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Systemic Review

Timing of Enteral Nutrition for Critically Ill Patients on Vasopressor Support

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Abstract

Background: Research on enteral nutrition in the critically ill population has demonstrated a general consensus that adequate nutrition improves overall patient outcomes. However, controversy exists regarding the timing of enteral feeds and whether it is better to initiate within the first 48 hours of ICU admission or after. This study aims to identify the benefits versus risks associated with the timing of enteral feeds for critically ill patients on pressor support.
Methods: The literature review was conducted in October 2023 to identify more potential benefits or risks from early enteral nutrition (EEN) interventions for critically ill patients on vasopressor support. Databases utilized for article identification included PubMed, Google Scholar, and the Journal of Parenteral and EN (JPEN) by ASPEN. All articles were reviewed for relevance, classified by study type, and graded using quality criteria checklists. A plus/positive grade was the final step in article qualification.
Results: Forty-five articles met the criteria. Of those, twenty-five were utilized based on inclusion and exclusion criteria. Further investigation narrowed down our results to twelve articles for our systematic review.
Conclusion: This systematic review of the literature indicates that critically ill patients who are hemodynamically stable and receiving early enteral nutrition support will have a shorter length of stay in the ICU, lower levels of inflammatory markers, a lower risk of debility, a lower 28-day mortality rate, and a lower readmission rate to the ICU.

Keywords: enteral nutrition, vasopressors, critically ill, early nutrition support

Introduction

Improving outcomes for patients who are critically ill and decreasing the length of stay in the intensive care unit (ICU) have been of increased concern in recent years. According to Viglianti and Iwashyna, more than 5.7 million individuals are admitted annually to the ICU in the United States.[2] Post-intensive care syndrome (PICS) results from extended stays in the ICU due to multiple comorbidities and potential delay in enteral nutrition.[3] Recent studies identified that initiating mobilization early during the ICU stay and decreasing bed rest duration will decrease the overall hospital length of stay.[4] In conjunction with early mobilization, providing early nutrition had the most significant outcome for the decreased

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length of stay and patient outcomes.[5]

Vasoactive agents, including vasopressors, are commonly used in managing hemodynamically unstable and critically ill individuals. Vasopressors raise blood pressure and maintain appropriate perfusion of organs and tissues.

Although necessary for immediate aid, some research has identified concern for potentially harmful secondary effects. Both vasopressor support and hemodynamic instability have been shown to induce changes in gastrointestinal physiology, which could be detrimental.[6] Bowel ischemia and nonocclusive bowel necrosis are of the utmost concern. Feeding the gut increases oxygen demand, whereas vasopressors reallocate this demand to other vital organs and organ systems. The inverse relationship may ultimately undermine the benefits of timely enteral nutrition for the critically ill patient. In addition, high vasopressor requirements contribute to delayed initiation and incomplete intake of enteral nutrition. Further evidence suggests that, despite the risks, nutrition should not be withheld entirely simply because a patient requires hemodynamic support.[7]

The significance of nutrition in the critically ill is increasingly acknowledged, especially in patients with prolonged stays in the ICU, who often require prolonged life-sustaining support and undergo severe catabolism. Intensive care unit patients who present with malnutrition or a high chance of developing malnutrition during their hospital stay and those not expected to be on a complete oral diet within three days should receive specialized enteral nutritional support.[8] In the case of enteral nutrition, feeding should be started early, within the first 24 - 48 hours following admission, to stimulate diet tolerance, lower the risk of intestinal barrier dysfunction and infections, and lower the length of hospital stay and mechanical ventilation.[9] Early enteral nutrition (EN) is associated with enhanced nutritional intake. Providing macronutrients and micronutrients reduces the risk of and/or complications from malnutrition.

Malnutrition is associated with poor patient outcomes and has a profound negative effect on healthcare resource use, leading to increased costs and economic burdens. In critically ill patients with an intact gastrointestinal tract who cannot receive adequate oral nutrition, enteral nutrition is the preferred feeding route.

Deciding when to initiate nutrition support in patients receiving pressure support remains an arduous topic.[10] Nutrition support is usually given a lower priority than other critical conditions and diagnoses. Once stabilized, medical personnel should pay attention to providing nutritional support immediately. The improved outcomes associated with early enteral nutrition include decreased length of stay, lower mortality, and lower perioperative morbidity.[8] In critically ill patients, enteral nutrition should be started within 48 hours of admission to the intensive care unit, with gradual advancement, with monitoring for symptoms and signs of gastrointestinal intolerance or unexplained worsening hemodynamic status.[11] When enteral nutrition initiation is delayed, establishing tolerance to the feeding regimen may be more difficult.[8]

The purpose of this systemic review is to determine if it is most effective for critically ill patients on pressor support to receive enteral nutrition support within 48 hours versus delaying nutrition support.

Methods

The literature review was conducted in October 2023 to identify more potential benefits or risks from early enteral nutrition (EEN) interventions for critically ill patients on vasopressor support. Included in the review was how early mobilization of the critically ill patient affects the length of stay (LOS) in the ICU setting. Databases utilized for article identification included PubMed, Google Scholar, and the Journal of Parenteral and EN (JPEN) by ASPEN. Search terms used were “enteral nutrition,” “late enteral nutrition,”

"delayed nutrition," "high vasopressor support," "timing enteral nutrition for the critically ill," "the role of enteral feeding," "feeding on pressor support," "critically ill," "hemodynamically unstable," "hemodynamic instability," "hemodynamically unstable enteral nutrition." Boolean terms included "AND" and "OR" between all search terms.

For an article to be included, it had to involve adult subjects (18-65 years old), the setting had to be an intensive care unit, host at least 45 participants if it were a primary study, and be published between 2008 and 2023. Exclusion criteria included a pediatric patient population and patients with any of the following diagnoses or interventions: on hypothermia protocols, paralyzed patients, major gastrointestinal surgery, ileus, nausea and vomiting unresolved, end-stage renal disease on hemodialysis, parenteral nutrition, or COVID-19.

Articles by the same author in a similar context were excluded, as was anything not published in English. The only study designs excluded from our search were case studies; all other study designs were considered. All articles were reviewed for relevance, classified by study type, and graded using quality criteria checklists. A plus/positive grade was the final step in article qualification.

Results

After careful review, our search yielded 45 articles for review. Preliminary elimination by relevance and inclusion criteria brought the initial pool down to 25 articles, which were designated for full review and grading. Of these, nine were considered primary research, while 16 were review articles. Table 1 Primary Article Quality Criteria and Table 2 Review Article Quality Criteria are below, including a quality grading of all our articles reviewed.

	Fu P-K et al, 2021	Harmandar et al, 2017	Savio RD et al, 2021	Huang et al., 2012	Dorken et al., 2021	Ong, et al. 2020	Al-Dorzi 2021	Gunst 2023	Heyland 2003	Melis 2006	Sena 2008	Ohbe et al., 2020	Reignier, et. al. 2014
Overall Quality Rating	(-)	(-)	(+)	(+)	(+)	(+)	(-)	(-)	(+)	(+)	(+)	(+)	(+)
Relevance Questions													
Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	Y	Y	Y	Y	Y	Y	Unclear	Y	Y	Y	Y	Y	Y
Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Is the intervention or procedure feasible? (NA for some epidemiological studies)	Unclear	Unclear	Y	Y	Y	Y	Y	Unclear	Y	Y	Y	Y	Y

Validity Questions													
1. Was the research question clearly stated? 1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified? 1.2 Was the outcome(s) (dependent variable(s)) clearly indicated? 1.3 Were the target population and setting specified?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Was the selection of study subjects/patients free from bias? 2.1 Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study? 2.2 Were criteria applied equally to all study groups? 2.3 Were health, demographics, and other characteristics of subjects described? 2.4 Were the subjects/patients a representative sample of the relevant population?	Y	Y	Y	Y	Y	Y	N/A	Y	Y	Y	Y	Y	Y
3. Were study groups comparable? 3.1 Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT) 3.2 Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline? 3.3 Were concurrent controls used? (Concurrent preferred over historical controls.) 3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis? 3.5 If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.) 3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., “gold standard”)?	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y
4. Was method of handling withdrawals described? 4.1 Were follow up methods described and the same for all groups? 4.2 Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.) 4.3 Were all enrolled subjects/patients (in the original sample) accounted for? 4.4 Were reasons for withdrawals similar across groups? 4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A	Unclear	Y	N/A	N/A	Unclear	Unclear	Unclear	N	Y	N	N/A	Unclear

5. Was blinding used to prevent introduction of bias? 5.1 In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate? 5.2 Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.) 5.3 In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded? 5.4 In case control study, was case definition explicit and case ascertainment not influenced by exposure status? 5.5 In diagnostic study, were test results blinded to patient history and other test results?	N	Unclear	Unclear	N	N	N	N/A	N	Unclear	N	N	N	N
6. Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described? 6.1 In RCT or other intervention trial, were protocols described for all regimens studied? 6.2 n observational study, were interventions, study settings, and clinicians/provider described? 6.3 Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect? 6.4 Was the amount of exposure and, if relevant, subject/patient compliance measured? 6.5 Were co-interventions (e.g., ancillary treatments, other therapies) described? 6.6 Were extra or unplanned treatments described? 6.7 Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups? 6.8 In diagnostic study, were details of test administration and replication sufficient?	unclear	unclear	Y	Y	Y	Y	Y	Y	Y	unclear	Y	Y	Y
7. Were outcomes clearly defined and the measurements valid and reliable? 7.1 Were primary and secondary endpoints described and relevant to the question? 7.2 Were nutrition measures appropriate to question and outcomes of concern? 7.3 Was the period of follow-up long enough for important outcome(s) to occur? 7.4 Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures? 7.5 Was the measurement of effect at an appropriate level of precision? 7.6 Were other factors accounted for (measured) that could affect outcomes? 7.7 Were the measurements conducted consistently across groups?	unclear	unclear	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y

8. Was the statistical analysis appropriate for the study design and type of outcome indicators? 8.1 Were statistical analyses adequately described the results reported appropriately? 8.2 Were correct statistical tests used and assumptions of test not violated? 8.3 Were statistics reported with levels of significance and/or confidence intervals? 8.4 Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)? 8.5 Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)? 8.6 Was clinical significance as well as statistical significance reported? 8.7 If negative findings, was a power calculation reported to address type 2 error?	unclear	Y	Y	Y	Y	Y	N/A	Y	Y	N/A	Y	Y	Y
9. Are conclusions supported by results with biases and limitations taken into consideration? 9.1 Is there a discussion of findings? 9.2 Are biases and study limitations identified and discussed?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
10. Is bias due to study's funding or sponsorship unlikely? 10.1 Were sources of funding and investigators' affiliations described? 10.2 Was there no apparent conflict of interest?	Y	Y	Y	Y	Y	Y	N	N/A	N	N	N	Y	Y

Table 1. Primary Article Quality Criteria

	Arvanitakis M et al, 2021	Hashem MD et al, 2016	Rousseau AF et al, 2021	Wischmeyer P.E., 2020	Wischmeyer P.E., 2021	Nutritional support 2012	Bruns, et. al. 2016	Patel, et. al. 2020	Covello, et. al. 2019	Preiser, et al. 2021	Bechtold, et. al. 2022	Flordelis Lasierra et al., 2015
Overall Quality Rating	(-)	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(-)
Relevance Questions												
Will the answer if true, have a direct bearing on the health of patients?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Is the outcome or topic something that patients/clients/population groups would care about?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Is the problem addressed in the review one that is relevant to dietetics practice?	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Will the information, if true, require a change in practice?	unclear	Y	Y	Y	Y	Unclear	Unclear	Unclear	Unclear	unclear	Y	Y

Validity Questions												
Was the question for the review clearly focused and appropriate?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the search strategy used to locate relevant studies comprehensive? Were the databases searched and the search terms used described?	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N
Were explicit methods used to select studies to include in the review? Were inclusion/exclusion criteria specified and appropriate? Were selection methods unbiased?	N/A	N/A	N/A	N	N	N	N	N	Y	Y	Y	N
Was there an appraisal of the quality and validity of studies included in the review? Were appraisal methods specified, appropriate, and reproducible?	N/A	Y	N/A	N	N	N	N	unclear	Y	Y	Y	N
Were specific treatments/interventions/exposures described? Were treatments similar enough to be combined?	unclear	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the outcome of interest clearly indicated? Were other potential harms and benefits considered?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were processes for data abstraction, synthesis, and analysis described? Were they applied consistently across studies and groups? Was there appropriate use of qualitative and/or quantitative synthesis? Was variation in findings among studies analyzed? Were heterogeneity issued considered? If data from studies were aggregated for meta-analysis, was the procedure described?	Y	Y	Y	N	N	N	unclear	unclear	Y	unclear	unclear	N

Are the results clearly presented in narrative and/or quantitative terms? If summary statistics are used, are levels of significance and/or confidence intervals included?	Y	Y	Y	Y	N	N	Unclear	Y	Y	Unclear	Unclear	N
Are conclusions supported by results with biases and limitations taken into consideration? Are limitations of the review identified and discussed?	Y	Y	Y	N	N	Y	Unclear	Unclear	N	N	N	N
Was bias due to the review's funding or sponsorship unlikely?	N/A	Y	Y	Y	Y	N	Y	Unclear	Y	Unclear	Unclear	Y

Table 2. Review Article Quality Criteria

A thorough evaluation and quality grading resulted in a total of 12 final articles to be used for our systematic review (Table 3). The 12 articles' commonalities were a consensus that early enteral feeding within 24-48 hours of ICU admission is preferred for critically ill patients.

All articles identified a positive relationship between targeted outcomes and early EN while on vasopressor support, including ICU length of stay, lower readmission rate to the ICU, lower risk of debility, and lower levels of inflammatory markers.

Author and Year	Study Type/Purpose	Study Population	Intervention	Outcomes	Limitations	Conclusions
Hashem, MD et al, 2016 Study Design: Prospective Cohort Study Cl	To determine if early mobilization and rehabilitation in critically ill patients would improve patient outcomes.	222 survivors of ARDS	The study followed patients for 2 years with adjustments made to determine risk factors for muscle weakness, noting only bed rest was the only potential risk factor.	Over a 3-, 6-, 12-, and 24-month follow-up, there was a 3%-11% decrease in muscle strength for each additional day of bed rest in the ICU.	The study did not account for biochemical changes and weight changes following ICU stay.	Bed rest shows short- and long-term physical impairments, early interventions will help decrease LOS.
Savio RD et al, 2021 Study Design: Prospective Observational Study	To determine the effectiveness of enteral feeding in critically ill patients in the prone position.	47 ICU patients. Patients scored moderate malnutrition on SGA or APACHE II score.	Enteral feedings were provided via NG or OG. Full-strength feedings. Patients were either supine at 30 degrees or prone at 15 degrees during continuous feedings. Feedings were administered within 24-48 hours of admission.	74% of patients received NG feedings, and 26% received OG feedings. Interruption of feedings was not significant.	Limitations include the usage of bolus feedings and intermittent feedings.	Early feeding in either supine or prone position in the critically ill patient receiving EN via NG or OG are comparable and well tolerated.
Huang et al., 2012 Study Design: Retrospective observational study	To determine the association between illness severity and commencement of enteral feedings	108 ICU patients	Full strength isotonic enteral feeding via NG or ND tubes administered to patients with critical illness identified as "less severe" or "more severe" per APACHE II scoring, then sub-grouped into early or late feeding.	40 patients received early feeding, and 68 patients received late feeding. No differences in measured outcomes for less severely ill early or late feeders. More severely ill experienced more feeding complications with early feeding.	The study population was within a single medical ICU, and it is difficult to generalize to other populations. The sample size of the early feeding group limits the study's power to analyze the measured outcomes.	Early feeding is shown to be a more beneficial nutritional intervention option than late feeding in patients with more severe illness.
Bechtold, et. al. 2022 Study Design: Systematic Review	To determine when to initiate EN safely	346 patients	The evidence was prioritized into each recommendation based on study quality. Randomized control trials were preferred, but prospective and retrospective observational studies, case studies, and nonrandomized cohort studies were utilized.	Initiate EN within 48 hours of vasopressor initiation, depending on dosage. EN may be administered in adults if the MAP is >/= to 60mmHG but should be held when the MAP is <50 mm Hg.	Randomized control trials were not readily available, so case studies were included. Three authors received honorariums from enteral formula companies.	Initiate enteral within 24-48 hours of admission to the hospital, including the intensive care unit. Vasopressor administration is not a contraindication to providing EEN with careful monitoring.

Ong, et al. 2020 Study Design: Retrospective Study.	The study describes the effect of vasoactive and inotropic support on the manner in which EN is delivered in cardiac surgery patients and its relation with ischemic gut complications.	3088 patients	The researchers reviewed cardiac surgery patients in a single institution, examined the effect of vasoactive and inotropic support on tube feed administration and evaluated ischemic gut complications.	Of the 249 patients receiving tube feeds, three suffered ischemic gut complications. In the 249 patients receiving tube feeds, as the vasoactive-inotropic support score (VISS) increased, the amount per day of tube feeding administered decreased, the number of hours per day tube feeding was held increased.	Results from a retrospective analysis. Patients not randomized to a nutrition strategy. Variability in day-to-day tube feed rates within groups. No control groups. Single-institution study.	Very few postoperative cardiac surgery patients receiving enteral support experienced gut ischemia as a complication. If EN is delivered as delivered in the study, its potential benefits need not be withheld from the postoperative cardiac surgery patient for fear of exacerbating intestinal hypoperfusion and ischemia.
Reignier, et. al. 2014 Study Design: Multi-center cohort observational study.	The study aimed to assess associations linking early nutrition (<48 hours after intubation), feeding route, and calorie intake to mortality and risk of ventilator-associated pneumonia in patients with invasive mechanical ventilation and shock.	3032 patients	The authors used an extensive prospective database and built a marginal structural model to create a pseudo-randomized population. The researchers detailed demographic, clinical, and outcome data of patients and entered the data prospectively into a database by trained physicians or monitors in each participating ICU. Researchers studied the effects of nutrition timing on patients who received nutrition < 48 hours or > 48 hours of intubation.	In mechanically ventilated patients with shock, early nutrition was associated with reduced 28-day mortality.	The study was observational, and the interventions were not randomized. Nutritional support modalities were not standardized but instead complied with the protocols of each ICU. The study did not provide information on the physiological mechanisms underlying the survival benefits associated with early nutrition.	In mechanically ventilated patients with shock, early nutrition was associated with reduced mortality. Early nutrition and enteral feeding were associated with ventilator-associated pneumonia.
Dorken, et al., 2021 Study Design: retrospective study	To compare in-hospital outcomes for early versus late EN in mechanically ventilated patients on vasopressor support.	1701 patients on pressor support and mechanical ventilation	Retrospective study design in which the experimenters observed in-hospital outcomes for patients receiving either EEN (within first 48 hrs of admission), or late EN (receiving EN between day 2 and day 7).	The primary outcome was 28-day mortality, secondary outcomes were ICU and hospital length of stay, 28-day ventilator-free days, acute in-hospital complications (ARDS, DIC, AKI, RRT, acute bowel ischemia, C. diff, hospital-acquired pneumonia, DVT/PE), and electrolyte abnormalities.	There was insufficient data for the dose of vasopressors, energy adequacy of EN, anatomical site of enteral access, and interruptions of EN delivery. Study design limits the ability to account for intangible factors that may have influenced the physician's decision to deliver EEN or LEN.	There was no difference in 28-day mortality between EEN and LEN in critically ill patients receiving vasopressor support. Acute bowel ischemia is a highly infrequent complication in hemodynamically unstable patients receiving EEN.
Ohbe et al., 2020 Study Design: Prospective observational study	The study aims to compare outcomes between early and late EN in critically ill, ventilated patients requiring low-, medium-, or high-dose noradrenaline.	53,563 patients split into 3 groups: 38,488 low-, 11,042 medium-, and 3033 high-dose	Eligible patients were stratified into 3 groups according to estimated dose of noradrenaline: low, medium, and high. Patients who started EN within 2 days of mechanical ventilation (MV) were designated to EEN group, all others were assigned to LEN group. Propensity score analyses were conducted separately for each of the 3 noradrenaline groups to account for differences in characteristics between EEN vs LEN patients.	The primary outcome was 28-day mortality. Secondary outcomes included incidence of nosocomial pneumonia, bowel ischemia, length of hospital stay, and length of mechanical ventilation.	The study did not account for total caloric intake, time to achieve full feeds, and interruptions of feeds. EEN assignment was not random - results might have been biased by unmeasured confounders. The diagnosis "bowel ischemia" was not well validated; gut function may have been more intensively assessed for EEN group. Researchers excluded 6.8% of patients who had missing data. Only patients who survived more than 2 days from ventilation were included. The high-dose group might have been too small to detect any significant difference.	EEN is associated with lower mortality in patients receiving low- or medium-dose noradrenaline. However, no significant difference in mortality was shown between EEN and LEN in patients with shock requiring high-dose.
Heyland, et. al., 2012 Study design: Randomized clinical trials or meta-analysis of randomized controlled trials,	This study was conducted to develop evidence-based clinical practice guidelines for nutrition support (ie, enteral and parEN) in mechanically ventilated critically ill adults.	Mechanically ventilated, critically ill adult patients (elective surgery patients were excluded)	Interventions were systematically reviewed for inclusion in the guidelines: EN versus parEN (PN), early versus late EN, dose of EN, composition of EN, strategies to optimize the delivery of EN and minimize risks, EN in combination with supplemental PN, use of PN versus standard care in patients with an intact gastrointestinal tract, dose of PN and composition of PN , and the use of intensive insulin therapy.	The outcomes considered were mortality (intensive care unit [ICU], hospital, and long term), length of stay (ICU and hospital), quality of life, and specific complications.	Data from randomized trials were sparse. Systematic reviews are advocated as the best method to summarize existing evidence to inform both clinical and policy decisions. However, not all systematic reviews or meta-analyses are created equal. A further limitation of our guidelines is that data on costs, feasibility, and safety were not systematically available or considered in developing the recommendations.	Specialized nutrition support should be initiated when it is anticipated that critically ill patients will be unable to meet their nutrients orally.

Melis, et. al., 2006 Study design: Lit review	Postoperative EN may sometimes be responsible for severe complications such as mesenteric ischemia.	All reports of mesenteric ischemia in the setting of postoperative enteral feeding were included.	Nine studies were retrieved in which enteral feedings were responsible for bowel ischemia. The common clinical picture is that of a patient without significant risk factors for mesenteric ischemia, which during the early postoperative course develops nonspecific abdominal symptoms and then rapidly progresses to septic shock and eventually to multisystem organ failure and death.	An increasing number of surgeons feed their patients postoperatively by means of a jejunal tube with little concern for complications. However, nonspecific signs of intolerance to tube feeding occasionally may progress to a syndrome of abdominal distension, hypotension, hypovolemic shock, and eventually to small bowel necrosis.	All reports were abstracted for a number of patients, including the presence of preoperative comorbidities, development of perioperative hypotension or mesenteric occlusion, and outcome.	The benefits of EN outweigh the likelihood of severe complications; when mesenteric ischemia develops, early diagnosis is challenging, and the prognosis is poor.
Sena, et. al., 2008 **S**tudy design: Retrospective cohort study	The purpose of this study is to determine whether early administration of parEN is associated with an increased risk for infection following severe injury.	Severely injured blunt trauma patients enrolled from eight trauma centers.	Compared patients receiving PN within seven days following injury to a control group who did not receive early PN. We then focused on patients who tolerated at least some EN during the first week and evaluated the potential influence of supplemental PN on outcomes in this “enteral tolerant” subgroup..	Of the 567 patients enrolled, 95 (17%) received early PN. Early PN use was associated with a greater risk of nosocomial infection (P=<0.001). In the an enteral tolerant subgroup, early PN was also associated with an increase in nosocomial infections (P=0.005) in part due to an increased risk of bloodstream infection, (P=0.002). Mortality tended to be higher in patients receiving additional EN + PN versus EN alone (P=0.06).	7 days to define both early PN and subsequent late infections could be considered arbitrary. Second, we characterized patients as enteral tolerant if they received ≥ 1000 kcal/day at any point within the first week. (190 never received PN, 32 received early PN, and 27 ultimately required delayed (after 7 days) PN.	In critically ill trauma patients who are able to tolerate at least some EN, early PN administration may contribute to increased infectious morbidity and a worse clinical outcome.

Table 3. Evidene Summary Table

Discussion

We hypothesized that early enteral nutrition (EEN) is preferred over delayed/late enteral nutrition (LEN) for critically ill patients. Current evidence from our search suggests that the benefits of early enteral nutrition outweigh the risks. Bed rest shows short- and long-term physical impairments, including early initiation of enteral nutrition and physical therapy interventions, to help decrease the length of stay (LOS).[4] Early nutrition reduced 28-day mortality in mechanically ventilated patients, but this outcome was not consistent across all of the studies.[12] Undoubtedly, undesirable side effects may be associated with EEN in the critically ill population. These include diarrhea, acute gastrointestinal bleeding, longer ICU length of stay, and ventilator-associated pneumonia.[12]

However, other research has identified that EEN does not necessarily contribute to complications such as abdominal distention, nausea and vomiting, and contraction of ventilator-associated pneumonia and that each complication has a potential alternative etiology.[13]

Early enteral nutrition has long since been recommended with caution in the critically ill population due to the likelihood of inducing bowel ischemia or increasing the risk of mortality.[13] The Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition Guidelines suggest, based on expert consensus, that EN should be withheld until the patient is fully resuscitated and/or stable in the setting of hemodynamic compromise or instability. As recently reported, the incidence of bowel ischemia and non-occlusive mesenteric ischemia (NOMI) ranges between 0.3% and 8.5%, with mortality ranging from 46% to 100%.[14] Very few patients receiving enteral support experienced gut ischemia as a complication. If enteral nutrition is delivered early, its potential benefits need not be withheld from the patient for fear of exacerbating intestinal hypoperfusion and ischemia.[15]

The "sickest" or most hemodynamically unstable patients are the only identified subjects who may benefit from delayed enteral nutrition after 48 hours due to a higher vasopressor dose. However, recent studies

show EN can be delivered safely to patients on vasopressors.[7] Many studies show an outcome benefit of early EN in ICU patients receiving vasopressors. There are doses of norepinephrine (or equivalent) that are safer and beneficial to provide EN.[14] Embracing a methodical approach to EN management in patients on vasopressors will help optimize their care. Inappropriate candidates for EN include those with active bleeding requiring ongoing transfusions, a mean arterial blood pressure consistently less than 60 mmHg, or an increasing requirement for vasoactive agents.

Suggested Experience-Driven Guidelines for Clinicians concluded appropriate candidates for EN: Patients should be considered for EN with monitoring of gastrointestinal (GI) tolerance if hemodynamically stable on:
– *Epinephrine 5 mcg/min or less, and/or Norepinephrine 5 mcg/min or less, and/or Dopamine 10 mcg/kg/min or less, and/or Vasopressin 0.04 units/min or less.* A thorough assessment was completed of pre-morbid medical conditions and nutritional history.[16]

Although enteral nutrition increases GI tract blood flow, it also increases intestinal metabolic demand and contributes to bowel necrosis in cases of impaired mesenteric perfusion. However, enteral nutrition may be undertaken safely using a thorough, four-phase process to select appropriate patients with subsequent monitoring once enteral nutrition has begun. In the first phase (Diagram 1), the practitioner considers a patient's relative risk for EN-related bowel complications. This evaluation includes a review of chronic conditions, pre-hospital health, and medications, as certain conditions and medications may predispose the patient to NOMI.[17]

In the Second phase, thoughtful analysis of the patient's physiologic state while on vasopressors and stable low-dose pressor requirements in the face of hemodynamic stability without transfusion suggest a lower likelihood of NOMI. In the third phase, once the benefits outweigh the risks of beginning EN, the type of nutrition formula should be carefully chosen.[17] Enteral formulas with modest osmolality and minimal fiber may minimize complications related to the feeding formula. When feeding patients receiving vasopressors, it is recommended to use a gastric feed with a 1.0-1.2 kcal/ml higher-protein, low-fiber formula. Both semi-elemental and polymeric formulas are well tolerated.[8] Additionally, early enteral feedings administered in either a supine (at 30 degrees) or prone (at 15 degrees) position were tolerated in critically ill patients.[5] In the last phase, after the initiation of EN, monitoring must be done for clinical signs of distress: serial abdominal exams, gastric residual checks, and periodic monitoring.[17]

There were several limitations to the articles included in this review, including studies not accounting for biochemical changes, weight changes, variability in day-to-day tube feed rates, and calorie intake. In addition, there was no standardization in the administration of the enteral feeds, the use of case studies, some studies using a single ICU when conducting the research, patients not randomized to a nutrition strategy, and insufficient data for vasopressor doses. Finally, none of the studies discussed the monetary costs of early versus delayed EN. Further research in this area needs to be done.

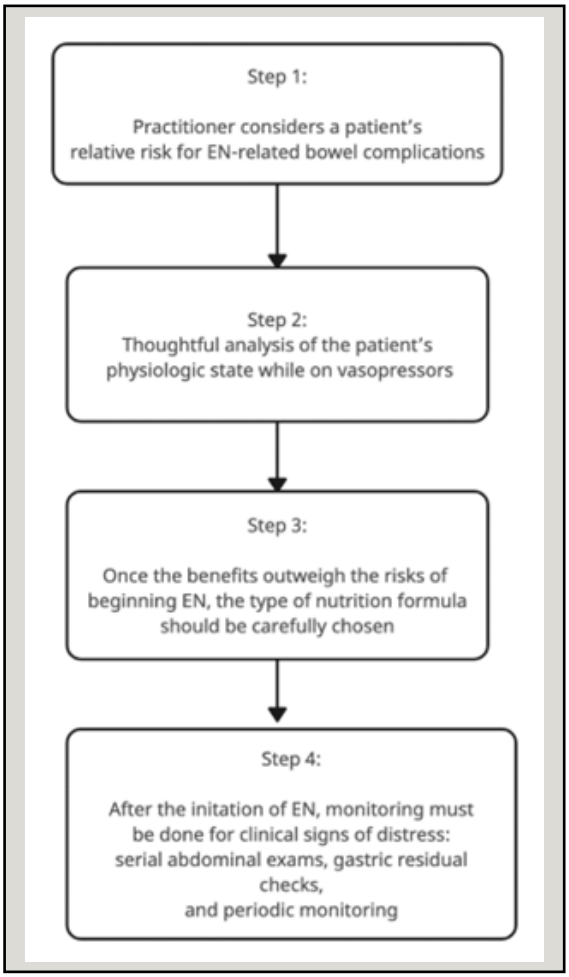

Diagram 1. Four-Step Process to Selecting Appropriate Patients for EEN

Conclusion

This systematic review of the literature indicates that critically ill patients who are hemodynamically stable and receiving early enteral nutrition support will have a shorter length of stay in the ICU, lower levels of inflammatory markers, a lower risk of debility, a lower 28-day mortality rate, and a lower readmission rate to the ICU.

Evidence Grade

Using the *Academy's Evidence Analysis Manual: Steps in the Academy Evidence Analysis Process*, the evidence grade is 1: Good/Strong. The evidence includes results from strongly designed review studies and primary studies addressing the research question asked. The results are both clinically important to the practice of nutrition and consistent, with minor exceptions and limitations. There are no significant concerns regarding the results' generalizability, bias, or research design flaws. Research exhibiting unfavorable outcomes possesses sample sizes that are large enough to ensure acceptable statistical power.

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