

Organization at the University of Pittsburgh in accordance with the Declaration of Helsinki. An independent data safety and monitoring board met prior to trial launch and every 6 months thereafter to monitor for complications and provide recommendations for continuing, modifying, or stopping the trial. Investigators remained blinded to group assignment for participants until completion of data analysis in October 2020. The authors are accountable for data accuracy and completeness and for trial fidelity to the protocol. All data are reported in concordance with Consolidated Standards of Reporting Trials guidelines (17).

### Sites and Participants

SEEDS enrolled adult participants 18 years old or older presenting with sepsis in an ICU at an academic tertiary-care medical center in Pittsburgh, PA (UPMC Presbyterian Hospital). Participants were enrolled within the first 48 hours of meeting sepsis criteria defined as a confirmed or suspected infection with an increase from baseline of two or greater in the Sequential Organ Failure Assessment (SOFA) score in accordance with Sepsis-3 guidelines (18). A modified SOFA score was used for screening purposes that excluded the bilirubin and neurologic criteria since liver function tests and Glasgow Coma Scale are not uniformly obtained for septic patients at our institution. We included patients with established enteral access defined by the presence of a nasogastric or orogastric tube, imminent plans to place a nasogastric or orogastric tube, or an existing percutaneous gastrostomy tube. We excluded patients who had already started enteral nutrition, were receiving treatment for diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome at the time of screening, or were deemed unable to tolerate enteral infusions by the treating team. Written informed consent was obtained directly from participants or from legally authorized representatives.

### Randomization and Blinding

Participants in SEEDS were randomized 1:1 into intervention and placebo arms. We stratified enrollment the presence or absence of self-reported diabetes mellitus, using separate randomization tables generated by the UPMC Investigational Drug Service. We had considered enrolling only nondiabetic patients in SEEDS to more directly test our preclinical findings since

diabetic patients can demonstrate both attenuated increases in incretins in response to enteral nutrients as well as decreased insulin secretion in response to GIP (19–21) but chose to prioritize recruitment of a sample representative of the population of critically ill septic patients treated at our institution. Investigational infusions were dispensed with an opaque cover to conceal contents. Participants and bedside clinicians remained blinded to group allocation throughout the study.

## Study Interventions

All participants underwent a preinfusion research blood draw no more than 2 hours prior to the start of investigational infusion. Subsequently, participants received an investigational infusion of either 50% dextrose (intervention) or free water (placebo) at 10 mL per hour for 24 hours via an existing enteral access tube using a standard infusion pump. The carbohydrate content provided from enteral dextrose over 24 hours (~400 kcal) was similar to that in most enteral tube feed formulations at trophic levels (~10–20 cc/hr) and was consistent with the level of caloric support provided in our preclinical studies (~10–40%) (14, 15). Capillary blood glucose was monitored every 6 hours with more frequent monitoring by the clinical team permitted if indicated. Corrective insulin use, if any, was at the discretion of the clinical team. Investigational infusions were paused as needed for clinical care. Gastric residuals were not monitored as part of the study, and any decision to interrupt or discontinue investigational infusion was made by treating clinicians. Initiation of enteral nutrition by the clinical team during the infusion period prompted cessation of investigational infusion. Administration of medications during the infusion period that could influence glucose metabolism (e.g., propofol and IV dextrose) or systemic inflammation (e.g., glucocorticoids) was recorded (22, 23). Notably, although IV dextrose does not directly stimulate incretin release, the magnitude of incretin release could be influenced by circulating blood glucose levels (8, 24). A second research blood draw was performed 24 hours after the start of infusion. After completing the infusion period, further nutrition support was at the discretion of treating ICU clinicians. Review of electronic medical records continued for 30 days following the start of infusion for clinical outcomes.

## Outcome Measures

The primary outcome was circulating levels of interleukin-6 (IL-6) measured 24 hours after the start of infusion. Prespecified secondary outcomes included: 1) glycemic control during the infusion period including occurrence of hypoglycemia (defined by any blood glucose less than 70 mg/dL) and hyperglycemia (any blood glucose greater than 180 mg/dL), 2) circulating endocrine hormone levels (insulin, C-peptide, GIP, and GLP-1), 3) other measures of the host immune response (interleukin-1 receptor antagonist [IL1ra], tumor necrosis factor receptor 1 [Tnfr1], suppressor of tumorigenicity 2 [ST2], procalcitonin, and pentraxin-3), 4) occurrence of emesis during the infusion period, and 5) clinical outcomes including hospital and ICU length of stay and inhospital mortality measured at 30 days after the start of infusion. Cutoff for hyperglycemia was selected based on the Surviving Sepsis guidelines (25) as well as local thresholds for the use of corrective insulin at our institution. Since cutoffs to define hyperglycemia have varied widely in critical care studies (26–29), in post hoc analyses, a range of cutoffs were tested. Both insulin and C-peptide levels were tested as the former may be influenced by exogenous insulin administered during clinical care. Measures of the host immune response were chosen based on previous studies supporting associations of the selected pathways with hyperglycemia (28, 30–33).

## Sample Processing

At each time point, 10-mL blood was collected by bedside nursing staff into serum, EDTA, and P800 tubes (BD Biosciences, Catalog Number 366420, San Jose, CA), the latter containing a proprietary cocktail of protease inhibitors to improve accuracy in the measurement of incretin hormones (34). Samples were processed within 60 minutes of collection. Samples were centrifuged for 10 minutes at  $800 \times g$  at either room temperature (EDTA tubes) or at  $4^\circ$  (P800 tubes). All samples were aliquoted and stored at  $-80^\circ\text{C}$  until final analysis. A custom Luminex panel was used to measure IL-6, Tnfr1, ST2, pentraxin-3, and procalcitonin in EDTA plasma samples (Fisher-Scientific, Waltham, MA). A Meso Scale Discovery U-plex panel was used to measure insulin, C-peptide, GIP, GLP-1, and IL-1ra in P800 plasma samples (Meso Scale Discovery, Rockland, MD). Biomarker analysis were performed

using a Bio-Plex 100 Analyzer (Bio-Rad, Hercules, CA) according to the manufacturers' instructions.

## Statistical Analysis

In primary statistical analyses, we assessed IL-6 measured 24 hours after starting investigational infusion compared between the intervention and placebo groups in an intention-to-treat analysis by the Wilcoxon rank-sum test. Based on published estimates of circulating cytokines in critically ill mechanically ventilated patients (35), we estimated seven patients per arm would provide 90% power to detect a 15% difference between the groups in IL-6 levels with an alpha error of 0.05. We planned to enroll 30 participants in each arm to decrease the risk of unbalanced covariates between the groups (36). In secondary analyses, we compared continuous variables measured during the infusion period and at the 24-hour time point by Wilcoxon rank-sum test and compared dichotomous variables with Fisher exact test. We assessed changes in endocrine hormones and in measures of the host response from baseline values by analysis of covariance (ANCOVA) with postinfusion values as the outcome and covariate adjustment for preinfusion values. We chose the ANCOVA approach to understand changes in continuous variables based on literature suggesting its superiority over comparisons of the absolute differences in randomized controlled trials (37, 38). CIs for ANCOVA estimates were generated from bootstrapped analyses utilizing 500 iterations. Results for secondary analyses involving biomarkers were adjusted for multiple comparisons by the method of Simes (39). Post hoc analyses explored differences between the groups in biomarkers stratified by diabetic status. Ventilator-free days were calculated at 30 days from the start of investigational infusion with a value of 0 assigned to participants who died before 30 days consistent with prior studies (40). Survival was visualized with Kaplan-Meier curves and analyzed by log-rank test.

## RESULTS

### Patients

From June 2018 to February 2020, 1,054 patients were screened for eligibility of which 186 met eligibility criteria (**eFig. 1**, Online Supplement, <http://links.lww.com/CCX/A814>). Of these, a total of 58 of a target 60 patients were successfully enrolled and underwent

randomization; one patient had clinical decompensation with rapid increases in vasopressor requirements prior to the start of investigational infusion and was not included in the analyses of biomarkers but was included in analyses of clinical outcomes. The SEEDS trial ended in March 2020 before completion of target enrollment secondary to shutdown of research operations during the coronavirus disease 2019 pandemic.

Of the 58 randomized participants, median age was 60.9 years (interquartile range, 50.4–70.7), 32 were male (55%), and 50 were White (86%). Twenty-five participants (43%) had preexisting diabetes, and median admission modified SOFA score (excluding the neurologic and liver components) was 7 (6–9). Pneumonia was the most common infection (74%). Baseline characteristics were similar between the groups (**Table 1**).

### Infusion Period

Median duration of investigational infusion was 24 hours (20.9–24 hr) in the placebo group and 23.9 hours (23–24 hr) in the enteral dextrose group ( $p = 0.59$ ). In terms of concomitant medications that could affect inflammation or glucose metabolism, we found similar use of propofol, glucocorticoids, and exogenous IV dextrose (used only as carriers for IV medications in enrolled patients) between the groups (**Supplementary Table 1**, <http://links.lww.com/CCX/A814>). Two patients in each group had infusions stopped due to emesis ( $p > 0.99$ ). One patient in the enteral dextrose group was switched from investigational infusion to enteral tube feeds when an insulin drip was started for euglycemic ketoacidosis. No patients developed mesenteric ischemia.

### Measures of the Systemic Host Immune Response

The primary outcome of circulating IL-6 measured 24 hours after the start of infusion did not differ between placebo (median, 24 pg/mL [interquartile range, 9–59 pg/mL]) and enteral dextrose (32 pg/mL [19–78]) groups ( $p = 0.240$ ). In secondary analyses, IL-1ra, Tnfr1, ST2, and procalcitonin were also similar between the groups (**Supplementary Table 2**, <http://links.lww.com/CCX/A814>). Pentraxin-3 measured at the end of infusion was increased in the enteral dextrose group (4,825 pg/mL [2,065–9,895 pg/mL]) compared with placebo



**TABLE 1.**  
**Participant Characteristics**

Variable	Placebo	Enteral Dextrose
<i>n</i>	29	29
Demographics		
Age	60.8 (50.4–71.4)	61.0 (54.1–68.3)
Male (%)	17 (58.6)	15 (51.7)
White (%)	26 (89.7)	24 (82.8)
Body mass index	29.1 (27.6–37.8)	24.5 (23–31.8)
Diabetes mellitus	12 (41.4)	13 (44.8)
Laboratory values		
WBC count ( $\times 10^9/L$ )	12 (8.0–17.2)	12.6 (8.4–19.4)
Hemoglobin (g/dL)	10.5 (8.7–12)	10.5 (9.2–12.3)
Platelet count ( $\times 10^9/L$ )	182 (132–272)	219 (129–249)
Sodium (mEq/L)	138 (135–142)	139 (135–140)
Potassium (mEq/L)	4.4 (3.9–4.9)	4.1 (3.7–4.4)
Chloride (mEq/L)	106 (104–109)	105 (102–108)
Blood urea nitrogen (mg/dL)	38 (27–48)	28 (16–38)
Bicarbonate (mEq/L)	22 (20–25)	21 (19–23)
Creatinine (mg/dL)	2 (1.4–2.7)	1.5 (0.9–1.7)
Site of infection		
Pulmonary	18 (62.1)	22 (75.9)
Urinary	7 (24.1)	2 (6.9)
Intra-abdominal	2 (6.9)	0 (0)
Endocarditis	0 (0)	2 (6.9)
Skin and soft tissue	0 (0)	1 (3.5)
Osteomyelitis	1 (3.5)	0 (0)
Multiple sites	1 (3.5)	2 (6.9)
Severity of illness		
Lactate (mmol/L)	1.5 (1.1–2.2)	1.5 (1.1–2.6)
Preinfusion interleukin-6 (pg/mL)	32 (13–138)	78 (31–220)
Number receiving vasopressors (%)	21 (72.1)	17 (58.6)
Number receiving mechanical ventilation (%)	28 (96.6)	28 (96.6)
Preadmission mSOFA	0 (0–1)	0 (0–0)
Admission mSOFA		
Respiratory	3 (3–3)	3 (3–4)
Cardiac	3 (1–4)	3 (0–4)
Renal	2 (1–2)	1 (0–1)
Coagulation	0 (0–1)	0 (0–1)
Total	7 (6–9)	7 (5–8)

mSOFA = Modified Sequential Organ Failure Assessment.

Data are represented as median (interquartile range) for continuous variables or *n* (%) for dichotomous variables. mSOFA includes all components of the Sequential Organ Failure Assessment score except for the neurologic and liver components.

(995 [216–2,391];  $p = 0.045$ ). However, after adjustment for preinfusion values or stratification by diabetic status, enteral dextrose did not significantly change any 24-hour immune response biomarker value compared with placebo (Fig. 1; Supplementary Table 2, <http://links.lww.com/CCX/A814>, and Supplementary Table 3, <http://links.lww.com/CCX/A814>).

### Glycemic Control During Infusion Period and Endocrine Outcomes

Capillary blood glucose values were not significantly different between the placebo and enteral dextrose groups at the start of investigational infusion (Supplementary Table 4, <http://links.lww.com/CCX/A814>). Mean glucose during the infusion period was significantly increased in the enteral dextrose group (158 mg/dL [128–206 mg/dL]) compared with the placebo group (109 mg/dL [93–154 mg/dL];  $p < 0.001$ ), and results were consistent in both nondiabetic and diabetic participants (Fig. 2). Capillary blood glucose at the end of the infusion period (153 mg/dL [119–223 mg/dL] vs 116 mg/dL [91–140 mg/dL];  $p = 0.004$ ) as well as maximum blood glucose (201 mg/dL [152–239 mg/dL] vs 126 mg/dL [107–191 mg/dL];  $p = 0.001$ ) during the infusion period were similarly increased in the enteral dextrose group; however, amount of corrective insulin administered did not differ between the groups ( $p = 0.132$ ). A trend toward increased occurrence of hyperglycemia (defined by any blood glucose above 180 mg/dL during the infusion period) was observed in the enteral dextrose group (55.2% vs 32.1%;  $p = 0.068$ ), with consistent results at other cutoff thresholds that reached statistical

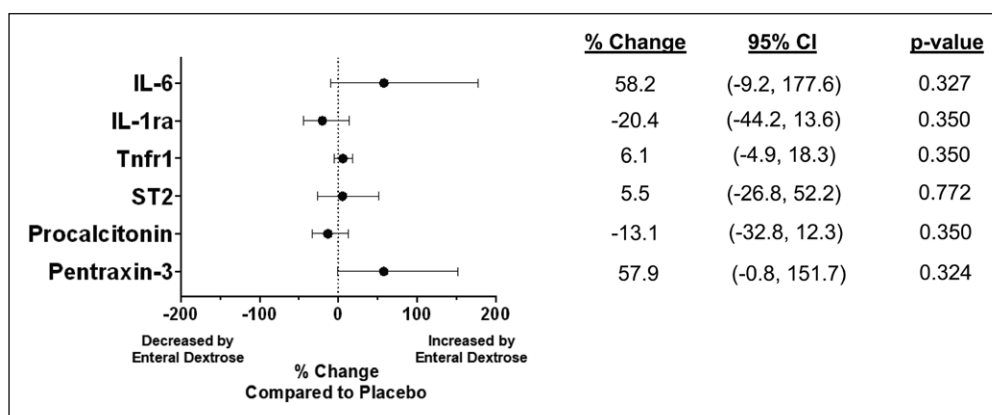
significance in post hoc analyses. Two patients in the placebo group (7.1%) developed hypoglycemia compared with one patient in the enteral dextrose group (3.5%;  $p = 0.487$ ).

At the 24-hr time point, participants in the enteral dextrose group had higher circulating GIP (1,396 pg/mL [764–1,973] vs 581 [267–838];  $p = 0.004$ ) and higher insulin levels (158 [86–215];  $p = 0.036$ ) compared with the placebo group. GLP-1 and C-peptide at the 24-hour time point did not differ significantly between the groups (Supplementary Table 5, <http://links.lww.com/CCX/A814>). After adjustment for preinfusion values, enteral dextrose significantly increased GIP, insulin, and C-peptide levels compared with placebo (Fig. 3). Post hoc analyses suggested consistent effects of enteral dextrose on increasing GIP regardless of diabetic status but also potential blunting of increases in insulin and c-peptide in diabetic participants (Supplementary Table 5, <http://links.lww.com/CCX/A814>, and Supplementary Table 6, <http://links.lww.com/CCX/A814>).

### Clinical Outcomes

All randomized participants ( $n = 58$ ) were included in intention-to-treat analyses of clinical outcomes regardless of receipt of investigational infusion. Ventilator-free days, ICU length of stay, and hospital length of stay did not significantly differ between the placebo and enteral dextrose groups (Supplementary Table 7, <http://links.lww.com/CCX/A814>). At 30 days after the start of infusion, seven participants each had died in placebo (24.1%) and enteral dextrose (24.1%) arms with no significant differences in survival ( $p = 0.98$ ;

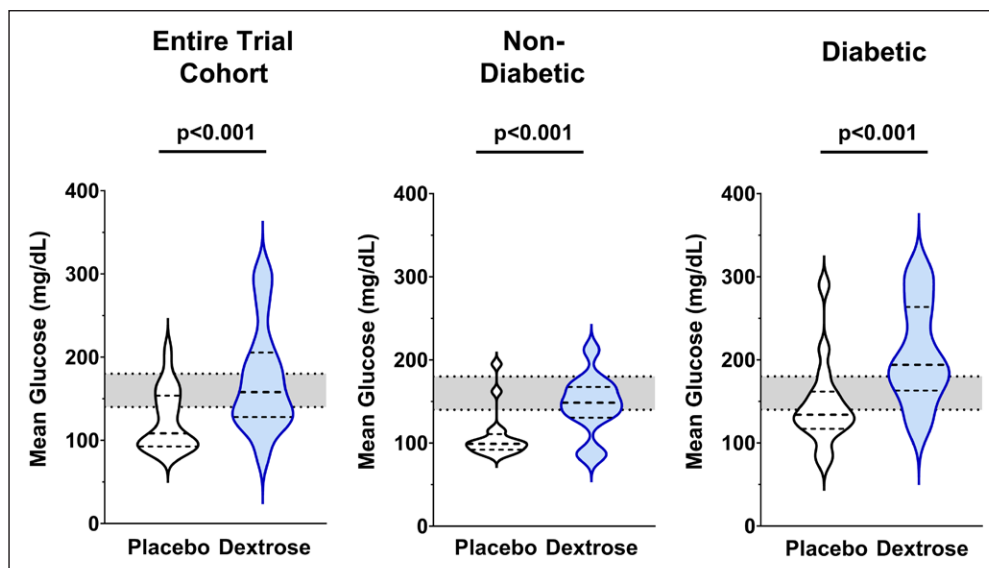
eFig. 2, <http://links.lww.com/CCX/A814>).



**Figure 1.** Effects of enteral dextrose on markers of the systemic host immune response. Data are presented as percent change compared with placebo with 95% CIs.  $p$  values represent results from ANCOVA analyses adjusting for preinfusion values. Multiplicity-adjusted  $p$  values are reported.

## DISCUSSION

The potential role of incretins and incretin-based therapies has recently been highlighted as a priority research goal for studies of nutrition and metabolism in critically ill patients (5). Prior randomized controlled trials have tested exogenous incretin-based



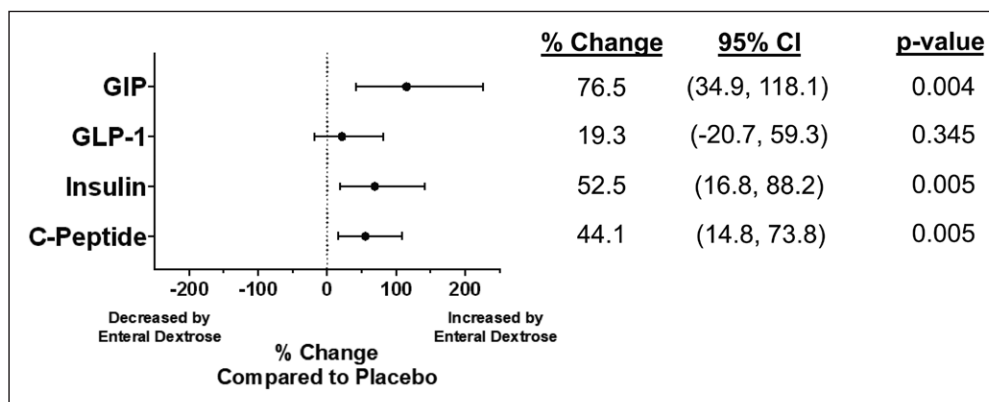
**Figure 2.** Mean glucose during the 24-hr infusion period compared between placebo and enteral dextrose groups. Data are represented as violin plots with median and interquartile range. Shaded areas represent range of blood glucose from 140 to 180 mg/dL.

therapies in critically ill patients with results suggesting reduced hyperglycemia; however, the prior trials used continuous IV infusions of incretins at supraphysiologic levels, which may be impractical in clinical practice (12, 13, 41). In this pilot randomized clinical trial, we investigated whether delivery of enteral nutrients could promote endogenous incretin release in septic patients with similar therapeutic benefits. We demonstrated that an early low-level enteral dextrose infusion increased circulating levels of the incretin GIP as well as insulin and c-peptide but did not decrease circulating IL-6 or hyperglycemia compared with a placebo control.

The findings from SEEDS contrast the preclinical studies from our laboratory that informed the trial (14, 15), where infusion of enteral dextrose in septic mice

increased GIP and endogenous insulin, resulting in euglycemia rather than the trend toward hyperglycemia observed in SEEDS. Despite the increase in GIP, enteral dextrose did not reduce circulating IL-6 in contrast to findings in the preclinical models. Notably, the variability in IL-6 observed in SEEDS was higher than the published estimates that informed our sample size calculations; thus, larger studies may be needed to definitively rule out differences. Clinical outcomes did not differ between intervention and placebo groups in SEEDS, but the study was underpowered in this regard as the focus of this pilot trial was the characterization of the physiologic response to enteral nutrients.

The challenges of translating findings from preclinical sepsis studies to clinical trials are well documented (42, 43). In preclinical studies, animals are exposed to identical insults with identical biospecimen collection to improve rigor and reproducibility of results. In contrast, in clinical trials, inciting insults vary, and timing from sepsis onset is never certain. Variability in age, demographics, comorbidities, and in the host response may all contribute to differential responses to a therapeutic intervention (44). Most relevant to SEEDS are the differences in response to enteral dextrose by



**Figure 3.** Percent change with 95% CIs in endocrine hormones with enteral dextrose compared with placebo. *p* values represent results from ANCOVA analyses adjusting for preinfusion values. Multiplicity-adjusted *p* values are reported.

diabetic status, whereby diabetic patients demonstrated a blunted endogenous insulin response despite increases in GIP. Incretin resistance, in particular to GIP, has been well documented in diabetic and obese patients (19, 20), and GLP-1 (which was not increased by enteral dextrose) may be required for beneficial effects of incretins in septic patients. Full

enteral nutrition (which includes lipids, amino acids, and complex carbohydrates) might promote GLP-1 but was not tested in SEEDS given limited safety data on its use in septic shock prior to study launch. Since then, a single-center pilot trial of 49 patients with septic shock demonstrated the safety of trophic enteral feeds compared with no nutrition with reductions in ICU length of stay (45). The potential contributions of GLP-1 to the therapeutic effects of enteral nutrition (if any) remain unknown. Additionally, although several pilot trials have tested the effects of exogenous GLP-1 infusion or GLP-1 analogs in mixed populations of critically ill patients and demonstrated reductions in hyperglycemia (6, 12, 13, 46–48), no large multicenter trial of incretin-based therapy has as yet been completed though conduct of such a trial has been encouraged in a recent research statement (5).

Importantly, our pilot study has several strengths including the use of a placebo control, maintenance of blinding and allocation, good protocol adherence, and successful randomization with minimal imbalances between the groups despite the small sample size. Few critical care studies have used a randomized clinical trial framework to understand how biomarker profiles change in response to nutritional strategies (49, 50), and studies of nutrition specifically in septic populations are rare (51).

## CONCLUSION

In this pilot trial, we demonstrated the feasibility of pairing an enteral intervention with specimen collection to understand changes in molecular pathways in response to nutrition in a translational bench to bedside study. We propose that future studies in critically ill septic patients similarly incorporate biomarker collection to understand mechanistic changes in response to nutritional support, to better characterize why patients differ in response to nutrition, and to inform strategies to better individualize care.

## ACKNOWLEDGMENTS

We thank coinvestigators Ali Al-Khafaji, Arun Rajaratnam, Nauman Farooq, Hyung Kook Kim, Aditya Kler, Florian Mayr, Raghavan Murugan, Raj Ramanan, Varun Shetty, Utsav Shrestha, and David Wallace for supporting recruitment efforts for Study of

Early Enteral Dextrose in Sepsis (SEEDS). We thank the Data Safety and Monitoring Board comprising Ian Barbash, Philip Lamberty, and Michael Myerburg for efforts supporting trial integrity and safety. We thank Tina Vita, Mary Stefanick, Caroline Gacka, and Dan Unikel of Multidisciplinary Acute Care Research Organization for supporting trial logistics. We thank Jennifer Kozar and the UPMC Investigational Drug Service for their invaluable support in trial procedures. We also thank the ICU nurses at UPMC Presbyterian Hospital for their generous support of the SEEDS trial and the care for their patients. Most importantly, we thank the patients and families that participated in SEEDS with the goal of advancing scientific knowledge.

- 1 Division of Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA.
- 2 VA Pittsburgh Healthcare System, Department of Medicine, Pittsburgh, PA.
- 3 Acute Lung Injury Center of Excellence, University of Pittsburgh, Pittsburgh, PA.
- 4 Center for Medicine and the Microbiome, University of Pittsburgh, Pittsburgh, PA.
- 5 VA Pittsburgh Healthcare System, Department of Critical Care Medicine, Pittsburgh, PA.
- 6 Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA.
- 7 Department of Internal Medicine, UPMC Mercy, Pittsburgh, PA.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (<http://journals.lww.com/ccejournal>).

Drs. Shah, Yende, O'Donnell, and McVerry conceived the study. Drs. Shah, Kitsios, Yende, Zhang, Morris, Huang, O'Donnell, and McVerry designed the trial protocol. Dr. Shah, Dr. Kitsios, Dr. Dunlap, Ms. Scholl, Dr. Huang conducted the study. Dr. Shah, Ms. Scholl, Dr. Al-Yousif collected data. Dr. Shah, Mr. Chuan, Dr. Al-Yousif, and Dr. Nouraie contributed to data analysis. Drs. Shah, Nouraie, Huang, O'Donnell, and McVerry contributed to interpretation of results. Drs. Shah and McVerry wrote the first draft of the article. All authors reviewed the article, provided critical revisions, and approved the final article.

Supported, in part, by the National Institutes of Health grants: (K23 HL139987 [to Dr. Kitsios], P01 HL114453 [to Drs. Zhang and McVerry], and K23 GM122069 [to Dr. Shah]). Statistical support was provided by the Clinical and Translational Science Institute at the University of Pittsburgh through the National Institutes of Health Grant UL1-TR-000005.

Dr. Kitsios has received research funding from Karius. Dr. McVerry has received research funding from Bayer Pharmaceuticals, the Translational Breast Cancer Research Consortium, and the UPMC Learning While Doing Program, and consulting fees from Boehringer Ingelheim. The remaining authors have disclosed that



they do not have any potential conflicts of interest. The SEEDS trial was registered on *ClinicalTrials.gov* on March 5, 2018. Further details and the trial protocol are available at <https://clinicaltrials.gov/ct2/show/NCT03454087>.

For information regarding this article, E-mail: [shahfa@upmc.edu](mailto:shahfa@upmc.edu)

## REFERENCES

- McClave SA, Taylor BE, Martindale RG, et al; Society of Critical Care Medicine; American Society for Parenteral and Enteral Nutrition: Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr* 2016; 40:159–211
- Rhodes A, Evans LE, Alhazzani W, et al: Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. *Crit Care Med* 2017; 45:486–552
- Casaer MP, Mesotten D, Hermans G, et al: Early versus late parenteral nutrition in critically ill adults. *N Engl J Med* 2011; 365:506–517
- Doig GS, Simpson F, Sweetman EA, et al; Early PN Investigators of the ANZICS Clinical Trials Group: Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: A randomized controlled trial. *JAMA* 2013; 309:2130–2138
- Arabi YM, Casaer MP, Chapman M, et al: The intensive care medicine research agenda in nutrition and metabolism. *Intensive Care Med* 2017; 43:1239–1256
- Shah FA, Mahmud H, Gallego-Martin T, et al: Therapeutic effects of endogenous incretin hormones and exogenous incretin-based medications in sepsis. *J Clin Endocrinol Metab* 2019; 104:5274–5284
- Baggio LL, Drucker DJ: Biology of incretins: GLP-1 and GIP. *Gastroenterology* 2007; 132:2131–2157
- Campbell JE, Drucker DJ: Pharmacology, physiology, and mechanisms of incretin hormone action. *Cell Metab* 2013; 17:819–837
- Lee W, Ku SK, Park EJ, et al: Exendin-4 inhibits HMGB1-induced inflammatory responses in HUVECs and in murine polymicrobial sepsis. *Inflammation* 2014; 37:1876–1888
- Lee W, Park EJ, Kwak S, et al: Trimeric PEG-conjugated exendin-4 for the treatment of sepsis. *Biomacromolecules* 2016; 17:1160–1169
- Neves FS, Marques PT, Barros-Aragão F, et al: Brain-defective insulin signaling is associated to late cognitive impairment in post-septic mice. *Mol Neurobiol* 2018; 55:435–444
- Deane AM, Chapman MJ, Fraser RJ, et al: Effects of exogenous glucagon-like peptide-1 on gastric emptying and glucose absorption in the critically ill: Relationship to glycemia. *Crit Care Med* 2010; 38:1261–1269
- Miller A, Deane AM, Plummer MP, et al: Exogenous glucagon-like peptide-1 attenuates glucose absorption and reduces blood glucose concentration after small intestinal glucose delivery in critical illness. *Crit Care Resusc* 2017; 19:37–42
- Shah FA, Singamsetty S, Guo L, et al: Stimulation of the endogenous incretin glucose-dependent insulinotropic peptide by enteral dextrose improves glucose homeostasis and inflammation in murine endotoxemia. *Transl Res* 2018; 193:1–12
- Chuan B, Guo L, Cooper B, et al: Physiologic effects of exogenous dextrose in murine *Klebsiella pneumoniae* sepsis vary by route of provision. *Nutrients* 2020; 12:E2901
- Shah FA, Kitsios GD, Zhang Y, et al: Rationale for and design of the study of early enteral dextrose in sepsis: A pilot placebo-controlled randomized clinical trial. *JPEN J Parenter Enteral Nutr* 2020; 44:541–547
- Schulz KF, Altman DG, Moher D; CONSORT Group: CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; 340:c332
- Singer M, Deutschman CS, Seymour CW, et al: The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016; 315:801–810
- Meier JJ, Gallwitz B, Kask B, et al: Stimulation of insulin secretion by intravenous bolus injection and continuous infusion of gastric inhibitory polypeptide in patients with type 2 diabetes and healthy control subjects. *Diabetes* 2004; 53(Suppl 3):S220–S224
- Nauck MA, Heimesaat MM, Orskov C, et al: Preserved incretin activity of glucagon-like peptide 1 [7-36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. *J Clin Invest* 1993; 91:301–307
- Holst JJ, Knop FK, Vilsbøll T, et al: Loss of incretin effect is a specific, important, and early characteristic of type 2 diabetes. *Diabetes Care* 2011; 34(Suppl 2):S251–S257
- Meduri GU, Tolley EA, Chrousos GP, et al: Prolonged methylprednisolone treatment suppresses systemic inflammation in patients with unresolving acute respiratory distress syndrome: Evidence for inadequate endogenous glucocorticoid secretion and inflammation-induced immune cell resistance to glucocorticoids. *Am J Respir Crit Care Med* 2002; 165:983–991
- Maeda K, Iwasaki M, Itou Y, et al: Effect of propofol continuous-rate infusion on intravenous glucose tolerance test in dogs. *Vet Sci* 2018; 5:E43
- Herrmann C, Göke R, Richter G, et al: Glucagon-like peptide-1 and glucose-dependent insulin-releasing polypeptide plasma levels in response to nutrients. *Digestion* 1995; 56:117–126
- Rhodes A, Evans LE, Alhazzani W, et al: Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* 2017; 43:304–377
- Green JP, Berger T, Garg N, et al: Hyperlactatemia affects the association of hyperglycemia with mortality in nondiabetic adults with sepsis. *Acad Emerg Med* 2012; 19:1268–1275
- van Vught LA, Wiewel MA, Klein Klouwenberg PM, et al; Molecular Diagnosis and Risk Stratification of Sepsis Consortium: Admission hyperglycemia in critically ill sepsis patients: Association with outcome and host response. *Crit Care Med* 2016; 44:1338–1346
- Nakamura M, Oda S, Sadahiro T, et al: Correlation between high blood IL-6 level, hyperglycemia, and glucose control in septic patients. *Crit Care* 2012; 16:R58
- Falciglia M, Freyberg RW, Almenoff PL, et al: Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. *Crit Care Med* 2009; 37:3001–3009
- Farooq N, Chuan B, Mahmud H, et al: Association of the systemic host immune response with acute hyperglycemia

- in mechanically ventilated septic patients. *PLoS One* 2021; 16:e0248853
31. Hotamisligil GS: The role of TNFalpha and TNF receptors in obesity and insulin resistance. *J Intern Med* 1999; 245:621–625
  32. Maedler K, Sergeev P, Ris F, et al: Glucose-induced beta cell production of IL-1beta contributes to glucotoxicity in human pancreatic islets. *J Clin Invest* 2002; 110:851–860
  33. Yu WK, Li WQ, Li N, et al: Influence of acute hyperglycemia in human sepsis on inflammatory cytokine and counterregulatory hormone concentrations. *World J Gastroenterol* 2003; 9:1824–1827
  34. Yi J, Warunek D, Craft D: Degradation and stabilization of peptide hormones in human blood specimens. *PLoS One* 2015; 10:e0134427
  35. Meduri GU, Headley S, Kohler G, et al: Persistent elevation of inflammatory cytokines predicts a poor outcome in ARDS. Plasma IL-1 beta and IL-6 levels are consistent and efficient predictors of outcome over time. *Chest* 1995; 107:1062–1073
  36. Whitehead AL, Julious SA, Cooper CL, et al: Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. *Stat Methods Med Res* 2016; 25:1057–1073
  37. Ritz C: Statistical analysis of continuous outcomes from parallel-arm randomized controlled trials in nutrition—a tutorial. *Eur J Clin Nutr* 2021; 75:160–171
  38. Van Breukelen GJ: ANCOVA versus change from baseline: More power in randomized studies, more bias in nonrandomized studies [corrected]. *J Clin Epidemiol* 2006; 59:920–925
  39. Simes RJ: An improved Bonferroni procedure for multiple tests of significance. *Biometrika* 1986; 73:751–754
  40. Kitsios GD, Yang L, Manatakis DV, et al: Host-response subphenotypes offer prognostic enrichment in patients with or at risk for acute respiratory distress syndrome. *Crit Care Med* 2019; 47:1724–1734
  41. Deane AM, Chapman MJ, Fraser RJ, et al: The effect of exogenous glucagon-like peptide-1 on the glycaemic response to small intestinal nutrient in the critically ill: A randomised double-blind placebo-controlled cross over study. *Crit Care* 2009; 13:R67
  42. Osuchowski MF, Remick DG, Lederer JA, et al: Abandon the mouse research ship? Not just yet! *Shock* 2014; 41:463–475
  43. Guillon A, Preau S, Aboab J, et al; Translational Research Committee of the French Intensive Care Society (Société de Réanimation de Langue Française): Preclinical septic shock research: Why we need an animal ICU. *Ann Intensive Care* 2019; 9:66
  44. Seymour CW, Kennedy JN, Wang S, et al: Derivation, validation, and potential treatment implications of novel clinical phenotypes for sepsis. *JAMA* 2019; 321:2003–2017
  45. Patel JJ, Kozeniecki M, Peppard WJ, et al: Phase 3 pilot randomized controlled trial comparing early trophic enteral nutrition with “no enteral nutrition” in mechanically ventilated patients with septic shock. *JPEN J Parenter Enteral Nutr* 2020; 44:866–873
  46. Galiatsatos P, Gibson BR, Rabiee A, et al: The glucoregulatory benefits of glucagon-like peptide-1 (7-36) amide infusion during intensive insulin therapy in critically ill surgical patients: A pilot study. *Crit Care Med* 2014; 42:638–645
  47. Plummer MP, Hermanides J, Deane AM: Incretin physiology and pharmacology in the intensive care unit. *Crit Care Clin* 2019; 35:341–355
  48. Deane AM, Summers MJ, Zaknic AV, et al: Exogenous glucagon-like peptide-1 attenuates the glycaemic response to postpyloric nutrient infusion in critically ill patients with type-2 diabetes. *Crit Care* 2011; 15:R35
  49. Arabi Y, Jawdat D, Bouchama A, et al: Permissive underfeeding, cytokine profiles and outcomes in critically ill patients. *PLoS One* 2019; 14:e0209669
  50. Bastarache JA, Ware LB, Girard TD, et al: Markers of inflammation and coagulation may be modulated by enteral feeding strategy. *JPEN J Parenter Enteral Nutr* 2012; 36:732–740
  51. Englert JA, Rogers AJ: Metabolism, metabolomics, and nutritional support of patients with sepsis. *Clin Chest Med* 2016; 37:321–331