



University of Kentucky  
**UKnowledge**

---

DNP Projects

College of Nursing

---

2016

## Effect of Enteral Feeding Timing in Septic Shock Patients

Shane D. Slone

*University of Kentucky*, [shane.slone@uky.edu](mailto:shane.slone@uky.edu)

[Right click to open a feedback form in a new tab to let us know how this document benefits you.](#)

### Recommended Citation

Slone, Shane D., "Effect of Enteral Feeding Timing in Septic Shock Patients" (2016). *DNP Projects*. 98.  
[https://uknowledge.uky.edu/dnp\\_etds/98](https://uknowledge.uky.edu/dnp_etds/98)

This Practice Inquiry Project is brought to you for free and open access by the College of Nursing at UKnowledge. It has been accepted for inclusion in DNP Projects by an authorized administrator of UKnowledge. For more information, please contact [UKnowledge@lsv.uky.edu](mailto:UKnowledge@lsv.uky.edu).

Final DNP Project Report

Effect of Enteral Feeding Timing in Septic Shock Patients

Shane David Slone

University of Kentucky

College of Nursing

Fall 2016

Melanie Hardin-Pierce, DNP, RN, APRN, ACNP-BC- Committee Chair

Chizimuzo (Zim) Okoli, PhD, MPH, MSN, RN - Committee Member

Theresa Loan, APRN, PhD, FNP-BC- Clinical Mentor

## **Dedication**

This DNP final project is dedicated to my beautiful and loving wife who has endured through this program and project with me. All of my successes are amplified by her encouragement and support.

## **Acknowledgments**

I am grateful to the many healthcare professionals, mentors, and teachers who have lent their knowledge and experience to me. The University of Kentucky College of Nursing and Hospital have prepared me for an exciting future in which I will better the care of critically ill patients.

**Dr. Hardin-Pierce** a special thank you for allowing me to transfer into the acute care program after I realized family practice was not an ideal fit for me. She has also enabled me to succeed in the program with my project and has provided excellent clinical opportunities.

**Dr. Chizimuzo Okoli** has been an excellent mentor and has helped me tremendously on the path to graduation.

**Dr. Terri Loan** has prepared me well as an undergrad and encouraged me to further my education. She has helped guide this project from the beginning and I am grateful for all of her assistance.

**Andrew McLaughlin** of the Center for Clinical and Translational Science deserves special thanks for his assistance in data collection. Without his help, a project of this size would be unmanageable.

**Dr. Amanda Wiggins** has been an excellent resource and has provided a plethora of time and resources in helping me decipher the statistical aspect of my project.

## Table of Contents

Acknowledgments.....	iii
List of Tables.....	v
Abstract.....	1
Introduction / Project Overview.....	2
Background and Significance.....	2
ASPEN and SCCM guidelines.....	4
Relevant literature.....	5
Objectives.....	10
Methods.....	11
Results.....	13
Report Conclusion.....	15
References.....	19
Appendix A: comprehensive literature review table.....	27
Appendix B: SOFA scoring system.....	38
Appendix C: Charlson comorbidity index.....	39
Report Bibliography.....	40

## **List of Tables**

Table 1: Demographic characteristics of the study sample and comparison by feeding.....	23
Table 2: Comparison of outcomes.....	24
Table 3: Multiple linear regression modeling LOS.....	25
Table 4: Multiple logistic regression modeling hospital mortality.....	26

## **Abstract**

The goal of this research project was to identify the effect of the timing of enteral nutrition (EN) initiation timing on in-hospital mortality, ICU LOS and hospital LOS among patients with septic shock requiring norepinephrine. The study design was a cross-sectional analysis of retrospective electronic health record data. Patients who had received norepinephrine for septic shock were divided into early EN initiation (within 48 hours of ICU admission) and late EN initiation (Greater than or equal to 48 hours after ICU admission) groups. 680 subjects were included; 469 in the early group and 211 in the late group. Demographics, comorbidities, and acuity were similar between the two groups. ICU and hospital LOS ( $P=.0002$ , CI 0.7-0.9,  $P<.0001$ , CI 0.59-0.77, respectively) were significantly shorter in the early EN group when controlling for demographics, comorbidities, and acuity. Mortality was not significantly different between the two groups when controlling for demographics, comorbidities, and acuity. There is a need for higher quality research on the subject, but these findings strengthen the argument that EN is safe and potentially beneficial for patients with septic shock requiring norepinephrine.

## **Introduction / Project Overview**

This project, titled “Effect of enteral feeding timing in septic shock patients” is a quasi-experimental retrospective study which aims to explore the relationship between enteral feeding (EN) timing and length of stay (LOS) and mortality in septic shock patients requiring norepinephrine. There is a lack of quality data on the subject and clinician practices vary considerably (Marik, 2014). In addition to the study itself, the relevant background, literature, and guidelines will be discussed.

## **Background and Significance**

Malnutrition is common among critically ill patients and is known to increase morbidity and mortality (Khalid, Doshi, & DiGiovine, 2010). For the purposes of this paper, malnutrition refers to inadequate provision of energy and nutrients during hospitalization (rather than chronic malnutrition as a result of pre-hospital conditions). Many critically ill patients are unable to ingest food due to weakness, mechanical ventilation, or altered level of consciousness (Khalid et al., 2010). In this instance, EN is supplied to the gastrointestinal tract via a tube inserted into the nose, mouth, or abdomen. The alternative to EN is parenteral nutrition, which is generally not recommended due to increased complication rates, such as infection (McClave et al., 2016).

In 2014 there were 2.1 million intensive care unit (ICU) admissions in the United States (CDC, 2016). A significant portion of those patients were hemodynamically unstable and required vasopressors. Vasopressors are medications that cause constriction of the vasculature, most often used to treat hypotension.

Critical illness induces a catabolic state but EN supplementation in this population is associated with decreased morbidity, mortality, and ICU LOS (McClave et al., 2016). However, during times of critical illness initiation, EN is often delayed or withheld. For example, in a



prospective study of a nurse-driven protocol to increase EN, Sameh, Halawa, Nisar, and Ahmed (2007) found that 50% of patients did not receive EN within the first 48 hours of ICU admission, yet the causes of the delay in treatment was not explored. Thus, understanding the effects of delayed EN administration is important for practice change.

Hemodynamically unstable patients requiring vasopressors present unique challenges for clinicians. In critically ill patients, EN can maintain the integrity of the gut, which is essential to recovery (Zaloga, Roberts, & Marik, 2003). Yet, EN supplementation among patients requiring vasopressors remains a controversial topic due to the potential compromise of the bowel by vasopressors and no major authority has specific recommendations regarding initiation and provision of EN (Patel et al., 2014).

### **Controversy and Concerns**

The safety and benefit of EN in hemodynamically unstable patients requiring vasopressors are largely unknown due to a paucity of research and conflicting theories. Some clinicians are concerned that vasopressors may increase the incidence of mesenteric ischemia and bowel necrosis in patients requiring vasopressors (Yang, Xigjiang, Wenku, & Jieshou, 2014). It is known that EN increases gastrointestinal oxygen needs; thus, in theory, patients requiring vasopressors and receiving EN would have increased oxygen demands, but decreased delivery, potentially leading to ischemia and necrosis (Zaloga et al., 2003).

There is also a concern regarding the hemodynamically failing body's ability to increase cardiac output in response to nutrition as compared to a healthy subject. For example, Revelly, Tappy, Gersbach, Cayeux, and Chioloro (2001) found that cardiac output increases when EN is initiated in patients requiring vasopressors but that systemic blood pressure decreases. This study demonstrates that the body's adaption to EN may be complex, involving both an increase in

cardiac output and peripheral shunting, presumably to provide more blood flow to the gut.

In the absence of high-quality research and/or guidelines, clinicians are given little direction on how to approach these patients. The lack of currently available information may lead to non-uniform and substandard care for these patients (Marik, 2014). Although popular theories state that EN supplementation may be dangerous (Marik, 2014), there may be an optimal delivery method (timing, dose) that may affect mortality and LOS. Recent literature supports this claim and suggests that fears may be overstated while considerable benefit may exist (Khalid et al., 2010; Lasierra et al., 2015; Patel et al., 2014; Mancl & Munzevich, 2013). It is important to explore the potential benefits of this treatment and engage in a realistic analysis of the safety concerns.

### **Sepsis: a Major Cause of Morbidity and Mortality**

Sepsis is directly responsible for about 258,000 deaths per year in America and is the ninth leading cause of disease-related mortality (CDC, 2015). Sepsis is the most expensive condition in the United States, costing an estimated \$20 billion in 2011 (NIH, 2015). Moreover, septic shock, a more severe form of sepsis carries a mortality of about 50% (Florian, Yende, & Angus, 2013). Norepinephrine is recommended as the first-line treatment of hypotension in patients with septic shock (Dellinger et al., 2013). However, various vasopressors may differentially affect EN tolerance.

### **ASPEN and SCCM guidelines**

The latest guidelines by the American Society of Parenteral and Enteral Nutrition (ASPEN) and the Society of Critical Care Medicine (SCCM) were released in February of 2016 (McClave et al., 2016). Of note, these guidelines recommend initiating EN within 24-48 of admission for critically ill patients. This practice is well-accepted and supported by adequate

literature (McClave et al., 2016). However, these guidelines and related research have not been validated in patients requiring vasopressors (McClave et al., 2016).

Special concern is given to patients who are hemodynamically unstable and requiring vasopressors. The recommendation is that patients who have hemodynamic compromise or instability should have EN withheld until resuscitation is complete and/or the patient is stable (not requiring vasopressors). Cautious initiation of EN may begin when vasopressor support is being weaned (titrated down) (McClave et al., 2016). However, the exact timing of EN initiation in patients requiring vasopressors is an area of much debate. Khalid, et al. (2010) observed that early initiation of EN (within 48 hours of admission) as compared to late initiation of EN (after 48 hours) was significantly associated with decreased mortality in the ICU (22.5% vs. 28.3%,  $p=.03$ ). The ASPEN and SCCM guidelines acknowledge this finding but do not specifically endorse this practice (McClave et al., 2016), likely due to the lack of strong evidence.

## **Relevant Literature**

### **Search Description**

A comprehensive search of PubMed, MEDLINE, Cochrane, EBSCOhost and CINAHL databases was performed. Search terms were: enteric feed(s), enteric feeding, enteral feeding, enteric nutrition, enteral nutrition, nutrition, nutritional support, feeding, tube feeding, hemodynamic failure, hemodynamic instability, unstable, vasopressors, and vasoactive. The timeframe for the search was January 2000 through February 2016. Inclusion criteria were: adult subjects (age greater than or equal to 18), patients requiring vasopressors (Norepinephrine, epinephrine, dopamine, phenylephrine and vasopressin) and concurrent EN, articles published in English and human subjects. Exclusion criteria were: pediatric patients (under age 18), animal subjects, meta-analysis, case reports, studies in any language other than English, non-

differentiation between patients requiring vasopressors and those not, patients not receiving vasopressors and EN concurrently, and studies published before 2000. After reviewing titles and abstracts of 42 articles, six articles met the inclusion criteria of which three were retrospective studies (Khalid et al., 2010; Patel et al., 2014; Mancl & Munzevich, 2013), two prospective observational studies (Lasierra et al., 2015; Berger, Revelley, Cayeux, & Chiolero, 2004) and one was a prospective cohort interventional study (Revelly et al., 2001).

A search for septic patients requiring norepinephrine was first attempted without result. Therefore, critically ill patients requiring vasopressors (a broader population) was reviewed.

### **The Evidence**

There are common themes in the topic of EN supplementation in patients requiring vasopressors and findings are mostly homogenous; it appears to be safe and potentially beneficial. Appendix A contains a summary of all relevant research, with additional related articles that did not fit the criteria of the literature review.

### **Safety**

First and foremost, one must consider the safety of EN supplementation in patients requiring vasopressors. The available evidence available strongly suggests that EN supplementation is relatively safe with a very low rate of complications. Additionally, in critically ill patients serious gastrointestinal (GI) complications may not be directly attributed to vasopressor use. Marik (2014) states that the fear of GI complications is often falsely assumed to be high.

Five studies (Lasierra et al., 2013; Revelly et al., 2001; Mancl & Muzevich, 2013; Patel et al., 2014; Berger et al., 2004) reported the occurrence of serious or life-threatening GI complications (such as bowel perforation or ischemia). Combined there were 441 patients

represented and three instances of serious GI complications. Furthermore, there were several confounding variables among the patients who experienced GI complications, such as initiating EN at an inappropriately high rate (greater than 20ml/hr) (Mancl & Muzevich, 2013). In a study by Steerfkerk, Beishuizen, and Groenveld (2014) a 500 milliliter EN bolus was given to patients requiring vasopressors (agents used not specified) without serious GI complications or measureable GI ischemia.

Lasierra et al. (2015) demonstrated that EN supplementation may be safe in patients with severe hemodynamic failure. The subjects in this study required mechanical circulatory support, mechanical ventilation, and at least two vasopressors (dopamine, epinephrine, or norepinephrine). Despite the severity of illness, these patients received EN without any serious complications, such as mesenteric ischemia. Furthermore, the authors found that minor GI complications (such as nausea and diarrhea) did not affect mortality.

### **Ability to physiologically adapt to EN supplementation**

There are concerns about the body's ability to increase GI blood flow and absorb nutrients in patients requiring intravenous vasopressors to treat shock. However, Revelley et al., (2000) found that EN supplementation was associated with a favorable hemodynamic response in cardiac shock patients requiring vasopressors. Cardiac output and splanchnic perfusion increased with EN supplementation, representing an appropriate physiologic response.

### **Timing of EN initiation**

Timing of EN initiation in patients requiring vasopressors is an area of much debate. Khalid et al., (2010) observed that early initiation of EN (within 48 hours of admission) was associated with decreased mortality compared to late initiation of EN (after 48 hours). The difference was pronounced, with 22.5% ICU mortality in the early EN group and 28.3% ICU

mortality in the late EN group ( $p=.03$ ). This study suggests that early initiation of EN, even during hemodynamic instability reduces mortality. The greatest mortality benefit was seen in those requiring two or more vasopressors (OR=.36, 95% CI; Khalid et al., 2010).

### **Dose of EN supplementation**

The dose of EN provided to critically ill patients requiring vasopressors is also an area of controversy. “Trophic” EN refers to a practice of permissive underfeeding (Marik, 2014), usually between 10-20 milliliters (ml) per hour of EN. Patel et al. (2014) examined the effect of withholding EN, trophic EN, or full EN to patients requiring vasopressors and mechanical ventilation. Mortality was not significantly different among groups, however LOS and duration of mechanical ventilation were. The trophic EN group had the lowest median LOS ( $p<.001$ ) and the shortest duration of mechanical ventilation ( $p<.001$ ). Furthermore, there were no instances of aspiration pneumonia in the trophic EN group, whereas the no EN and full groups experienced 6.7% and 7.2%, respectively (Patel et al., 2014). Overall, this study suggests that trophic EN may be the optimal dose for patients requiring vasopressors.

### **Dose of vasopressor**

The dose of vasopressor may also have in predicting tolerance of EN. Mancl and Muzevich (2013) found that there is a dose-dependent relationship between vasopressors and EN tolerance (defined as absence of gastric residuals less than 300ml, emesis, positive abdominal imaging, or bowel ischemia/perforation). The authors found that above a 12.5mcg/min “norepinephrine equivalency” EN intolerance is very likely ( $p=.009$ ). The authors provide a table detailing the calculation for each vasopressors equivalency. This information may be useful in stratifying a patient’s risk of EN intolerance based on vasopressor infusion doses.

## **Type of vasopressor**

A common theme among the research was that certain types of vasopressors are more likely to cause EN intolerance than others. Mancl and Muzevich (2013) found that vasopressin and dobutamine were associated with EN intolerance while phenylephrine alone did not cause EN intolerance. Berger et al., (2004) concluded that norepinephrine and dopamine were associated with feeding intolerance to a greater degree than dobutamine.

## **Appraisal of Evidence**

Overall the evidence supporting EN supplementation in patients requiring vasopressors is weak. There are no randomized controlled trials represented in the review. This is reflected in the weak recommendation (Grade E) provided by the Society of Critical Care Medicine and American Society of Parenteral and Enteral Nutrition to withhold EN in hemodynamically unstable patients (McClave et al., 2016).

The studies included in the review also lack power due to small sample sizes which impacts ability to generalize. Overall the review included 1615 subjects. Four of the six studies (Lasierra et al., 2015; Revelly et al., 2001; Patel et al., 2014; Berger et al., 2004) had less than 100 subjects. Most of the research did not specify the diagnoses and/or demographics of the subjects. This is a major limitation; as the safety and benefit of EN supplementation may vary among populations.

The themes listed above are limited by lack of raw data available in each study report. For example, not all of the authors provided data on when EN supplementation was initiated. Based on the study by Khalid et al., (2010) timing may be an important variable but the authors did not specify type or dose of vasopressor. Likewise, Mancl and Muzevich (2013) identified dose and type of vasopressor as a variable associated with EN tolerance but did not provide data

on timing. Ideally, more data would have been provided by each study so that the author could have examined data to validate themes across studies.

The strength of the available research is that the findings are mostly congruent and in agreement with one another. Expert opinion on the subject (see Appendix A), while based mostly on clinical experience is also consistent. All of the available research suggests that EN supplementation is likely safe and beneficial in patients requiring vasopressors. Unpublished research was not included in this review.

### **Selection of Timing as a Variable to Examine**

There are a plethora of potential variables that may affect the administration of EN in patients requiring vasopressors, as evidenced above. Timing was chosen as the variable to be studied because it represents a potentially modifiable variable that could affect the outcome of patients. Dose of EN was not studied as information on titration and dose of EN are not readily available at the institution being studied.

### **Objectives**

The goal of this research project was to identify the effect of the timing of EN supplementation on in-hospital ICU LOS, hospital LOS, and mortality in patients diagnosed with septic shock requiring norepinephrine (levophed). Specific objectives are as follows:

- 1.) Explore the relationship between EN initiation timing and ICU LOS in septic shock patients requiring norepinephrine.
- 2.) Explore the relationship between EN initiation timing and hospital LOS in septic shock patients requiring norepinephrine.
- 3.) Explore the relationship between EN initiation timing and in-hospital mortality in septic shock patients requiring norepinephrine.



- 4.) Explore the relationship between demographic data (gender/age) and mortality, ICU LOS, and hospital LOS.

## **Methods**

### **Study Design**

The study was a cross-sectional analysis of retrospective medical record data from patients at the University of Kentucky Medical Center. Institutional review board approval was obtained on August 10, 2016. Data were electronically collected by the University of Kentucky's Center for Clinical and Translational Science department.

Patients were divided into "early" (EN initiation less than 48 hours after ICU admission) and late (EN initiation greater than 48 hours after ICU admission) for data analysis. A total of 469 patients were in the early EN group and a total of 211 were in the late EN group.

### **Population**

The sample for this study was 680 patients that were admitted and discharged (or deceased) from the University of Kentucky's Chandler Hospital. Data were collected from January 1, 2005 to July 31, 2015 on patients who were: between 18 and 89 years of age, required norepinephrine within 48 hours of admission to the ICU with a diagnosis of "SIRS, sepsis, severe sepsis, or septic shock," and received EN supplementation during ICU stay.

Exclusion criteria were: Age less than 18 years or greater than 89 years, not requiring norepinephrine within 48 hours of admission, not having been supplied EN during ICU stay, death or transfer within 48 hours of admission.

### **Variables Collected**

ICU LOS, hospital LOS, outcome (deceased or alive) age (in 10 year increments), gender, Charlson Comorbidity Index (CCI), and Sequential Organ Failure Assessment (SOFA)

score were collected for each patient. CCI was used to control for chronic (pre-hospital) conditions and SOFA was used to control for acuity.

### **Definition of Variables**

Diagnosis of septic shock was obtained by including patients who were diagnosed with systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, or septic shock and prescribed norepinephrine during ICU stay. EN initiation time was obtained by collecting the time of order entry for any tube feeding supplement at any rate. Mortality was obtained by coding patients with a “notification of death” during their hospital stay as deceased. ICU LOS was obtained from electronic chart and included all ICU days during an admission. Hospital LOS was obtained from the patients EHR and included all hospital days during an admission.

### **SOFA Score**

SOFA scores were calculated using the earliest recorded lab values after ICU admission. Oxygen requirements, vasopressor doses, Glasgow coma scale, and mean arterial pressure were calculated with the highest score (points on scale) while in the ICU.

The SOFA score was originally developed to predict the outcome of SIRS patients. It is often used as an acuity indicator. It assigns a score to six categories based upon normalcy/dysfunction: respiration, coagulation, liver, cardiovascular, central nervous system and renal (See Appendix B). A higher score indicates increasing organ failure (Vincent et al., 1996). The SOFA score has been validated and is well-accepted for patients on the SIRS/ sepsis continuum (Jones, Trzeciak, & Kline, 2009).

### **CCI**

CCI scores were calculated upon hospital admission, based on previous chronic conditions. The CCI is frequently used to quantify chronic, comorbid conditions in critically ill

patients. It was originally designed to predict one-year patient mortality by calculating morbidity. The index accounts for 18 broad conditions with varying point allotment; a higher score indicates more chronic conditions (See Appendix C). It is an accepted and well validated scale (Needham, Scales, Laupacis, & Pronovost 2005).

### **Statistical Analysis**

Age differences between the early and late EN groups were compared using the Mann-Whitney U test, sex was compared using the Chi-square test, and CCI and SOFA were compared using t-tests. The Mann-Whitney U test was used to compare the early and late EN groups' ICU LOS and hospital LOS. The Chi-square test was used to compare mortality between the early and late EN initiation groups.

ICU LOS and hospital LOS log-transformed to adjust for the non-normal distribution of the original data. Multiple linear regression was performed to assess whether or not EN initiation timing (early vs late) was predictive of ICU and Hospital LOS while controlling for age, sex, CCI, and SOFA scores.

### **Results**

Demographics, CCI and SOFA scores were similar between the early and late EN groups (see Table 1). There was no significant difference between any variable except sex; a higher proportion of females were in the late EN group ( $p=.043$ ). 98.9% of patients (673) were mechanically ventilated.

ICU LOS and hospital LOS were significantly shorter in the early EN group ( $p<.001$  for both comparisons). The median ICU LOS for the early EN group was 9.3 days compared to 12.7 days for the late EN group. The median hospital LOS for the early EN group was 14.6 days,

compared to 21.6 days for the late EN group (see Table 2). There was no significant relationship between EN initiation and mortality ( $p=.68$ ).

The overall linear regression model for ICU LOS was significant ( $F = 5.96$  ;  $R^2 = .09$ ,  $p < .001$ ). The geometric mean, as opposed to the log-transformed mean (in Table 3) is interpreted in this section. ICU LOS was significantly shorter in the early EN group ( $p < .001$ ) when controlling for age, sex, CCI and SOFA scores (see Table 3). The early EN group had an average of 20% fewer ICU days than those in the late EN group. Sex was a significant predictor of ICU LOS ( $p = .013$ ). Females had a 15% average increase in ICU days compared to males. There was a significant association between ICU LOS and CCI ( $p < .001$ ). For every one-point increase in CCI, there was an additional 5% increase in ICU days; a five-point increase was associated with an average of 30% increase in ICU days. There was also a significant association between SOFA scores and ICU LOS ( $p < .001$ ). For every one-point increase in SOFA there was an additional 5% ICU days; a five-point increase added 15% to ICU days. There was no association between age and ICU LOS.

The overall linear regression model for hospital LOS was significant ( $F = 6.49$  ;  $R^2 = 0.10$ ,  $p < .001$  ). Hospital LOS was significantly shorter in the early EN group ( $p < .001$ ) when controlling for age, sex, CCI and SOFA scores. The early EN group had an average of 33% fewer hospital days than the late EN group. There was also a significant association between age and hospital LOS ( $p = .007$ ). Those aged 18-19 had an average of 61% shorter hospital LOS ( $p < .001$ ). There was a significant association between CCI and hospital LOS ( $p < .001$ ). For every one point increase in CCI, there was an average of 6% increase in hospital days; a five-point increase was associated with an additional 33% hospital days. There was no significant association between sex or SOFA and hospital LOS.

Overall logistic regression was significant ( $X^2 = 67.8, p < .001$ ). Hospital mortality was not statistically different between the early and late EN groups, controlling for age, sex, CCI, and SOFA score (see Table 4). There was a significant association between age and hospital mortality ( $p = .002$ ). Younger subjects were less likely to experience death than older subjects. SOFA score had a significant association with hospital mortality ( $p < .001$ ); those with higher SOFA scores were more likely to experience mortality. Sex and CCI were not associated with hospital mortality.

### **Report Conclusion**

The findings of the study demonstrate that ICU and hospital LOS may be reduced by initiating EN within 48 hours of ICU admission for patients in septic shock. The difference between the median ICU days for early and late EN was 3.4 ICU days. Given that there was no significant difference between CCI or SOFA scores among the early and late EN groups, the mean differences in ICU days between groups cannot be attributed to those factors. However, in the multiple linear regression model the  $R^2$  value of 0.09 and 0.10 indicates that the variables collected in this study poorly controlled for ICU and hospital LOS. A similar study examined patients on vasopressors exclusively and found no difference in ICU LOS between those supplied with EN early (before 48 hours) or late (after 48 hours) of mechanical ventilation initiation (Khalid et al., 2010).

Possible confounding variables include dose of provider/nursing care, pre-ICU care quality and total pre-ICU time. It is possible that patients who were ordered EN earlier also received higher quality provider and/or nursing care. For example, patients who were fed earlier may have also been more likely to receive standardized sepsis care in accordance to evidence-

based bundles or guidelines. However, pre-ICU care quality and pre-ICU time are difficult to measure and were not included in this study.

Hospital LOS was also lower in the early EN group. The difference between the median among the two groups was seven hospital days. As previously discussed, the linear regression model demonstrated that there were other confounding variables contributing to LOS. The hypothesized confounding variables (dose of provider/nursing care, pre-ICU care quality, and total pre-ICU time) are similar for hospital and ICU LOS.

Early EN initiation may result in increased efficiency and decreased cost when compared to late EN initiation. In this study, there were 3.4 greater ICU days in the late versus early EN group. The cost of an ICU day is between \$3,496 and \$10,794 (Dasta, McLaughlin, Moody, & Piech, 2005). That represents a cost saving of between \$11,886 and \$36,699 per patient for ICU care. Furthermore, the median hospital days were seven days shorter in the early EN group. The cost of a non-ICU day is between \$1,470 and \$1,716 in Kentucky (Kaiser Family Foundation, 2016). This represents a cost saving of between \$10,290 and \$12,012 per patient. Additionally this opens hospital beds (both ICU and non-ICU) so that other patients may receive care.

There was no association between EN initiation and hospital mortality, even when controlling for sex, age, CCI and SOFA scores. This finding differs from that of Khalid et al. (2010) who found that a mortality benefit was realized for patient who were supplied with EN within 48 hours of mechanical ventilation ( $p=.03$ ). However, Khalid et al.'s (2010) study was larger ( $n=1174$ ) and included patients in various types of shock, whereas this study only included septic shock patients. Furthermore, Khalid et al.'s (2010) study began the 48 hours at time of mechanical ventilation, as opposed to time of ICU admission this study.

The results of this study are best interpreted in the context of previous research. To the author's knowledge, there is no study demonstrating an increase in mortality when providing EN to patients on vasopressors. However, one study has found a mortality benefit (Khalid et al., 2010). Patel et al (2014) found that LOS was decreased among patients requiring vasopressors when supplied EN. The LOS benefit represents significant cost-saving and efficiency potential.

### **Limitations**

This study has several key limitations. First, the nature of the study (observational, retrospective) is an inherent limitation. The timespan of this study, which was approximately 10 years, is also significant. There may have been changes in both medical education and practice relating to sepsis treatment and EN initiation / timing practices. The definition of septic shock used in this study may have also captured some patients who were not truly in septic shock.

### **Implications for Practice and Research**

Due to the sample size and limitations listed above, there is no practice change recommended at this time. However, this study does add to the pool of evidence stating that early EN initiation for patients requiring vasopressors is likely safe and beneficial. Furthermore, this study demonstrates that there is a need for high quality research on the subject. There are several retrospective studies on the subject; a prospective randomized controlled trial would best control for the confounding variables and give providers the evidence needed for a practice change.

Ideally, future research would include all of the variables discussed above: type of vasopressor, dose of vasopressor, patient diagnosis, EN initiation timing, and EN supplementation dose. There is currently one study titled "A randomized controlled trial of enteral nutrition in septic shock," which is currently recruiting subjects (U.S. National Institutes of Health, 2016).

## **Conclusions**

In conclusion, this study found that early EN supplementation may decrease ICU and hospital LOS, but did not affect mortality. There are several variables such as dose of EN, dose of vasopressor, and additional types of vasopressors required which represent identified confounding variables not accounted for in this study. There is no practice change recommended at this time based upon the findings of this study and a review of the relevant literature. A randomized controlled trial which comprehensively accounts for all known confounding variables is necessary to drive practice change.



## References

- Berger, M., Revelly, J.P., Cholero, R. (2004). Enteral nutrition in critically ill patients with severe hemodynamic failure after cardiopulmonary bypass. *Clinical Nutrition*, 24, p124-132. DOI: 10.1016/j.cinu.2004.08.005.
- Center for Disease Control. (2015). Sepsis. Retrieved from <http://www.cdc.gov/sepsis/>
- Center for Disease Control. (2016). Emergency department visits. Retrieved from <http://www.cdc.gov/nchs/fastats/emergency-department.htm>
- Dasta, J.F., McLaughlin, T.P., Mody, S.H., Piech, C.T. (2005). Daily cost of an intensive care unit day: the contribution of mechanical ventilation. *Critical Care medicine*, 33(6), P1266-71.
- Dellinger, R.P., Levy, M.M., Rhodes, A., Annane, D., Gerlach, H., Opal S., ... Moreno, R. (2013). Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Critical Care Med*, 41(2), p580–637. DOI: 10.1097/CCM.0b013e31827e83af
- Florian, M., Yende, S., Angus, D. (2013). Epidemiology of Severe Sepsis, 2013. *Virulence*, 5(1), p4-11. DOI: 10.4161/viru.27372
- Jones, A., Trzaciak, S., & Kline, J. (2009). The sequential organ failure assessments score for predicting outcome in patients with severe sepsis and evidence of hypo perfusion at the time of emergency department presentation. *Critical care med*, 37(5), p1649-1654. DOI: 10.1097/CCM.0b013e31819def97
- Kaiser Family Foundation. (2016). Hospital adjusted expense per inpatient day by ownership. Retrieved from <http://kff.org/other/state-indicator/expenses-per-inpatient-day-by->

ownership/?currentTimeframe=0&sortModel=%7B%22colId%22:%22Location%22,%22  
sort%22:%22asc%22%7D

Khalid, I., Doshi, P., DiGiovine, B. (2010). Early enteral nutrition and outcomes of critically ill patients treated with vasopressors and mechanical ventilation. *American Journal of Critical Care*, 19(3), p261–268. DOI: 10.4037/ajcc2010197

Lasierra, J., Perez-vela, J., Makikado, L., Sanchez, E., Gomez, L., Rodriguez, B., Lopez, P., Camara, A., Gonzalez, J. (2015) Early enteral nutrition in patients with hemodynamic failure following cardiac surgery. *Journal of Parenteral and Enteral Nutrition*, 39(2), p154-162. DOI: 10.1177/0148607113504219

Marik, Paul. (2014). Enteral nutrition in the Critically Ill: Myths and Misconceptions. *Critical care medicine*, 42(4) p962-969. DOI: 10.1097/CCM.0000000000000051

Mancl, E.E., Muzevich, K.M. (2013). Tolerability and safety of enteral nutrition in critically ill patients receiving intravenous vasopressor therapy. *Journal of parenteral and enteral nutrition*, 37(5), p641-51. DOI: 10.1177/0148607112470460.

McClave, S., Taylor, B., Martindale, R., Warren, M., Johnson, D., Braunschweig, C., McCarthy, M., Davanos, E., Rice, T., Cresci, G., Gervasio, J., Sacks, G., Roberts, P., Compher, C., & the Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition (2016). Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient. *Journal of Parenteral and Enteral Nutrition*, 40(2), p159-211. Doi: 10.1177/0148607115621863

Melnyk, B.M., & Fineout-Overholt, E. (2011). Evidence-based practice in nursing and healthcare: A guide to best practice. Philadelphia: Lippincott, Williams & Wilkins.

- National Institutes of Health. (2015). Sepsis fact sheet. Retrieved from [https://www.nigms.nih.gov/Education/Pages/factsheet\\_sepsis.aspx](https://www.nigms.nih.gov/Education/Pages/factsheet_sepsis.aspx)
- Needham, Scales, Laupacis, & Pronovost (2005). A systematic review of the Charlson comorbidity index using Canadian administrative databases: a perspective on risk adjustment in critical care research. *Journal of critical care*,20(1) p12-9.
- Patel, J.J., Kozeniecki, M., Biesboer, A., Peppard, W., Ray, A.S., Thomas, S., Jacobs, E.R., Nanchal, R., & Kumar, G. (2014). Early trophic enteral nutrition is associated with improved outcomes in mechanically ventilated patients with septic shock: a retrospective review. *Critical Care Medicine* (2011) 39(5): 967–974. DOI: 10.1097/CCM.0b013e31820a905a
- Revelly, J.P., Tappy, L., Berger, M.M., Gersbach, P., Cayeux, C., Chioloro, R. (2001). Systemic and splanchnic hemodynamic response to early enteral nutrition in postoperative patients treated for circulatory compromise. *Intensive Care Medicine*, 27, p450-457.
- Sameh, T., Demian, M., Nehad, N., Halawa, M., Batool, N., & Raees, A. (2007). Nurse-Driven enteral feeding protocol improves caloric intake in critically ill patients. *Chest*, 132(4) p442c-443. DOI:10.1378
- Steerfkerk, J., Beishuizen, A., Groenveld, J. (2014) .Gastric feeding intolerance is not caused by mucosal ischemia Measured by intragastric air tonometry in the critically ill. *Clinical Nutrition*, 25(3), p731-734. DOI: 10.1016/j.clnu.2015.05.015
- Turza, K., Krenitsky, J., Sawyer R. (2009). Enteral Feeding and Vasoactive Agents: Suggested Guidelines for Clinicians. *Practical gastroenterology*, 33(9), p11-22.
- U.S. National Institutes of Health. (2016). A randomized controlled study of enteral nutrition in septic shock. Retrieved from <https://clinicaltrials.gov/ct2/show/NCT02025127>

- Vincent, J.L., Moren, R., Takala, J., Willatts, S., De Mendonca, A., Bruining, H., Reinhart, C.K., Suter, P.M., & Thijs, L.G. (1996). The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. *Intensive Care Med*, 22(7), p707-710.
- Yang, S., Xingjiang, W., Wenku, Y., Jieshou, L. (2014). Early enteral nutrition in critically ill patients with hemodynamic instability: an evidence-based review and practical advice. *Nutrition clinical practice*, 29(1), p90-106. DOI: 10.1177/0884533613516167
- Zaloga, G., Roberts, P., & Marik, P., (2003). Feeding the hemodynamically unstable patients: a critical evaluation of the evidence. *Nutrition in clinical practice*, 18, p285-293. DOI: 10.1177/0115426503018004285

**Table 1****Demographic characteristics of the study sample and comparison by feeding (N=680)**

	Early (n =469 )	Late (n =211)	<i>p</i>
<b>Age</b>			<i>.73</i>
18-19	2 (0.4%)	0 (0%)	
20-29	21 (4.5%)	7 (3.3%)	
30-39	41 (8.7%)	18 (8.5%)	
40-49	63 (13.4%)	37 (17.5%)	
50-59	124 (26.4%)	53 (25.1%)	
60-69	121 (25.8%)	56 (26.5%)	
70-79	72 (15.4%)	30 (14.2%)	
80-89	25 (5.3%)	10 (4.7%)	
<b>Sex</b>			<i>.043</i>
Male	246 (52.5%)	93 (44%)	
Female	223 (47.5%)	118 (56%)	
<b>CCI</b>	Mean=5.1 Standard Deviation=2.06	Mean=5.04 Standard Deviation=2.28	<i>.71</i>
<b>SOFA score</b>	Mean=9.0 Standard Deviation=4.0	Mean=8.96 Standard Deviation=4.37	<i>.89</i>

**Table 2****Comparison of outcomes (N=680)**

	Early (n =469 ) <i>Median (IQR)</i> or <i>n (%)</i>	Late (n =211) <i>Median (IQR)</i> or <i>n (%)</i>	<i>p</i>
ICU LOS	9.3 (5.8 – 16.0)	12.7 (6.9-19.9)	<.001
Hospital LOS	14.6 (8.8-25.5)	21.6 (13.6-40.5)	<.001
Mortality			.68
Yes	143 (30.5%)	61 (28.9%)	
No	326 (69.51%)	150 (71.09)	

**Table 3****Multiple linear regression modeling LOS (N=680)**

	ICU LOS (R2 =0.09 , F =5.96 , p = <.001)			Hospital LOS (R2 = 0.10, F =6.49, p = <.001)		
	estimate	CI	p	estimate	CI	p
Age			.7			.007
18-19	-.8	.16-1.13		.94	.13-1.17	.09
20-29	.37	1.01-2.07		.71	1.38-3.02	<.001
30-39	.24	.95-1.73		.17	.85-1.65	.32
40-49	.08	.82-1.43		.24	.94-1.71	.12
50-59	.12	.87-1.46		.2	.92-1.62	.16
60-69	.15	.9-1.51		.23	.95-1.66	.12
70-79	.13	.87-1.5		.14	.85-1.55	.36
80-89	ref			ref		
Sex						
Female	.14	1.03-1.28	.013	-.02	.87-1.09	.70
Male	ref			ref		
CCI	.05	1.03-1.08	<.001	.06	1.03-1.09	<.001
SOFA	.03	1.06-1.04	<.001	.003	.99-1.02	.72
Feeding						
Early	-.022	.7-9	<.001	-.39	.59-.77	<.001
Late	ref			ref		

\*This analysis uses the log-transformed versions of the LOS variables to adjust for the non-normal distribution of the original data. Data described in text are in actual days format.

**Table 4****Multiple logistic regression modeling hospital mortality (N= 651, Chi-square=67.8, p<.001)**

	Odds Ratio	CI for OR	<i>p</i>
Age			.002
18-19	1.44	.07-28.03	.81
20-29	.09	.02-.37	<.001
30-39	.28	.109-.72	.008
40-49	.26	.109-.6	.002
50-59	.26	.118-.58	<.001
60-69	.39	.179-.84	.02
70-79	.56	.25-1.27	.17
80-89	Reference		
Sex	1.02	.71-1.45	.92
CCI	1.02	.94-1.11	.6
SOFA	1.19	1.13-1.25	<.0001
EN initiation			.59
early	.9	.61-1.32	
late	Reference		

\*SOFA score calculated with n=448 in early EN group and n=203 in late EN group. 29 Subjects without necessary data to calculate the SOFA score.



## Appendix A: Comprehensive Literature Review Table

<u>Author/ Year Published</u>	<u>Conceptual Framework</u>	<u>Design/ Method</u>	<u>Sample/ Setting</u>	<u>Variables</u>	<u>Measurements</u>	<u>Data Analysis</u>	<u>Findings</u>	<u>Level of Evidence</u>	<u>Quality of Evidence / Implications/ Comments</u>
Enteral nutrition in critically ill patients with severe hemodynamic failure after cardiopulmonary bypass									
Berger M, Revely JP, Cholero R. 2005	None utilized	Quantitative, prospective, observational.  Followed 70 patients as EN was begun and advanced to goal over 5 days.	70 Patients requiring ECMO with cardiovascular failure.	Independent variables: route of nutritional support, vasopressor use.  Dependent variables: Total energy delivery from all routes.	One-way ANOVA used to compare patient variables and two-way ANOVA used to compare changes over time.	Dopamine use negatively related with daily enteral energy delivery (p=.03, F ratio=4.69).  Norepinephrine use negatively associated with daily enteral energy delivery (P=.0003, F ratio=8.96).  Dobutamine use negatively associated with daily enteral energy delivery (P=.09, F ratio=2.82).	Norepinephrine and dopamine were associated with intolerance to goal feed, but partial feeds were possible.  Dobutamine was slightly associated with decreased feeding tolerance.  There were no recorded incidences of serious GI complications.	4	This study strengthens the argument that caution must be used when feeding on vasopressors and inotropes, but evidence suggests it can be done to some degree safely.  The study examined patients on ECMO, which is a very specific subset of patients.  The study did not examine ICU/Hospital mortality



					from mechanical ventilation to death.	On multiple vasopressors, benefit of early EN more evident (OR=.36, 95% CI)			
--	--	--	--	--	---------------------------------------	---	--	--	--

Early enteral nutrition in patients with hemodynamic failure following cardiac surgery

Lasierra J., Perez-vela J., Makikado L., Sanchez E., Gomez L., Rodriguez B., Lopez P., Camara A., Gonzalez J.  2015	None utilized.	Quantitative, Prospective observational.  Examined patients with hemodynamic failure examining primarily the safety of EN.	37 post-cardiac surgery patients on 2 or more vasopressors and/or mechanical circulatory support and at least 24 hours of mechanical ventilation and receiving EN.	Independent: Hemodynamic failure  Dependent: EN safety.	Fisher exact test used for qualitative variables in contingency table, Wilcoxon-Mann-Whitney test or student t test used to compare ordinal or continuous distributions.	EN related complications observed in 62% of patients.  No instances of serious or life-threatening complications.  No significant difference in mortality between those with and without EN complications.	No significant safety events in hemodynamic failure patients receiving EN.  No cases of mesenteric ischemia noted.	4	This study exhibits that feeding on vasopressors may be safe in this population.  The study does not differentiate between type of vasopressor or dose.  Some patients were supplemented with parenteral nutrition, may represent a confounding variable.
---	----------------	--	--	---	--	--	--	---	---

Tolerability and safety of enteral nutrition in critically ill patients receiving intravenous vasopressor therapy

<p>Mancl E.E., Muzevich K.M. 2013</p>	<p>None utilized.</p>	<p>Quantitative Retrospective analysis. Patients examined for evidence of enteric feeding tolerability with concurrent vasopressor use.</p>	<p>259 adult ICU patients and 346 occasions of tube feeding and vasopressors concurrent use.</p>	<p>Independent: Type of vasopressor used, dose of vasopressor used, use of pro-motility agents. Dependent: EN tolerance (see article for definition), mortality rates.</p>	<p>X<sup>2</sup> test of independence for nominal data, Fisher exact test for continuous data, Brown-Forsythe test for unequal variances, Welch's analysis for heterogeneous unequal variances, multivariable regression for independent predictors of reduced EN tolerance.</p>	<p>Dose-dependent relationship observed between norepinephrine equivalent vasopressor use and EN tolerance. Lower vasopressor use for those who tolerated EN (12.5 vs 19.4 norepinephrine equivalent mcg/min, P=.0009). EN tolerance did not correlate with mortality. Patients never prescribed vasopressin more likely to tolerate EN (77.9% vs 58.9%, P=.0027). Patient never prescribed dopamine more likely to tolerate EN (77.6% vs 63.8%,</p>	<p>Risk of EN intolerance increases as dose of vasopressor does. Equivalent of 12.5mcg/min of norepinephrine is tolerated well 3 cases of perforated bowel during study. 1 was on 3 vasopressors, the other 2 were started on high-dose feeds initially. Vasopressin was related to highest incidence of feeding intolerance; Dopamine was 2<sup>nd</sup>. Phenylephrine was associated with increased tolerance.</p>	<p>4 This study gives us some indication as to when the risk EN intolerance is greatest (above 12.5mcg/min norepinephrine equivalent). This study demonstrates that vasopressin may significantly decrease the ability to tolerate EN. More data is needed on each vasopressor in individual diagnoses or settings (sepsis, MI, etc.) in order to drive practice change. Much of the variability in medication response could be due to drug of choice in varying settings/diagnoses.</p>
---------------------------------------	-----------------------	---	--	--	--	--	---	---

								P=.018). Patient who received phenylephrine more likely to tolerate EN (100% vs. 73%, P=.0023).		
Enteral Nutrition in the Critically Ill: Myths and Misconceptions										
Marik, P. 2014	Non e utili zed.	Expert opinion with reference s.  Discusses common myths regarding nutrition in the critically ill, including the topic of vasopress ors.	N/A	N/A	N/A	N/A	N/A	The author believes that vasopress ors are not a contraindi cation to EN. Furthermo re, he believes that this common myth. He cites studies showing benefits of EN even while requiring vasopress ors.	7	Author does not directly address argument against EN. He presents some studies that utilized animal models to demonstra te safety.
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 of Parenteral and Enteral Nutrition (A.S.P.E.N.)										
McClave S., Taylor B., Martindale R., Warren M., Johnson D., Braunschweig C., McCarthy M., Davanos,E., Rice	Non e utili zed.	Expert/A uthority opinion. Use of literature review and expert	n/a	n/a	n/a	n/a	n/a	Grade E recommen dation to hold EN in hemodyna mically unstable	7	Authority of subject, but provides very little guidance on when to initiate

T., Cresci G., Gervasio J., Sacks G., Roberts P., Compher C.,		opinion with grading scheme (A-E).					patient.		EN on hemodynamically unstable patient (i.e., those requiring vasopressors).
---	--	------------------------------------	--	--	--	--	----------	--	--

Early trophic enteral nutrition is associated with improved outcomes in mechanically ventilated patients with septic shock: a retrospective review

Patel, J.J., Kozeniecki, M., Biesboer, A., Peppard, W., Ray, A.S., Thomas, S., Jacobs, E.R., Nanchal, R., & Kumar, G.,  2014	Non utilized.	Quantitative, Retrospective analysis.  Examined effect of EN on multiple patient outcome variables.	66 patients in septic shock requiring mechanical ventilation and vasopressors.	Independent: No EN, trophic EN, full EN,  Dependent: Duration of mechanical ventilation, aspiration pneumonia rates, EN-specific complications, length of stay, in-hospital mortality.	Categorical variables compared with chi-square test with Bonferroni correction.  Kruskal-Wallis test for table 1, which contains log transformed duration of mechanical ventilation and length of stay.	Multiple vasopressors used in 40% of no EN, 13.5% of trophic EN and 21.4% of full EN.  In-hospital mortality was 33.3% in no EN, 21.6% in trophic EN and 21.4% in full EN (P=.64).  Length of stay was 12 days in no EN, 5 in trophic EN and 13 in full EN (P<.001).  Duration of mechanical	Multiple vasopressors used least in the trophic group, could represent a confounding variable.  Mortality lowest in trophic EN, but not statistically significant.  Length of stay shortest in trophic EN.  Duration of mechanical ventilation lowest in trophic EN group.  No instances of aspiration	4	Multiple vasopressors or use least in trophic group, concerning that this may represent confounding variable (acuity) However, APACHE 2 scores similar among all groups.  Shows possible benefit to trophic feeds in septic shock patients requiring vasopressors, but may not be able to extrapolate to other populations.  Most current practice guidelines
--	---------------	---	--	--	---	--	--	---	---

						<p>cal ventilation was 2.41 times longer in no EN (P=.14) and 1.49 times longer in full EN (P=.004) compared to trophic EN.</p> <p>No instances of aspiration pneumonia in trophic EN, compared to 6.7% and 7.2% in no EN and full EN, respectively.</p> <p>No instances of non-occlusive mesenteric ischemia in any group.</p>	<p>pneumonia in trophic EN group, comparable among other 2 groups.</p> <p>No life-threatening complications of EN noted.</p>	<p>advocate for no or low amounts of EN for hemodynamically unstable patients. This gives evidence that “low” or “trophic” may be better than no EN.</p>
<p>Systemic and splanchnic hemodynamic response to early enteral nutrition in postoperative patients treated for circulatory compromise</p>								

<p>Revelly J.P., Tappy L., Berger M.M., Gersbach P., Cayeux C., Chiolo R.</p> <p>2001</p>	<p>None utilized.</p>	<p>Quantitative, Prospective.</p> <p>EN was initiated and multiple metabolic and hemodynamic measurements were collected in the fasted state and after enteric feeds began.</p>	<p>Nine post-op cardiac surgery patients requiring vasopressors and/or inotropes.</p>	<p>Independent: Fasted state vs fed state.</p> <p>Dependent: Cardiac index, mean arterial pressure, pulmonary capillary wedge pressure, ICG clearance, gastric tonometry, plasma glucose/insulin and plasma lactate.</p>	<p>One-way analysis of variance for data collected every 60 minutes, compared by Dunnett's test.</p>	<p>Cardiac output increased progressively and was statistically significant (10% greater than baseline) two hours after EN initiation.</p> <p>Mean arterial pressure decreased by 11%, after EN initiation, but returned to baseline within 300 minutes.</p> <p>Pulmonary capillary wedge pressure remained constant.</p> <p>Insulin and glucose levels increased after EN initiation.</p> <p>Gastric</p>	<p>EN increases CI progressively and decreases mean arterial pressure transiently.</p> <p>Metabolic response was not impaired splanchnic blood flow seemed to increase. This indicates that these patients were able to respond appropriately to EN initiation.</p>	<p>4</p>	<p>This study demonstrates that small amounts of enteric feeds can be well tolerated in hemodynamically unstable post-op cardiac patients, with favorable increases in cardiac output and splanchnic blood flow.</p> <p>It is very limited in the fact that there were nine participants and it measured five hours.</p> <p>Despite limitations, indicates that at least some hemodynamically unstable patients respond favorably to EN initially.</p>
---	-----------------------	---	---	--	--	---	---	----------	--



						tonometry and ICG clearance indicate an increased splanchnic blood flow after EN initiation.				No evidence of EN intolerance noted.
Gastric feeding intolerance is not caused by mucosal ischemia Measured by intragastric air tonometry in the critically ill										
Steerfkerk, J., Beishuizen, A., Groeneveld, J. 2014	None Utilized	Interventional, Non-randomized, convenience sample. Patients selected consecutively based on criteria, given 500ml bolus of EN and intolerance endpoints measured.	30 patients, all critically ill mechanically ventilated, most requiring vasopressors.	Independent: 500ml bolus of EN Dependent: Gastric residual volume, Mucosal PCO2.	Fisher exact test for categorical data, student t test for continuous data.	PCO2 gradient did not change after feeding (p=0.80) Gastric residual volume did not correlate with increase PCO2 gradient (p=0.75) No instances of intolerance in all 30 patients.	Bolus feedings were tolerated and not associated with gut mucosal ischemia in patients requiring vasopressors.	4	Provides some evidence that EN does not cause gut ischemia and that vasopressors do not cause feeding intolerance.  Many limitations; most of the raw data is not available in the article, the sample is very small, and data was only collected 2 hours	

										post EN on one occasion.
--	--	--	--	--	--	--	--	--	--	--------------------------

Enteral Feeding and Vasoactive Agents: Suggested Guidelines for Clinicians

Turza K., Krenitsky J., Sawyer R., 2009	None utilized	Expert opinion with supporting references.	n/a	n/a	n/a	n/a	Propose a four-phase process for initiating EN in patients requiring vasopressors based mostly on experience but some research integrated.  Acknowledges lack of high-quality research on the subject.	7	Interesting proposal of four-phase EN feeding protocol.  Heavy emphasis on monitoring once EN begun, theme is common in several articles among experts.  Recommends against any EN in patients requiring high-dose vasopressors.
--	---------------	--	-----	-----	-----	-----	--	---	--

Early enteral nutrition in critically ill Patients with hemodynamic instability: an evidence-based review and practical advice

Yang S., Xingjiang W., Wenku Yu., Jieshou, Li. 2014	None utilized	Expert opinion with supporting references.	n/a	n/a	n/a	n/a	Acknowledges that there is a gap in literature on the subject. Recommends not withholding EN due to probable benefit, but advocates very careful monitoring for complications.	7	Echoes popular sentiment of not withholding EN due to lack of current knowledge.  Chinese physicians, evidences that this issue is international and not specific to the U.S.
--	---------------	--	-----	-----	-----	-----	--	---	---

EN=Enteral nutrition

ECMO= extra corporeal membrane oxygenation

Level of evidence appraisal per Melynck & Fineout-Overholt (2011).

**Level 1** – Systematic review of all relevant randomized controlled trials (RCT) or clinical practice guideline based on systematic review of RCT's.

**Level 2** – One or more RCT

**Level 3** – Controlled trials without randomization

**Level 4** – Cohort and/or control studies

**Level 5** – Systematic review of qualitative or descriptive studies

**Level 6** – Descriptive or qualitative study

**Level 7** – Expert/ authority opinions

### Appendix B: SOFA Scoring System

Variable	0	1	2	3	4
<b>Respiratory:</b> <b>PaO<sub>2</sub>/FI<sub>O</sub><sub>2</sub></b> <b>mmhg</b>	>400	≤400	≤300	≤200 with mechanical ventilation	≤100 with mechanical ventilation
<b>Coagulation:</b> <b>Platelets</b> <b>x10<sup>3</sup>/μL</b>	>150	≤150	≤100	≤50	≤20
<b>Liver:</b> <b>Bilirubin</b> <b>mg/dL</b>	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
<b>Cardiovascular:</b> <b>Hypotension</b>	No hypotension	Mean arterial pressure <70	Dop ≤5 or dob any dose	Dop >5, epi ≤ 0.1, or norepi ≤0.1	Dop >15, epi >0.1, or norepi >0.1
<b>Central nervous system:</b> <b>Glasgow coma scale</b>	15	13-14	10-12	6-9	<6
<b>Renal:</b> <b>Creatinine</b> <b>mg/dL or urine output mL/day</b>	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 or <500	>5.0 or <200

\*Norepi=orepinephrine, Dob=dobutamine, dop=dopamine, Epi= epinephrine, FI<sub>O</sub><sub>2</sub>= fraction of inspired oxygen.

\*Vasopressors/Inotropes are in μg/kg per minute.

### Appendix C: Charlson comorbidity index

Assigned Weight	Conditions
1	Myocardial infarction Congestive heart failure Peripheral vascular disease Cerebrovascular disease Dementia Chronic obstructive pulmonary disease Connective tissue disease Peptic ulcer disease Mild liver disease Diabetes mellitus (uncomplicated) Age 50-59 years
2	Hemiplegia Moderate or severe renal disease Diabetes mellitus with end organ damage Any tumor (without metastases) Leukemia Lymphoma Age 60-69 years
3	Moderate or severe liver disease Age >70 years
6	Metastatic cancer Acquired immune deficiency syndrome (AIDS)

## Bibliography

- Acharya, S.P., Pradhan, B., & Marhatta. (2007). Application of the “sequential organ failure assessment (SOFA) in predicting outcome in ICU patients with SIRS. *Kathmandu University Medical Journal*, 5(4), p475-483.
- Berger, M., Revelly, J.P., Cholero, R. (2004). Enteral nutrition in critically ill patients with severe hemodynamic failure after cardiopulmonary bypass. *Clinical Nutrition*, 24, p124-132. DOI: 10.1016/j.cinu.2004.08.005.
- Center for Disease Control. (2015). Sepsis. Retrieved from <http://www.cdc.gov/sepsis/>
- Center for Disease Control. (2016). Emergency department visits. Retrieved from <http://www.cdc.gov/nchs/fastats/emergency-department.htm>
- Dasta, J.F., McLaughlin, T.P., Mody, S.H., Piech, C.T. (2005). Daily cost of an intensive care unit day: the contribution of mechanical ventilation. *Critical Care medicine*, 33(6), P1266-71.
- Dellinger, R.P., Levy, M.M., Rhodes, A., Annane, D., Gerlach, H., Opal S., ... Moreno, R. (2013). Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Critical Care Med*, 41(2), p580–637. DOI: 10.1097/CCM.0b013e31827e83af
- Florian, M., Yende, S., Angus, D. (2013). Epidemiology of Severe Sepsis, 2013. *Virulence*, 5(1), p4-11. DOI: 10.4161/viru.27372
- Jones, A., Trzaciak, S., & Kline, J. (2009). The sequential organ failure assessments score for predicting outcome in patients with severe sepsis and evidence of hypo perfusion at the time of emergency department presentation. *Critical care med*, 37(5), p1649-1654. DOI: 10.1097/CCM.0b013e31819def97

- Kaiser Family Foundation. (2016). Hospital adjusted expense per inpatient day by ownership. Retrieved from <http://kff.org/other/state-indicator/expenses-per-inpatient-day-by-ownership/?currentTimeframe=0&sortModel=%7B%22colId%22:%22Location%22,%22sort%22:%22asc%22%7D>
- Khalid, I., Doshi, P., DiGiovine, B. (2010). Early enteral nutrition and outcomes of critically ill patients treated with vasopressors and mechanical ventilation. *American Journal of Critical Care*, 19(3), p261–268. DOI: 10.4037/ajcc2010197
- Lasierra, J., Perez-vela, J., Makikado, L., Sanchez, E., Gomez, L., Rodriguez, B., Lopez, P., Camara, A., Gonzalez, J. (2015) Early enteral nutrition in patients with hemodynamic failure following cardiac surgery. *Journal of Parenteral and Enteral Nutrition*, 39(2), p154-162. DOI: 10.1177/0148607113504219
- Marik, Paul. (2014). Enteral nutrition in the Critically Ill: Myths and Misconceptions. *Critical care medicine*, 42(4) p962-969. DOI: 10.1097/CCM.0000000000000051
- Mancl, E.E., Muzevich, K.M. (2013). Tolerability and safety of enteral nutrition in critically ill patients receiving intravenous vasopressor therapy. *Journal of parenteral and enteral nutrition*, 37(5), p641-51. DOI: 10.1177/0148607112470460.
- McClave, S., Taylor, B., Martindale, R., Warren, M., Johnson, D., Braunschweig, C., McCarthy, M., Davanos, E., Rice, T., Cresci, G., Gervasio, J., Sacks, G., Roberts, P., Compher, C., & the Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition (2016). Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient. *Journal of Parenteral and Enteral Nutrition*, 40(2), p159-211. Doi: 10.1177/0148607115621863

- Melnyk, B.M., & Fineout-Overholt, E. (2011). Evidence-based practice in nursing and healthcare: A guide to best practice. Philadelphia: Lippincott, Williams & Wilkins.
- National Institutes of Health. (2015). Sepsis fact sheet. Retrieved from [https://www.nigms.nih.gov/Education/Pages/factsheet\\_sepsis.aspx](https://www.nigms.nih.gov/Education/Pages/factsheet_sepsis.aspx)
- Needham, Scales, Laupacis, & Pronovost (2005). A systematic review of the Charlson comorbidity index using Canadian administrative databases: a perspective on risk adjustment in critical care research. *Journal of critical care*, 20(1) p12-9.
- Patel, J.J., Kozeniecki, M., Biesboer, A., Peppard, W., Ray, A.S., Thomas, S., Jacobs, E.R., Nanchal, R., & Kumar, G. (2014). Early trophic enteral nutrition is associated with improved outcomes in mechanically ventilated patients with septic shock: a retrospective review. *Critical Care Medicine* (2011) 39(5): 967–974. DOI: 10.1097/CCM.0b013e31820a905a
- Revelly, J.P., Tappy, L., Berger, M.M., Gersbach, P., Cayeux, C., Chiolero, R. (2001). Systemic and splanchnic hemodynamic response to early enteral nutrition in postoperative patients treated for circulatory compromise. *Intensive Care Medicine*, 27, p450-457.
- Sameh, T., Demian, M., Nehad, N., Halawa, M., Batool, N., & Raees, A. (2007). Nurse-Driven enteral feeding protocol improves caloric intake in critically ill patients. *Chest*, 132(4) p442c-443. DOI:10.1378
- Steerfkerk, J., Beishuizen, A., Groenveld, J. (2014) .Gastric feeding intolerance is not caused by mucosal ischemia Measured by intragastric air tonometry in the critically ill. *Clinical Nutrition*, 25(3), p731-734. DOI: 10.1016/j.clnu.2015.05.015
- Turza, K., Krenitsky, J., Sawyer R. (2009). Enteral Feeding and Vasoactive Agents: Suggested Guidelines for Clinicians. *Practical gastroenterology*, 33(9), p11-22.



U.S. National Institutes of Health. (2016). A randomized controlled study of enteral nutrition in septic shock. Retrieved from <https://clinicaltrials.gov/ct2/show/NCT02025127>

Vincent, J.L., Moren, R., Takala, J., Willatts, S., De Mendonca, A., Bruining, H., Reinhart, C.K., Suter, P.M., & Thijs, L.G. (1996). The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. *Intensive Care Med*, 22(7), p707-710.

Yang, S., Xingjiang, W., Wenku, Y., Jieshou, L. (2014). Early enteral nutrition in critically ill patients with hemodynamic instability: an evidence-based review and practical advice. *Nutrition clinical practice*, 29(1), p90-106. DOI: 10.1177/0884533613516167

Zaloga, G., Roberts, P., & Marik, P., (2003). Feeding the hemodynamically unstable patients: a critical evaluation of the evidence. *Nutrition in clinical practice*, 18, p285-293. DOI: 10.1177/0115426503018004285