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NUTRITION AND CLINICAL CARE (J PATEL, SECTION EDITOR)

Optimizing Enteral Nutrition in Medical Intensive Care Patients

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Abstract
Purpose of Review Critically ill patients have increased metabolic requirements as well as increased protein catabolism. Nutrition support and in particular enteral nutrition have been recently a topic of increased research and commentary in the critical care literature.
Recent Findings Although there remains a paucity of large randomized multi-center trials to answer definitively the questions of best timing, delivery, how to monitor for tolerance, and enteral formula selection, there is good overall data to support the use of enteral nutrition in critically ill patients.
Summary In applying the existing evidence, clinicians must be cautious to use the evidence based on the trial population and the nutritional status of patients enrolled and not make broad-based clinical decisions that what is best for one patient population is good for all. This review focuses on evidence and existing guidelines to help clinicians optimize use of enteral nutrition in medical critical care patients.

Keywords Enteral nutrition · Critical care, pulmonology · Catabolism

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Introduction

Delivery of adequate enteral nutrition (EN) is challenging in the intensive care unit (ICU). Once admitted, patients quickly begin to develop a caloric and protein debt, frequently secondary to iatrogenic underfeeding [1, 2]. Previous research has shown that patients receive approximately half of the prescribed calories via enteral nutrition when admitted to the ICU; this is due to several factors which all increase caloric and protein debt during the patients' admission [3]. Initiation of EN is typically delayed for 48–60 h following admission. Once started, there is slow delivery of EN as delivery may start as low as 10 ml/h and take 24 h or more to advance to goal rate. Finally, there is frequent cessation of EN for various reasons throughout the patient's period of critical illness which further contributes to an increasing caloric and protein debt [3].

The field of enteral nutrition in critically ill patients has evolved significantly over the past several years. Recent large randomized clinical trials have shown conflicting results compared to earlier studies, particularly in medical critically ill patients. Therapies of trophic vs full feeding and immunonutrition have been the focus of much of the recent debate in the literature. This change in evidence has left many unsure of the best method to administer nutrition, timing, amount, and formula for critically ill patients. Many clinicians will now withhold nutrition for fear of improperly administering enteral feeds or do not consider it important early in a patient's admission. The early and optimal delivery of enteral nutrition remains an important proactive therapeutic strategy for critical patients that may reduce infection rates, length of stay, and in some studies mortality [4, 5•]. This review will focus on optimizing enteral nutrition for patients who are critically ill and review some of the outstanding questions that may limit delivery of EN for critically ill patients.

When Should Enteral Nutrition Be Initiated?

One of the easiest means to optimize the benefits of EN in critically ill patients is to start provision of enteral feeding as soon as possible. Early initiation of EN has non-nutritional benefits in critically ill patients. EN has been shown to preserve the gut integrity via maintained tight junctions between intraepithelial cells, stimulating blood flow, and release of endogenous trophic agents. This also helps to maintain the structure of villous height and secretory IgA immunocytes [6, 7•]. Gut integrity can be preserved with trophic feeding (between 10 and 20 ml/h) typically and therefore does not require full feeding early in critical illness to optimize the non-nutritional benefits of EN [8].

Early EN is also associated with improved patient outcomes in several trials and meta-analyses. A meta-analysis by Heyland et al. showed a trend towards decreased mortality when EN was started within 48 h of admission [9]. A subsequent meta-analysis by Doig et al. published in 2009 actually showed a decrease in pneumonia and mortality when EN was started within 24 h of admission to the ICU [5•]. Another analysis has shown reduced infectious complications and lower hospital length of stay associated with early vs late EN (within 36 h of admit) [4]. Although the exact timing for the best benefit of enteral nutrition is unknown, once patients have been fully resuscitated, there are no studies showing harm from initiating EN to provide calories and protein.

Patients admitted to the intensive care unit frequently experience hypotension secondary to septic shock or other multi-organ failure. Given the lack of direct evidence for safe EN on vasopressors, all nutrition guidelines and recommendations suggest patients be fully resuscitated prior to starting enteral nutrition [7•]. There is however increasing evidence and acceptance of providing EN on low or stable doses of vasopressors. The data supporting this is mainly retrospective but shows that EN is tolerated in patients receiving vasopressors [10, 33]. Two retrospective trials show that patients tolerated early EN on vasopressors well and had improved outcomes with fewer ventilator days and lower hospital mortality [11, 12]. One analysis further showed that EN on multiple vasopressors was tolerated and also showed improved outcomes [12]. It was further noted in the EDEN trial (which will be discussed in detail in the following section) that trophic feeding to the stomach was generally well tolerated in critically ill patients on various vasopressor doses [13].

The retrospective nature of these studies makes a definitive recommendation impossible, but the studies show overall good tolerance to EN during vasopressor therapy. One additional retrospective analysis of patients receiving EN with vasopressors found that tolerance was improved with doses of norepinephrine less than 12.5 mcg/min. There was decreased EN tolerance in patients receiving dopamine and vasopressin. The majority of intolerances were at higher dose (average 19.4 mcg/min norepinephrine) and included (1) increased lactate, (2) high gastric residual volume, (3) vomiting, (4) positive imaging findings, and (5) three episodes of bowel ischemia or perforation [14]. Additional studies are needed in this area, but the data to date suggest that EN may be considered safe in patients on low dose vasopressors.

What Type of Enteral Support Should Various Patients Receive?

The idea of nutrition as therapy led to the development of multiple organ-specific tube feeding formulas. These formulas were developed for pulmonary failure and renal failure, as well as liver and pancreatic insufficiency. The formulas were heavily marketed and are expensive compared to other standard formulas. Clinical trials have shown no overall benefit to using these formulas in medical critical care patients when compared to standard tube feeding formulas [7•]. Given the multitude of formulas on the market, it can be confusing as to which one to select for various disease processes in the ICU; Table 1 outlines formula and nutrition support recommendations based on the 2016 ASPEN/SCCM Guidelines.

Table 1 Nutrition Support Recommendations based on 2016 ASPEN/SCCM Guidelines

ALI/ARDS	Consider trophic feeding for initial 7 days of hospitalization if there is no evidence of malnutrition or obesity present. May consider an enteral formula which is fluid restricted and energy dense
Sepsis and septic shock	Standard polymeric formula avoid immunonutrition formulas
Trauma and TBI	Consider formula with immunonutrition over standard polymeric formula
Hepatic	Standard enteral formula
Acute Pancreatitis	Standard polymeric formula
Burn patient	No specific formula but patients should receive early initiation (4-6) hours, protein should be between 1.5-2.0 g/kg/d
CRRT/HD	Standard formulas are encouraged over disease specific. Increase protein to 2.0–2.5 g/kg/day
Obese patient	May consider hypocaloric/high protein support. BMI 30-50 provide 11-14 kcal/kg ***actual*** body weight/day BMI > 50 provide 22-25 kcal/kg ***ideal*** body weight/day. Protein should be provided as follows; BMI 30-40 should receive 2g/kg ***ideal*** body weight/day and BMI of 40 or more should receive up to 2.5g/kg ***ideal*** body weight/day of protein.
Evidence of malnutrition on admit	Begin at 50% of goal and attempt to achieve 100% goal EN at 72 h with standard formula, monitor closely for re-feeding syndrome

How Much EN Should Critically Ill Patients Receive? (Tropic vs Full Feeding)

Much of the recent literature regarding critical care nutrition has compared trophic feeds vs full feeding. Trophic feeding is not universally defined in the literature and, in studies, can vary from 400 kcal/day to approximately 800 kcal/day. Generally, trophic feeds are considered to be between 25 and 40% of a patient's estimated caloric needs over 24 h. The initial large multi-center randomized trial suggesting this method of nutrition therapy was the EDEN trial [13]. The study showed no difference in ventilator-free days, organ failure-free days, infection, or 60-day mortality for patients who were fed 400 kcal/day vs patients received 1300 kcal/day. The study, however, was criticized as only patients with acute lung injury or acute respiratory distress syndrome were included in this trial and overall patients were at a healthy weight with no evidence of malnutrition on admission.

A second trial comparing trophic feeding to full caloric feeding was published in 2015 and included a broader range of patients (75% were medical ICU patients) [15]. This trial increased the amount of trophic feeds to approximately 800 kcal/day compared to 1300 kcal/day in the full feeding group. Both groups of patients received similar amounts of protein (mean 57 g/day). The trial protocol outlined equal amounts of protein with a goal to provide 1.2 to 1.5 g/kg/day protein to all patients enrolled. The trial did not show any difference in the primary outcome of 90-day mortality between the two groups. Patients in this trial were given trophic feeding for up to 14 days compared to the EDEN trial which fed patients' trophic amounts for 7 days.

Both trials have brought up important questions regarding delivery of EN in medical ICU patients and should be evaluated carefully prior to being broadly applied. The trials only enrolled patients who were considered well nourished prior to critical illness. Patients with a high or low extreme of BMI were not included in either trial and the outcomes noted in the trials may not be similar in these populations. Patients who are considered nutritionally at risk should receive their goal caloric and protein intake and not receive trophic or permissive underfeeding as there is no evidence to support these practices in such patients [15]. In addition, the EDEN trial enrolled a very specific subset of patients with acute lung injury and therefore results may not be generalizable to all critically ill medical patients [13]. It is reasonable to apply trophic feeding per the EDEN trial but this should be limited to well-nourished patients experiencing acute lung injury and not to all ICU patients. Permissive underfeeding as done in the Arabi trial should also only be applied to patients similar to those enrolled in the trial (well nourished without significant comorbidities) and provisions for additional protein should be provided as this was not limited in the trial.

These trials further reaffirm common nutrition support practices by showing that EN was well tolerated by patients in both trials. During the EDEN trial, 85% of patients were fed via gastric tubes and there were few complications associated with this method of nutrition support. In the trial, regurgitation, constipation, diarrhea, vomiting, and aspiration were uncommon in either group. Patients were also fed while in shock (requiring vasopressors) and receiving various doses of sedatives and narcotics and tolerated this well overall [13]. The early initiation of EN is generally well tolerated and clinicians should consider starting a standard formula even if as trophic feeds as there is benefit to maintaining gut mucosa with this type of feeding and minimal patient risk.

What Is the Best Delivery of EN? (Gastric vs Small Bowel Feeding)

One of the largest concerns with enteral nutrition is the possibility of aspiration pneumonia or ventilator-associated pneumonia (frequently caused by aspiration) and the increased associated morbidity and mortality [32]. Much research has been devoted to determining the best route for enteral feeding and how to minimize risk of aspiration while safely delivering enteral nutrition. There is some evidence the patients who are at high risk for aspiration may benefit from placement of a post-polyric feeding tube. However, there is no definitive evidence for use of a small bowel feeding tube vs a nasogastric feeding tube. The ASPEN/SCCM Guidelines recommend a small bowel feeding tube for patients who are high risk for possible aspiration pneumonia but also recognize that gastric access is often easier to obtain and quicker to implement.

The 2016 ASPEN/SCCM Guidelines reviewed a total of 13 trials and found that overall, there was less risk of pneumonia with small bowel feeding. The guidelines also show aggregate data from six studies that show improved delivery of EN with small bowel feeding tubes [7•]. However, the largest randomized trial to date evaluating gastric vs small bowel feeding did not show any difference in energy delivered or pneumonia between the two methods [16]. Post-polyric feeding tubes may have some increased risk of being placed in the lung and result in pneumothorax or pneumonitis if placed blindly vs the risk of transport for placement under fluoroscopy [17•]. Electromagnetic navigation devices are available for placing tubes at bedside; these devices are effective and improve safety but increase cost and are not available at all facilities. A randomized trial comparing both methods showed that there was an increase in minor gastrointestinal hemorrhage in nasojejunal feeding tubes, but no increased risk of major hemorrhage or other complications [16].

Delivery of EN is likely best tailored to each individual patient based on their risk vs benefit in gastric vs small bowel feeding. Patients at high risk for gastric feeding intolerance

may require a small bowel feeding tube in order to have EN adequately delivered. These patients include those with gastroparesis, severe gastroesophageal reflux, status post resection or altered gastric anatomy, or demonstrated intolerance (vomiting not high gastric residual volume). Other patients even those on sedatives, paralytic agents, and mechanical ventilation have been shown to tolerate gastric feeding relatively well overall [13]. Clinicians may elect to use a post-polyric feeding tube particularly in patients who are at high risk for aspiration pneumonia; however, this should not slow the initiation of EN. It is reasonable to start patients with a gastric tube and advance to a small bowel tube if there is increased risk of pneumonia or based on physician preference.

How Should Tolerance to EN Be Monitored?

Tolerance to EN should be monitored in critically ill patients similar to monitoring tolerance to any therapy patients' receive. Evaluation of tolerance should include the patients' overall clinical picture and not simply focus on one or two markers. Patients should be followed for intolerance by physical exam to include abdominal distention and absence of bowel sounds. Other signs and symptoms that require close monitoring in the ICU include the presence or absence of flatus, stool, diarrhea, abdominal pain and tenderness, and vomiting. Radiographs and other imaging may also be useful in some patients particularly those who are heavily sedated or on mechanical ventilation [7•, 17•].

High gastric residual volumes have long been feared as causing a higher incidence of aspiration and/or pneumonia and considered the primary method to evaluate tolerance to EN. Recent studies, however, have proven these to not be linked as previously thought. In several studies, changing the tolerated gastric residual volume from less than 150 to over 250 mL did not change the rate of pneumonia in patients [18, 19]. Three studies have now shown that eliminating the monitoring of gastric residuals altogether does not change the rate of pneumonia and in some studies increased the amount of EN delivered [20, 21•]. Based on the most recent studies, it is no longer recommended to follow gastric residual volumes as a marker of tolerance to EN. In intensive care units where gastric residuals are followed, EN should not be stopped for a volume less than 500 mL [7•].

Intolerance to EN and elevated gastric residual volumes should prompt physicians to consider a prokinetic agent. In a meta-analysis of 13 randomized trials, these agents were shown to be effective and safe for critically ill patients. The trials evaluated in this analysis showed that prokinetic agents reduced gastric intolerance significantly as well as reduced gastric residual volumes. In this trial, there was no difference in rates of pneumonia, diarrhea, or vomiting [22]. ASPEN/SCCM Guidelines recommend the use of a prokinetic agent as needed in low-risk patient but suggest that patients who are high risk for aspiration, should be started prophylactically on prokinetic agents in order to optimize EN and reduce potential adverse events [7•].

Do Feeding Protocols Improve EN Delivery?

Significant practice variation for delivery of EN exist between healthcare systems and even among physicians within the same system. One survey study showed that as many as 40% of eligible patients remain unfed past 48 h of ICU admission [23]. Evidence-based guidelines are widely implemented in hospitals for best practices; examples include venous thromboembolism prevention, sepsis awareness and treatment, and ventilator-associated pneumonia bundles. An ICU feeding protocol is the best way to ensure compliance with guidelines and optimize delivery of EN.

Two cluster randomized trials have found varying results of energy delivery but in both studies, the protocol was well tolerated by patients and accepted by clinicians. Each of these studies showed faster initiation of EN to patients in the ICU with protocols in place compared to those without a protocol. Doig et al. initially published a trial evaluating implementation of a physician and clinical dietician developed protocol vs usual care. The trial showed an improvement in the mean time to start EN from 0.75 vs 1.37 days. Also, there was a statistically significant difference in the number of patients who were completely unfed during their ICU admission and more patients received parenteral nutrition in the control group [24].

The trial by Doig et al. however did not show a difference in the total average daily energy delivered via EN between the intervention and control groups. The trial also did not show a difference in clinical outcomes between the two groups. Although there was less parenteral nutrition used at the intervention sites and earlier delivery of EN, daily averages were not statistically different. It is possible that there was a Hawthorne effect given that sites volunteered to enroll in a nutrition study [24]. A second possibility is that these sites already had good nutrition support in place prior to the trial beginning and therefore there was less effect of the protocol on total EN received.

Heyland et al. conducted a randomized cluster trial in 2013 to evaluate implementation of a nutrition protocol but in this study, they chose sites with a previously identified history of poor nutrition support practices. In this trial, delivery of EN was increased; both caloric and protein deliveries were statistically significantly increased between the control and intervention groups. This trial did not evaluate any differences in clinical outcomes but rather focused solely on the improved delivery of nutrition support through a protocol. Although the trial favored the implementation of feeding protocol, the authors point out that this is likely only one aspect of good

nutrition support and optimal delivery of EN. Hospitals and clinicians must also seek to eliminate barriers and create a culture to make nutrition support a priority for patients [25].

In creating a culture of good nutrition support, it is necessary to realize that an effective feeding protocol which is accepted within an organization will need to be specific to the health system's culture and clinical practice. Options to consider include indirect calorimetry if available as this is the best method to assess daily energy requirements. However, this is frequently not available and if not, simple equations can be used [7•]. Secondly when developing a protocol for ICU patients, clinicians may wish to consider volume-based feeding and this helps to minimize lost caloric intake secondary to NPO time and other stoppages for EN. Volume-based feeding has been shown to be safe and effective in multiple studies and may be effective in patients who will undergo multiple procedures or frequent EN interruptions [26, 27].

Recently, the authors have observed some physicians have begun to interpret the results of the EDEN and other permissive underfeeding trials to suggest that EN is not important; if it does not matter that patients receive full feeding, does it matter that they receive EN at all. Evidence does not suggest this and in fact shows multiple benefits of EN in critically ill patients [31•]. A feeding protocol may be developed and implemented for both trophic feeding and patients who will receive full EN. Regardless of the feeding strategy prescribed for a patient, it should be implemented in a means that follows evidence-based guidelines and a protocol can help ensure this.

How Can Diarrhea Be Managed and Prevented

Diarrhea is the bane of the ICU nurse and physician and frequently causes a quick change in patient orders, often to stop prescribed EN. Diarrhea is a common complication of critical illness and contributes to morbidity for these patients. Diarrhea can increase a patient's risk of skin breakdown, pressure ulcers, fluid loss, and electrolyte imbalances [28]. EN may induce diarrhea, in particular the polymeric formulas, but often the delivery method of a continuous rate contributes to diarrhea as well. In some trials, prokinetic agents increase diarrhea but not in others and certainly other drugs given to critically ill patients may contribute to diarrhea [29]. Medications commonly associated with diarrhea include antibiotics, proton pump inhibitors, glucose-lowering agents, non-steroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, anti-hypertensives, cholinergics, and drugs containing sorbitol as an excipient [7•, 28].

Strategies should be implemented and part of a feeding protocol to minimize diarrhea and further to minimize any decrease in EN delivery secondary to diarrhea. Patients with diarrhea first and foremost should have their diarrhea worked up to make sure there is no infection, significant GI pathology, or complications. Following this, clinicians should consider changing from continuous feed to bolus feeds in patients who can tolerate this method of feeding. Medications that may cause diarrhea should be stopped if possible, to ensue this a complete review of all medications is required. If tolerated, the EN formula may also be switched in the appropriate patient to one that contains more fiber (soluble fiber is generally preferred in ICU patients). A second alternative would be to consider a peptide formula although this recommendation is based only on expert opinion [7•, 30].

Conclusion

EN has proven benefits for critically ill patients and should be integrated into the patients overall therapy plan. An easy standardized approach using a nutrition feeding protocol is a good starting point and can help optimize enteral nutrition early in a patient's ICU admission. Most medical critically ill patients can be started on a standard formula and should be fed fully unless specific evidence-based protocols are followed for trophic feeding or permissive underfeeding. Finally, clinicians should work to minimize interruptions to EN (including trophic and permissive underfeeding) in order for patients to receive the full benefit of EN.

Compliance with Ethical Standards

Conflict of Interest Kellie Jones, Karen Allen, Steven McClave, and Pinckney Maxwell declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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