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Enteral Nutrition in the Mechanically Ventilated Patient

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Abstract

Mechanically ventilated patients are unable to take food orally and therefore are dependent on enteral nutrition for provision of both energy and protein requirements. Enteral nutrition is supportive therapy and may impact patient outcomes in the intensive care unit. Early enteral nutrition has been shown to decrease complications and hospital length of stay and improve the prognosis at discharge. Nutrition support is unique for patients on mechanical ventilation and, as recently published literature shows, should be tailored to the individuals' underlying pathology. This review will discuss the most current literature and recommendations for enteral nutrition in patients receiving mechanical ventilation. (*Nutr Clin Pract.* 2019;34:540–557)

Keywords

critically ill; enteral nutrition; intensive care unit; malnutrition; mechanical ventilation; nutrition support; tube feeding

Introduction

Critical illness, particularly for patients who are mechanically ventilated, causes anorexia and the inability for oral intake. Critical illness is further associated with catabolism and often altered gut absorption. Many critically ill patients often have preexisting conditions, including malnutrition (undernutrition and/or overnutrition). All of this predisposes patients to nutrition deficits, muscle wasting, delayed wound healing, slower recovery, and increased risk of morbidity and mortality. Although there is recently a significant amount of debate regarding the type, timing, and amount of nutrition support patients who are mechanically ventilated require, there is a consensus that supplemental nutrition support is needed and improves outcomes for patients.[1]

Patients receiving mechanical ventilation in the intensive care unit (ICU) are a heterogeneous population. In the recent past, more research has focused on nutrition support during mechanical ventilation, which has addressed some questions regarding best practices but has generated many more additional questions. The increase in nutrition support research has demonstrated that for patients in the ICU requiring mechanical ventilation, enteral nutrition (EN) is not one size fits all. This review will focus on the emerging literature and medical evidence for EN supplementation in patients requiring mechanical ventilation.

Who to Feed

Nutrition support for mechanically ventilated patients is essential, as these patients are critically ill and unable to take nutrition by mouth. This patient population is often in a catabolic state with an elevated level of metabolic stress secondary to a systemic inflammatory response. They have an increased risk for developing complications, including infections, organ failure, prolonged hospitalization, and death. EN has evolved to be considered therapy for patients unable to take nutrition by mouth. EN is thought to modulate the stress response to critical illness, as it helps to maintain gut integrity by maintaining tight junctions and villous height. Gut integrity is essential in maintaining function of gut-associated lymphoid tissue. This supports the release of gastrin and other gastric hormones as well as secretory immunoglobulin A, which helps to modulate the systemic immune response to stress and attenuate disease severity.[2,3]

EN is the preferred route for nutrition support for patients requiring mechanical ventilation if they have a functioning gut. EN has been shown to reduce complications in critically ill patients, many of whom are receiving mechanical ventilation. A retrospective study of 4049 mechanically

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ventilated patients showed that patients fed within 48 hours of admission had a lower mortality.[4] A second retrospective study of patients in septic shock requiring mechanical ventilation (n = 66) showed that patients who received some EN within 48 hours had a decreased length of stay (LOS) and fewer ventilator days.[5] A small prospective trial of 54 patients provided comparable results. In this study, patients who received EN within 24 hours of admission had a lower incidence of pneumonia, decreased mechanical ventilator days, and a decrease in mortality.[6] Although these studies are small and some are flawed by the retrospective nature, a meta-analysis of early (within 24–48 hours) EN showed decreased mortality and reduced infectious complications.[1] In addition, patients fed via EN have lower infectious complications compared with those fed via parenteral nutrition (PN), and EN is associated with a shorter LOS.[1,7] The current (2016) Society of Critical Care/American Society of Parenteral and Enteral Nutrition Guidelines for the Provisions and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient guidelines (SCCM/ASPEN guidelines) recommend that EN be initiated within 24–48 hours of admission for all critically ill patients, which would include all patients receiving mechanical ventilation.[1]

Malnutrition

Malnutrition is common in hospitalized patients and is associated with increased morbidity and mortality.[8] Prevalence in the hospital setting can vary depending on the location and population. One study estimates that 30%–50% of hospitalized patients in the United States have at least some evidence of malnutrition.[9] A study by Mogensen et al evaluating malnutrition and outcomes found that of the 4644 mechanically ventilated patients included in this study, approximately 30% had a history of decreased oral intake or clinical signs of malnutrition, and 3% had evidence of weight loss or were underweight based on a low body mass index (BMI).[10] A study by Sheean et al found that in 56 patients, 46% had moderate (n = 25) or severe (n = 1) malnutrition based on sarcopenia evaluated by computed tomography (CT) imaging.[11]

Sarcopenia is common in patients with respiratory failure and is difficult to identify. In the study by Sheean et al, approximately 60% of ICU patients who were classified as normally nourished when evaluated by the subjective global assessment (SGA) were found to have sarcopenia based on CT evaluation of muscle mass.[11] Sarcopenia was also seen in patients who were overweight and obese; in this study, 12 of 18 patients in this subgroup had evidence of sarcopenic malnutrition, which was not identified by the SGA.[11] This is in line with other studies that have shown that patients with obesity are rarely viewed as malnourished by clinicians but frequently suffer from sarcopenia and loss of muscle mass.[12] A study by Moisey et al evaluated sarcopenia in elderly trauma patients (N = 149) requiring mechanical ventilation. Patients in this study with sarcopenia (n = 106) were found to have a higher mortality as well as fewer ICU and ventilator-free days.[13]

Identification of malnutrition (as defined by reduced oral intake, body composition, and evidence on physical exam) is as important as identifying sarcopenia in high-risk patients receiving mechanical ventilation. In the study by Mogensen et al, 23,575 critically ill patients were evaluated by experienced clinical dietitians to determine if they had malnutrition. In this study, all patients who were identified as having malnutrition by the treating dietitian were noted to have an increased 90-day mortality post discharge after controlling for comorbidities and severity of illness (approximately 20% of the patients in this retrospective review required mechanical ventilation). Malnourished patients were also more likely to be discharged to a rehabilitation care facility or require readmission to the hospital.[10]

Refeeding Syndrome

Patients receiving mechanical ventilation in the ICU are at risk for refeeding syndrome. For susceptible patients, a brief period of starvation can be associated with symptoms of refeeding syndrome.[14] A small prospective study of 62 mixed ICU patients showed that 35% had some clinical evidence of refeeding syndrome after 48 hours without oral intake.[15] Although possible in all patients with decreased oral intake, refeeding syndrome is more commonly seen in patients with extremes of body weight, recent significant weight loss, preexisting electrolyte abnormalities, on insulin or diuretic therapy or chemotherapy, and patients with a history of substance abuse.[16] Refeeding syndrome is also difficult to identify in patients, as there may be minimal clinical symptoms, particularly in mechanically ventilated patients. Typically, electrolyte abnormalities (hypophosphatemia, hypokalemia, and hypomagnesemia) are the most common clinical sign, but other serious complications (rhabdomyolysis, hypotension, shock, seizure, and coma) can occur as well. [13,16,17] There are case reports specific to mechanically ventilated patients with refeeding syndrome. In both cases, hypophosphatemia appears to be the most detrimental, as it may be associated with acute respiratory failure as well as failure to wean from mechanical ventilation.[18,19]

Patients admitted to the ICU and receiving EN should therefore be monitored for possible refeeding syndrome as identification can be difficult. Treatment of refeeding syndrome is supportive care. At-risk patients should be screened for thiamin deficiency, and this should be corrected prior to initiating EN. Serum phosphate, potassium, and magnesium should be monitored daily and supplemented as needed for approximately 4 days. EN (and PN) should be started at approximately half of the patients' goal calorie with the rate slowly increased over a 72-hour period.[16]

Energy Needs

Providing adequate energy via nutrition support to the mechanically ventilated patient is critical. In the mechanically ventilated patient, overfeeding, even for short periods of time, can lead to hyperglycemia and increases time on the ventilator.[20] Conversely, an increasing caloric deficit (persistent underfeeding) also increases time on the ventilator.[21,22] However, an accessible and accurate method to determine energy needs remains elusive.

Indirect calorimetry is the recommended method of determining energy needs but remains inaccessible to most clinicians.[1] A 2015 estimate showed that only 2% of ICUs were regularly using indirect calorimetry.[22] Predictive equations have therefore been the most commonly practiced method of determining energy needs; however, the literature clearly indicates that each equation has a large potential for error. This makes it difficult to accurately predict an individual patient's energy requirements during critical illness. Most studies define an "accurate" estimation of resting energy requirement as within 10% of what is determined by indirect calorimetry. In general, predictive equations estimate accurately only 50% of the time in ICU patients.[23] Results tend to have wide variation, especially in subpopulations such as in patients with obesity or who are underweight, the elderly, or patients with specific types of underlying illness.[24-29]

In addition to lack of reliability with regard to using predictive equations, individual patient characteristics contribute to difficulty in determining and meeting energy needs. Many patients on mechanical ventilation receive nonnutrition sources of calories in sedation (propofol), hydration (intravenous [IV] glucose solutions), and/or dialysate solutions.[30] To prevent overfeeding, clinicians generally subtract the calories provided by these sources from the caloric goal but must also acknowledge that the caloric goal may be flawed if using predictive equations.

As nebulous as predicting energy needs may be, a larger issue exists: regardless of the method of determining energy requirement, delivery of kilocalories remains suboptimal.[31] Even in patients already known to be nutritionally at risk, 74% do not receive minimum nutrition goals.[24] If calories provided is low (even intentionally low because of permissive underfeeding strategies), protein delivery is likely to be inadequate; this low protein delivery has been associated with longer LOS (ICU and overall hospitalization) and increased ventilator time.[32]

Protein Requirements

The role of protein intake in a mechanically ventilated patient is difficult to separate from overall energy intake and is independently important for supporting clinical outcomes. Song et al demonstrated that patients who received adequate protein were more likely to be weaned from the ventilator and had a lower ICU and overall in-hospital mortality and greater 60-day survival than those who did not meet protein needs, even when their overall energy intake was adequate.[33] Similarly, Weijs et al found that non-septic ventilated patients (N = 843) who received adequate protein (>1.2 g/kg of body weight) but were not overfed (defined as energy intake >110% of energy expenditure measured by indirect calorimetry) experienced lower mortality than those with a lower protein intake.[34] Comparable results were found in a mostly septic population (N = 113); patients with higher protein intake were significantly more likely to be discharged alive from the ICU than those with the lowest protein intake.[35] These trials were observational in nature, limiting their generalizability, but their results indicate that protein goals may need to be a focus separately from caloric intake.

Based on these trials, the SCCM/ASPEN guidelines recommend a protein target range of 1.2–2.0 g/kg actual body weight for critically ill patients, with higher requirements possible for patients with burns or multiple trauma.[1] It is notable that both Allingstrup et al and Song et al used weight-based equations (1.2–1.5 g/kg in both studies) only until nitrogen balance studies could be completed to provide patient-specific goals.[33,35] It is possible that, similar to the use of an indirect calorimeter for energy requirements, nitrogen balance could provide more specific goals for an individual patient, but whether this level of detail is clinically necessary remains to be seen in further research.

Although further research is clearly needed on protein needs independent of energy needs, protein intake does seem to be important for good clinical outcomes in a patient on the ventilator. Delivery of EN with adequate protein is challenging when patients are receiving mechanical ventilation. Patients admitted to the ICU often quickly develop a protein debt, frequently caused by iatrogenic underfeeding.[36] Clinicians should evaluate protein as a goal separate from overall energy intake and modify nutrition support as needed (such as utilizing protein modulars or a higher protein formula) to meet these needs.

Feeding Protocol

Many studies have evaluated the impact of a feeding protocol for mechanically ventilated patients. Depending on the nutrition management plan of the protocol, patients who are fed earlier (within 24–48 hours) receive a higher percent of goal calories and protein and have fewer feeding intolerances. [1,37-41] However, these studies have not consistently shown an improvement in clinical outcomes related to implementation of a specific feeding protocol. In a recently published narrative review of feeding protocols, 19 studies were evaluated with only 4 showing an improved clinical outcome (decreased complications or lower mechanical ventilation days or LOS).[37] EN

protocol studies have further shown that improved delivery of EN can be achieved without increased complications.[42,43] Unfortunately, however, some nutrition protocol studies also reveal poor overall physician compliance or acceptance of feeding protocols.[44-46] Doig et al conducted a cluster randomized trial of 27 ICUs comparing implementation of nutrition evidence-based, guideline-driven practice vs control ICUs (utilizing standard practice for the facility). The guideline-driven practice ICUs were given a specific algorithm for management of EN developed by the study authors. The trial evaluated 1118 (561 intervention and 557 control) patients from the 27 ICUs. The mean time to start EN was lower by 0.75 days vs 1.37 days ($P < 0.01$), and the number of patients completely unfed decreased (32 vs 157, $P < 0.001$), favoring the guideline-driven ICUs in this study.[47] However, the total average daily energy patients received via EN between the intervention and control groups did not differ. There was also no difference in clinical outcomes between the guideline-driven ICUs and ICUs following standard nutrition practice. The study authors note that there may be a Hawthorne effect, as the sites volunteered to participate in a nutrition study. In addition, ICUs willing to participate in a nutrition protocol study may already have a good nutrition support program in place, which minimized the difference between the groups.[47]

Although not found to have a significant impact on patient outcomes, protocols likely have a positive effect on patient care. The protocol should be viewed as a part of a care bundle in which several interventions are grouped together to improve patient care. It is unlikely that separately each intervention improves care-related outcomes, but together the entire bundle of interventions as part of a complete protocol improves outcomes.[37] Nutrition bundles have not yet been fully developed and implemented for critically ill mechanically ventilated patients. These would include a multitude of elements and would likely be strongly associated with ventilator-associated pneumonia prevention bundles. As outlined by McClave et al, potential elements are early initiation, rapid advancement of calorie and protein goals, elevation of head of bed, probiotic and prokinetic use, assessment by nutrition specialist, consideration of nurse-driven protocols or volume-based feeding, and participation in national databases for quality improvement and evaluation.[48]

As with all aspects of care for mechanically ventilated patients, adherence to treatment protocols and bundles is a cultural change. This is certainly the case for a successful nutrition protocol. Bundles to improve clinical nutrition require a team approach and dedication within the hospital system to implement. The best approach to implementation is continued feedback on a local level to identify barriers and inadequacies within the protocol so that it fits the local practice and standard of care. In creating a culture of good nutrition support with an effective feeding protocol, an organization's specific culture and clinical practice must be considered and incorporated into the design.

Volume-Based Feeding Protocols

Most feeding protocols are based on providing EN for a continuous 24 hours at a set rate to meet the patients' ordered daily EN targets. This method has inherent flaws, as EN is frequently stopped for numerous reasons, causing a lower amount of energy delivery than what is prescribed within a 24-hour period. One possible solution to this situation is volume-based feeding, referring to a feeding protocol that changes the rate of feeding to adjust for periods when feeding is stopped during ICU care. An initial single-center trial published in 2015 compared a volume-based protocol with a standard rate/hour feeding method in 63 mechanically ventilated patients (37 intervention and 20 control). The volume-based protocol used in this study calculated the total EN requirements for an individual patient and provided bedside nurses with guidelines to increase feeding rates during a 24-hour period to reach the total prescribed EN. Patients in the intervention group received a higher percentage of energy requirements (92.9% vs 80.9%, $P = 0.01$) than control patients who were fed a standard rate/hour.[49]

Two larger trials conducted by Heyland et al have shown similar results. The protocol for these trials is commonly referred to as the PEPuP protocol. It includes (1) starting EN at a higher initial rate compared with common practice of starting at 10–20 mL/h and (2) targeting a 24-hour goal as opposed to an hourly rate similar to the previously mentioned single-center trial.[50,51] The initial publication in 2013 was a randomized cluster trial of 18 ICUs (1059 total patients) to evaluate implementation of the PEPuP protocol at hospital ICUs with a known history of poor nutrition support practices. The intervention group received both increased caloric and protein delivery. The proportion of prescribed calories in the intervention group was 48.2 ± 34.3 (mean $\pm$ SD) compared with 35.9 ± 31.0 prior to implementation of PEPuP and 37.9 ± 30.3 in the control group.[50] However, the trial did not evaluate any differences in clinical outcomes.

Although the trial favored the implementation of feeding protocol, the authors note that this is only 1 aspect of optimal delivery of EN. Hospitals and clinicians need to work to eliminate barriers to nutrition support, creating a culture in which nutrition support is a priority of patient care.[50] A second study published in 2015 evaluated implementation of the PEPuP protocol in 6 ICUs utilizing the PEPuP protocol compared with 11 standard-care ICUs. In this trial, patients in the intervention group received a higher proportion of prescribed calories (60.1% compared with 49.9%; $P = 0.02$) as well as a higher proportion of prescribed protein (61% vs 49.7%; $P = 0.01$).[51] This study again did not

show any difference in clinical outcomes, although it was not designed to evaluate this.

Trophic vs Full EN

There is a growing body of literature that endorses trophic feeding over full EN for mechanically ventilated patients. One of the earlier trials to evaluate this was the EDEN trial published in 2012.[52] Since that time, additional studies have been completed evaluating various caloric and protein intake, but the debate between trophic vs full-feeding EN continues. There is no agreed-upon definition of trophic feeding, and the amount of EN delivered as "trophic" is between 400 kcal/d and 800 kcal/d (25%–40% of goal kcal/d) depending on the study.

The EDEN trial (N = 1000) was a multisite, randomized trial that compared trophic (approximately 400 kcal/d) vs full (1300 kcal/d) feeding in patients with acute respiratory distress syndrome (ARDS) for the initial 6 days of mechanical ventilation. In this trial, the type of EN as well as the location of enteral tube position and prokinetic use were at the discretion of the treating physician. The study did not show any difference in ventilator-free days, organ failure–free days, infection, or 60-day mortality between the 2 groups. The study is limited in that it did not monitor protein intake and included only patients with a diagnosis of ARDS. In addition, the average BMI in this study was 30, and therefore patients in this group had decreased nutrition risk compared with other patients on mechanical ventilation.[52]

A follow-up study from the EDEN trial further showed no difference in functional outcomes between the 2 groups of patients. The study was conducted 1 year post discharge, and patients were evaluated based on assessments of patients' arm anthropometrics, strength, pulmonary function, 6-minute-walk distance, and cognitive function. The study did, however, show that patients who survived ARDS had a shorter 6-minute-walk distance and greater decrease in cognitive function than predicted.[53] The results in this patient population are likely unique to patients with ARDS and are not generalizable to all patients who require mechanical ventilation. ARDS is a severe illness, and studies have shown that surviving patients experience significant long-term sequelae.[54] Long-term outcomes of trophic feeding in a different population may not show comparable results, and therefore these results cannot be applied to all patients receiving mechanical ventilation.

A second prospective randomized trial (PERMIT) comparing trophic (800 kcal/d) feeding with full caloric feeding (1300 kcal/d) was published in 2015 and included a broader range of patients (N = 894 with 75% being medical ICU patients).[55] In this trial, both groups (n = 448 in the permissive underfeeding group and n = 446 in the standard feeding group) received similar amounts of protein (mean 57 g/d). The primary outcome was defined as 90-day mortality and was not statistically significant between the 2 groups ($P = 0.58$). Like the EDEN trial, patients enrolled in this trial had an average BMI of 29 and did not have evidence of malnutrition on hospital presentation. The study investigators recommended EN per the SCCM/ASPEN 2016 guidelines but allowed the treating physician to make the final decision for the type of EN and enteral access device for each patient. Patients in the PERMIT trial were given trophic feeding for a maximum of 14 days compared with the EDEN trial, which fed patients trophic amounts for only 6 days. Unfortunately, there is not a long-term follow up of patients in this trial published at this time.

Neither study showed a difference between trophic vs full delivery of EN in mechanically ventilated patients. Each trial enrolled well-nourished patients, and therefore data for trophic feeing in undernourished patients is lacking. A post hoc analysis of the PERMIT trial did not show a difference in outcomes based on the Nutrition Risk in the Critically Ill (NUTRIC) score.[56] The NUTRIC score was designed to help determine the risk of experiencing malnutrition for patients admitted to the ICU. The score considers the patients' age, disease severity, any comorbidities, and number of days in the hospital to determine if an individual patient is more likely to benefit from receiving EN. Patients with a score from 5 to 9 are more likely to benefit from EN compared with patients with a score from 0 to 4.[57]

In this post hoc analysis, patients in the trophic group with a high NUTRIC score did not have worse outcomes compared with other patients in the trial.[56] This analysis has some flaws in that there is no difference in total protein between the 2 groups, which may account for the similar outcomes. Also, patients with an abnormal BMI (either high or low) were not included in the initial trial, and the outcomes noted in the trials may not be similar in these populations regardless of NUTRIC score. A trial by Compher et al showed different results to the post hoc analysis by Arabi et al.[58] In this observational study, improved nutrition intake was associated with a lower mortality and faster time to discharge alive in patients with a high NUTRIC score.[58] Additional studies are required to determine the best protein and caloric needs for patients considered to be nutritionally at risk. A summary of studies evaluating trophic vs full-feeding EN strategies is outlined in Table 1.

Disease-Specific EN

Disease-specific diets have been marketed to improve outcomes for patients with a particular pathology. Many of the developed enteral formulas on the market do not have significant medical evidence to support their widespread use.[59] In addition, these formulas are often more expensive than regular formulas. The SCCM/ASPEN guidelines recommend against the use of disease-specific formulas.[1] However, there

Table 1. Summary of Literature on Goal Caloric vs Hypocaloric Enteral Nutrition Supplementation.

Author Year Published	Methods	>Participants	>N	>Full[a]	>Trophic[a]	>Days (maximum)	>Protein[c]	>Outcomes	>Notes
Rice[120] 2011	Single-center, randomized, open-label	ALI Pneumonia	200	1418 (686)	300 (149)	6	Not reported	No difference at 28 days in VFD[c] ($P = 0.90$) or all-cause mortality ($P = 0.62$)	Subgroup analysis of ALI patients showed no difference in VFD ($P = 0.59$) or all-cause mortality ($P = 0.95$)
Rice[52] 2012 EDEN Trial	Multicenter, randomized, open-label	ALI	1000	1300	400	6	Not reported	No difference at 28 days VFD ($P = 0.89$) or mortality at 60 days ($P = 0.77$)	No difference in VAP ($P = 0.72$); trophic group experienced less regurgitation ($P = .003$), vomiting ($P = 0.05$), elevated GRV ($P < 0.001$), and constipation ($P = 0.003$)
Braunschweig[121] 2015[b]	Single-center, randomized	ALI	78	1798 (509)	1221 (423)	Full admit	Full: 82 (23) Trophic: 60.4 (24)	No difference in hospital LOS ($P = 0.33$), ICU LOS ($P = 0.82$)	This study was stopped early for a mortality difference favoring the standard-care group ($P = 0.017$)
Arabi[56] 2015 PERMIT Trial	Multicenter, randomized, open-label	Medical ICU nonoperative trauma	894	1299 (467)	835 (297)	14	Full: 59 (25) Trophic: 57 (24)	No difference at 90-day mortality ($P = 0.58$) or VFD ($P = 0.48$), ICU death ($P = 0.24$), ICU LOS ($P = 0.46$), hospital death ($P = 0.24$), or hospital LOS ($P = 0.24$)	96.8% of participants received mechanical ventilation in this study; there was no difference in feeding intolerance ($P = 0.26$) or diarrhea ($P = 0.11$)
Petros[122]	Single-center, randomized, open-label	Medical ICU	100	19.7 ± 5.7 kcal/kg/d	11.3 ± 3.1 kcal/kg/d	7	No average given, but was higher in the full group	Nosocomial infections were higher in the trophic group ($P = 0.046$); no difference in hospital mortality ($P = 0.67$)	Some patients in this study received parental nutrition; 49% of the total nutrition provided in the full feeding group and 8% in the trophic group was via the parenteral route

All full and tropic calories provided and protein amounts are average for study intervention days.
ALI, acute lung injury; GRV, gastric residual volume; ICU, intensive care unit; LOS, length of stay; VAP, ventilator-associated pneumonia; VFD, ventilator-free days.
[a]Mean kcal/d received in each study group (± SD, if provided).
[b]This study was not designed as a trophic vs full feeding but evaluated intensive medical nutrition intervention vs standard care.
[c]Mean grams of protein per day (±SD).

are some specific disease states and interventions related to provision of EN that deserve additional comment.

Pulmonary Failure

Patients with pulmonary failure were previously thought to benefit from EN with a high-fat and low-carbohydrate formula. Hypercapnic pulmonary failure occurs when a patient is unable to fully ventilate and excrete carbon dioxide (CO_2) from the lungs. This is commonly seen in patients with acute exacerbations of chronic obstructive pulmonary disease, obesity hypoventilation syndrome, and neuromuscular disorders that affect the respiratory muscles. The respiratory quotient (RQ) is a ratio comparing CO_2 produced relative to oxygen consumed and is used to calculate the basal metabolic rate. The RQs for fats and carbohydrates are 0.7 and 1, respectively. It was therefore hypothesized that the limited ventilatory ability (inability to excrete CO_2) of patients with hypercapnic respiratory failure could be complicated by higher production of CO_2 from nutritional carbohydrate supplementation. In theory, the high CO_2 levels experienced by these patients could decrease the patients' ability to wean from mechanical ventilation.[60]

The low-carbohydrate formulas were initially thought to decrease CO_2 production, leading to decreased mechanical ventilation days (this decrease in mechanical ventilation was shown in a small study, N = 20).[60] However, these results could not be replicated.[61] Consensus is that CO_2 production only becomes clinically significant to prolong mechanical ventilation when patients are overfed.[1] EN with a high-fat, low-carbohydrate formula is generally not recommended as studies show an overall lack of clinical benefit.[62] Patients with pulmonary failure, however, are susceptible to fluid accumulation, which has been associated with worse outcomes.[63] Therefore, a fluid-restricted, energy-dense formula may be considered for patients with pulmonary failure.[1]

ARDS is a different form of pulmonary failure and is caused by acute hypoxia instead of hypercapnia. Patients with ARDS were previously thought to benefit from an anti-inflammatory fat profile provided through enteral immunonutrition with increased ω-3 fatty acids. The initial multicenter trial by Gadek et al (N = 146) randomized patients to receive EN enriched in eicosapentaenoic acid, docosahexaenoic acid, γ-linolenic acid, and antioxidants vs a control isonitrogenous, isocaloric EN. Patients receiving the enriched EN had improvements in oxygenation (from baseline), fewer days on mechanical ventilation, and decreased ICU LOS.[64] The control group, however, received EN with increased amounts of ω-6 fatty acids (which are considered proinflammatory fatty acids). This may have increased the benefit seen in the patients receiving enriched EN compared with the control group. Two additional trials also using a control EN high in ω-6 fatty acids reported similar outcomes.[65,66]

Contrary to the results of the trials using a control formula with ω-6 fatty acids, Stapleton et al using only EN with ω-3 in a randomized trial demonstrated that there was no difference in proinflammatory markers and no benefit in duration of mechanical ventilation, ICU days, or mortality (N = 90).[67] The largest trial to date evaluating the use of ω-3 fatty acids in ARDS, the OMEGA trial (N = 272), was stopped early for futility (at the first interim analysis by the data safety monitoring board as the trial would not be able to reach statistical significance in the primary outcome).[68] In this study, patients in the ω-3 group were found to have fewer ventilator-free days and ICU-free days. The patients in the study group also showed a trend toward increased mortality, although this was not statistically significant. Finally, a meta-analysis of 7 randomized controlled trials evaluating ω-3 fatty acid supplementation in ARDS failed to show improved outcomes related to mortality, ventilator-free days, and ICU-free days.[66] The trials evaluating enteral immunonutrition enriched in ω-3 fatty acids for patients with ARDS are limited by lack of homogeneity. There is inconsistency in the ω-3 formulation, delivery method, placebo formulas (as some included other anti-inflammatory compounds), and duration of therapy.[65-69] The SCCM/ASPEN 2016 guidelines could not make a recommendation regarding the use of EN with an anti-inflammatory fat profile in patients with ARDS given the overall low evidence.[1]

Renal Disease

The nutrition assessment of patients requiring mechanical ventilation is complicated when acute kidney injury (AKI) is present as many of these patients have coexisting underlying disease or organ dysfunction that further complicates nutrition deficiencies. AKI is commonly defined by the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) or the AKIN (Acute Kidney Injury Network) definition. Although these are different definitions, each defines initial renal injury (in part) as a $\geq$25% decrease in glomerular filtration rate or a significant decrease in urine output.[70] AKI (defined by either of the two methods) occurs in 30% of patients who are admitted to the ICU and is associated with worse outcomes in ICU patients.[71]

Special EN formulas have been developed to assist in preventing electrolyte derangements, which can be common with AKI. Many serum electrolytes are regulated by renal function, including potassium, phosphate, magnesium, and calcium. Potassium abnormalities can be the most severe and may cause arrhythmia and death in extreme cases. Therefore, potassium levels should be frequently monitored in AKI and managed aggressively with renal replacement therapy when needed. Although frequently altered in AKI, calcium, phosphate, and magnesium levels are rarely life-threatening. These electrolytes still should be monitored

and replaced as necessary.[72] In the absence of significant electrolyte abnormalities, standard EN formulas may be prescribed for patients with AKI. EN should never be withheld as a method to manage changes in serum electrolytes.[1]

AKI is further associated with changes in the normal metabolism of protein, carbohydrate, and fats. Impaired lipolysis from altered fat metabolism is often associated with AKI, resulting in an increase in triglycerides and low-density lipoproteins and a decrease in total cholesterol and high-density lipoprotein. Fatty acid oxidation, however, is maintained and is an essential energy source for these patients.[72] Carbohydrate metabolism is altered with AKI, and patients experience exacerbated insulin resistance. This is likely related, at least in part, to a reduction in renal gluconeogenesis. Patients with AKI who also experience significant insulin resistance have an increased risk of mortality compared with patients with AKI alone.

Finally, AKI is a catabolic state and severely alters normal protein metabolism. This is further complicated in patients requiring renal replacement therapy, as they experience significant protein losses secondary to dialysis. Therefore, protein requirements increase when patients are placed on any form of renal replacement therapy. The amount of additional protein required by patients with AKI is unknown, and it has been shown that even elevated levels of replacement may not be adequate.[73] One study found that 65% of patients on renal replacement therapy did not achieve a positive nitrogen balance on a diet of 2.5 g/d of protein.[74] However, another small study showed that patients could achieve a positive nitrogen balance with protein supplementation up to 2.5 g/kg/d. There was no improvement in outcomes with the improved nitrogen balance.[75] Protein intake should be increased in patients receiving renal replacement therapy, up to a maximum of 2.5 g/kg/d per the SCCM/ASPEN 2016 guidelines. Patients with AKI without renal replacement therapy should have between 1.2 and 2 g/kg/d of protein.[1]

Liver Disease

Malnutrition is common in chronic liver disease. The prevalence ranges from 20% to over 80% in patients with compensated and decompensated cirrhosis, respectively.[76] In addition, malnutrition is independently associated with decreased survival in patients with liver disease.[77] Currently, there is limited data regarding liver-specific EN during mechanical ventilation and critical illness. The recommendation for energy requirements from the 2006 European Society for Clinical Nutrition and Metabolism (ESPEN) and the SCCM/ASPEN 2016 guidelines ranges from 25 to 40 kcal/kg/d.[1,78] The ESPEN guidelines recommend using a simplistic weight-based equation (35–40 kcal/kg/d), but SCCM/ASPEN guidelines suggest indirect calorimetry (if available), given energy requirements are variable and difficult to predict in this population. Both guidelines recommend the use of dry weight for calculating energy requirements to minimize cirrhosis-related complications resulting from fluid shifts and volume status changes (related to ascites, intravascular volume depletion, portal hypertension, and hypoalbuminemia).[1,78]

Protein restriction has been a common practice for patients with advanced liver disease as a means to reduce the incidence of hepatic encephalopathy (HE), but more recent studies now show no benefit associated with protein restriction.[79,80] On the contrary, protein restriction can worsen nutrition status by decreasing lean muscle mass and actually decreasing ammonia removal. Expert opinion now recommends avoiding protein restriction for all patients with liver disease, except for patients with evidence of significant protein intolerance (eg, HE Grade III–IV) and then reducing protein for only a brief time as clinically appropriate.[81] Concentrated high-energy EN formulas are recommended for patients with ascites to minimize fluid shifts.[78] For ICU patients with liver disease, the SCCM/ASPEN 2106 guidelines recommend using a standard polymeric isotonic or near isotonic 1–1.5 kcal/mL EN formula. There is no evidence to support the routine use of specialty EN formulas in this patient population.[1]

Branched-chain amino acids (BCAAs) are an EN option for patients with advanced liver disease. However, these formulas are expensive. The BCAA formulas contain a higher proportion of BCAAs compared with aromatic amino acids (AAAs).[81] Cirrhosis leads to a low ratio of BCAA to AAA secondary to impaired ability for hepatic deamination of AAA in the liver. As a result, the brain uptake of BCAA and AAA is altered. As a result of this, tryptophan (an AAA) has increased uptake in the brain compared with BCAA, which leads to an imbalance of neurotransmitter synthesis. This imbalance is thought to contribute to confusion in these patients. BCAA is also thought to reduce hyperammonemia as it has a stimulating effect on ammonia detoxification to glutamine.[82] Although there has been controversy regarding the benefit of BCAA formulas in patients with advanced liver disease, the ESPEN 2006 guidelines recommend formulas with BCAA for patients with HE. On the contrary, the SCCM/ASPEN 2016 guidelines recommend against the use of EN formulas with BCAA.[1,78] The ESPEN recommendation is based on 1 large randomized controlled trial that showed that long-term (12 months) supplementation with BCAA formulas resulted in decreased frequency of hepatic failure and related complications.[83] The SCCM/ASPEN guidelines recommendation, however, is focused on critically ill patients and the lack of evidence available to support improvement in outcomes for patients who are already on first-line therapy for HE.[1]

Obese Patients

Morbidly obese patients are complex to manage, as they often experience more complications compared with

patients with a normal BMI.[84] As previously mentioned, clinicians often, however, fail to recognize the existence of malnutrition and sarcopenia, which are frequently present in this patient population. It has been shown that patients with a BMI of 30 experience malnutrition and sarcopenia, which may not be identified by standard bedside screening tools.[9,11] In addition, obese patients experience altered energy metabolism. A small study of mechanically ventilated obese trauma patients (N = 17) showed this by evaluating energy metabolism in mechanically ventilated patients during a continuous glycerol infusion.[85] Obese patients derived only 39% of their energy expenditure from fat compared with 61% in patients with a normal-range BMI. The obese patients also metabolize lean mass at higher rates, creating an increased risk for loss of lean body tissue.[85]

Therefore, determining caloric and protein needs in the obese population is a challenge. Previous studies have shown that the use of published predicative equations is not reliable when compared with indirect calorimetry.[86,87] In addition, studies regarding the adequacy of nutrition supplementation have shown that a dose of 2.0 g/kg/d of protein was not sufficient to achieve a positive nitrogen balance in obese patients.[88] This makes determining nutrition supplementation with accuracy even more challenging in this population. The SCCM/ASPEN guidelines recommend indirect calorimetry as the gold standard.[1] However, as this is not available in many facilities, hypocaloric feeding with increased protein supplementation based on a simplistic weight-based formula is often utilized with some validity.[89] The standard recommendation is 11–14 kcal/kg/d and 2.0 grams/kg/d of protein based on actual body weight for a BMI of 30–50 and 22–25 kcal/kg/d with 2.5 g/kg/d of protein for a BMI >50.[1]

Prone Position

Placing mechanically ventilated patients in a prone position has recently been found to improve outcomes in patients with ARDS.[90] In the landmark trial, patients randomized to prone positioning were placed in this position for a minimum of 16 hours per day. This trial did show a decrease in mortality, now making this practice standard of care in severe ARDS. This change in patient position is challenging from a nutrition perspective; however, EN in this patient population has been described.

There are several small published studies that describe EN for patients in a prone position with mixed findings, shown in Table 2. These studies are not randomized and are small, with the largest having 72 total patients (38 received EN in a prone position). This largest trial, published in 2010, fed prone patients with a 25% head-of-bed elevation, gave prophylactic erythromycin, and fed at an increased rate (up to 85 mL/h). This resulted in successful delivery of EN and good overall tolerance. In this study, prone position patients received more EN and demonstrated lower gastric residuals without an increase in complications.[91] Other studies, however, have shown increased gastric residual volumes and vomiting with EN delivery during prone positioning. In this study there was no elevation of the head of bed during the prone position or routine use of prokinetic agents.[92] Finally, Saez de la Funente et al published a case series of 34 patients who received EN in the prone position compared with supine-fed patients. This group of patients had a head-of-bed elevation to 10% in the prone position and showed no difference in volume of EN delivered, gastric residuals, or vomiting between the 2 groups.[93]

Vasopressors/Sepsis

Patients admitted to the ICU and started on mechanical ventilation frequently experienced hypotension, often related to septic shock and/or multi-organ failure. As there is no direct evidence supporting safe use of EN on vasopressors, nutrition guidelines recommend that patients be fully resuscitated prior to initiating EN.[1] There are several studies that report outcomes for mechanically ventilated patients who are on vasopressor support and receive EN. In both the previously mentioned EDEN and PERMIT studies, 38% and 55%, respectively, of patients were on vasopressors when initially enrolled in the trials and started on EN.[52,55] Both trials excluded patients on high-dose vasopressors at the time of enrollment; a rate of epinephrine or norepinephrine >0.4 μg/kg/min in the PERMIT study and a dose >30 μg/min in the EDEN trial were excluded. Neither trial reports complications related to vasopressor use, and a subgroup analysis of the PERMIT study reported no difference in the mortality for patients receiving vasopressors compared with those who did not.[55,94]

There are several retrospective and observational studies that suggest that EN may be safe when patients are receiving low doses of vasopressors.[6,95,96] One retrospective trial (N = 1174) showed that patients receiving vasopressors tolerated early EN and had improved outcomes with lower ICU and hospital mortality.[96] The study, however, did not report on vasopressor doses or amount of EN provided while patients were receiving vasopressors.[96] Additionally, a retrospective analysis of 66 patients with septic shock showed that patients receiving <600 kcal/d of EN had a lower ICU LOS and shorter mechanical ventilation time than patients who were not fed or received >600 kcal/d of EN.[6] Mortality and complications were not different between the groups in this study. Another retrospective analysis of patients who received EN and vasopressors evaluated factors that contributed to poor tolerance of combined vasopressors and EN. This study found that EN tolerance was improved with lower doses of norepinephrine (<12.5 mcg/min). Patients receiving dopamine, vasopressin, or norepinephrine doses >19.4 mcg/min were less likely to

Table 2. Evaluating Evidence for Enteral Nutrition in the Prone Position.

Study Author/Year	Methods	Participants	N	Feeding Protocol	Efficacy	Safety
Saez de la Fuente[93] 2016	Prospective observational	Medical and surgical ICU	34	Continuous goal of 25 kcal/d	Days of EN were higher in supine vs prone ($P = 0.01$); % of volume ordered was not different ($P = 0.21$); gastric residual volume per day was not different ($P = 0.54$)	High gastric residual events (>500) were not different ($P = 0.39$); vomiting episodes were not different ($P = 0.53$); regurgitation trended higher in prone group compared with the supine group ($P = 0.51$)
Reignier[91] 2010	Before and after study (following implementation of a feeding protocol for prone-position patients)	Medical ICU patients	Control: 34 Intervention: 38	Control: continuous (18 h/d) gradual daily increase to median of 1170. Intervention: continuous (24 h/d) gradual increase to median or 1945. All patients receive a prokinetic	There was an increase in EN delivery ($P = 0.001$); no difference in gastric residual volume on days 1–5 ($P = NS$)	No difference in ventilator-associated pneumonia ($P = 0.58$); no difference in secondary infection ($P = 0.81$)

(*continued*)

Table 2. (continued)

Study Author/Year	Methods	Participants	N	Feeding Protocol	Efficacy	Safety
Reignier[92] 2004	Prospective observational for initial 5 days of ICU admit; patients were intermittently in prone position	Medical ICU	71 total; 34 received prone position, 37 supine position only	Continuous feeding via nasogastric tube gradually increased as tolerated to goal of 2000 mL by day 4	Higher gastric residual volume in prone group compared with supine group on days 1, 2, and 4 ($P = 0.001$, 0.001, and <0.01, respectively); daily feeding volume was higher in supine group for all 5 days ($P < 0.05$); EN was stopped more frequently in the prone position compared with the supine position ($P < 0.05$); EN was stopped for vomiting and gastric residual volume >250 mL	Increased vomiting was noted in prone position ($P < 0.001$)
van der Voort[123] 2001	Crossover trial design	Medical ICU	19	Patients were fed for 6 hours supine and for 6 hours in prone position at the same feeding rate; average total volume was 360 mL for 12 hours	No difference in mean gastric residual ($P = 0.69$)	Did not evaluate

EN, enteral nutrition; ICU, intensive care unit; NS, not significant; PN, parenteral nutrition.

tolerate EN in this study. Evidence of decreased tolerance was defined as increased lactate level, high gastric residual volume, any episode of vomiting, positive imaging findings, and episodes of bowel ischemia or perforation (observed in 3 patients).[97] A summary of studies specifically focused on EN during vasopressor use in ICU patients is provided in Table 3.

The NUTRIREA-2 trial published in 2018 further suggests that EN may be associated with increased bowel ischemia. The trial (N = 2410) was a randomized, controlled, open-label, multisite study to evaluate EN compared with PN in mechanically ventilated patients.[98] The study did not show any difference between the groups for the primary outcome of 28-day mortality. However, in the EN group, there was a statistically significant increase in bowel ischemia (2% vs <1%, $P = 0.007$). Although the trial was not designed to evaluate this in relation to the use of combined EN and vasopressors, 81% of patients in the trial were on vasopressors at the time of enrollment. In addition, the trial allowed for EN to begin at a higher vasopressor dose (0.53 μg/kg/min) than allowed in the EDEN or PERMIT trials.[52,55,98] Although the overall incidence of bowel ischemia was low in the EN group (2%), it is associated with significant morbidity and mortality.[98] Given the findings of the NUTRIREA-2 trial, caution should be exercised when providing EN to patients on vasopressors, and EN should only be given to patients on low to moderate doses.[1,94]

Pancreatic Disease

Frequently, patients with severe acute pancreatitis require mechanical ventilation. Small trials show fewer complications with EN compared with PN.[99] Eckerwall et al showed lower multi-organ failure with EN compared with PN (N = 69), and Abou-Assi et al showed fewer septic complications (N = 53).[100,101] The Dutch PYTHON trial (N = 208), however, showed no difference in the outcomes of patients started on early EN via a nasogastric (NG) tube within 24 hours of admission compared with an oral diet started at 72 hours following admission.[102] Only approximately 30% of patients in this trial received mechanical ventilation, so the lack of benefit cannot be broadly assumed in all ICU patients with pancreatitis and respiratory failure. Given the paucity of evidence, the SCCM/ASPEN guidelines recommend starting patients on trophic feeding and advancing this as tolerated and as disease severity decreases. This provides some EN support and prevents nutrition deterioration.[1]

Although not largely studied, historically semi-elemental and elemental EN formulas have been recommended for pancreatitis. Current recommendations, however, are for standard polymeric formulas to be initiated first in patients with pancreatitis. This is based on results of a small study comparing the 2 formulas, which showed no difference in outcomes. This study included 30 patients with acute pancreatitis receiving jejunal nutrition who were fed either Peptamen or Sondalis-Iso at 35 kcal/kg/d. There was no difference between the 2 groups for any of the outcomes, including pain level, bloating, and feeding tolerance. In addition, there was no difference in the absorption of EN (based on 24-hour stool weight, 24-hour steatorrhea, and mean number of stools).[103] Both groups experienced resolution of pancreatitis based on abdominal CT scan results. Additionally, a meta-analysis comparing polymeric (standard) and semi-elemental formulas showed that standard formulas do not lead to an increased risk of intolerance to EN, infectious complications, or death in patients with acute pancreatitis.[104]

There is a developing amount of literature regarding the placement of an enteral feeding tube in patients with severe acute pancreatitis, but none are specific to mechanically ventilated patients. Most of the studies relating to this topic are small (including both mechanically ventilated and nonventilated patients) and compare an NG tube with a nasojejunal (NJ) tube. The physiological argument favors an NJ tube, as the NG tube may cause more stimulation of the pancreas, and delayed gastric emptying may be present.[99] However, studies to date do not show a consistent clinical benefit for NJ tubes. A meta-analysis that reviewed 157 patients found that NG feeding was not inferior to NJ feeding.[105] A second meta-analysis (N = 147) further found no difference between the 2 strategies in tube displacement, exacerbation of pain, diarrhea, change to PN, or delivery of energy requirements.[106] Although the literature to date does not show a clear benefit to an NJ tube, high-quality randomized trials are lacking.

In addition to EN, probiotics are recommended in patients with pancreatitis in the ICU setting. Although 1 large study of 296 patients showed increased harm associated with administration of a prebiotic and a probiotic to the jejunum compared with controls, other studies have not replicated this result.[107] A large meta-analysis, which included the previously mentioned study, showed an overall benefit (decreased hospital LOS and reduced infectious complications) favoring probiotic administration in this population.[108] A more recent study by Wang et al (N = 183) showed a reduction in pancreatic sepsis and multi-organ failure in patients receiving a probiotic compared with controls.[109] However, currently, data are lacking regarding the best probiotic to give patients, as there is little consistency in the trials.

Managing Enteral Tube Feeding

Once the nutrition assessment is complete and the EN formula is chosen, optimal delivery of EN for mechanically ventilated patients depends on the daily management of the patients' tube feeding. Many ICU physicians fear

Table 3. Studies Evaluating Vasopressors and EN.

Author Year	N, Study Type	Patient	EN Received	Vasopressor Dose	Findings
Rai[95] 2010	44, Retrospective review	ICU patients with sepsis (n = 10) and septic shock (n = 33)	Evaluated EN over 7-day period, patients received an average of 65% of goal calories	Not described	Mean time to initiation of feeding was not different between patients with sepsis vs septic shock ($P = 0.16$); septic shock patients had higher gastric residuals ($P = 0.02$); no difference in percent of goal calorie received ($P = 0.2$)
Khalid[92] 2010	1174, Retrospective review	Mixed ICU (receiving mechanical ventilation)	n = 707 received EN within 48 hours, n = 467 did not receive EN within 48 hours (rate of EN not given)	Not provided	ICU mortality was lower in patients receiving EN ($P = 0.03$); hospital mortality was low in patients receiving EN ($P < 0.001$)
Mancl[94] 2013	259, Retrospective review (346 episodes of receiving EN and vasopressor >1 hour)	Adult ICU patients given concurrent EN and vasopressors for >1 hour	13 (7.5) (mean [SD]) kg/kcal/d received (average for all study patients)	0.062 Norepinephrine,[a] 4 dopamine,[a] 0.046 epinephrine,[a] 0.538 phenylephrine,[a]	74.9% tolerated,[b] 14.5% had elevated gastric residuals,[b] 9.0% had emesis,[b] 0.9% had bowel ischemia[b]
Patel[93] 2014	66, Retrospective review	ICU patients with septic shock	n = 15 No EN, n = 37 <600 kcal/d, n = 14 >600 kcal/d	Norepinephrine was most common vasopressor but strength not given; 13.5% of <600 kcal/d group were on multiple vasopressors	Lower ICU LOS and decreased mechanical ventilator days in patients fed <600 kcal/d; no difference in mortality or complication rate
Lasierra[124] 2015	37, Prospective observational	Cardiac surgery patients with hemodynamic failure	36/37 received EN; mean volume: 1199 mL, mean: 1228.4 kcal/d	Not given; 27.9% received mechanical circulatory support	EN was associated with constipation (46% patients)

EN, enteral nutrition; ICU, intensive care unit; LOS, length of stay.
[a]Mean mcg/kg/min dose during study of patients who tolerated vasopressors and EN.
[b]Reported as incidence based on 346 episodes of concurrent EN and vasopressors for >1 hour.

vomiting in patients receiving mechanical ventilation and therefore may take a conservative approach to EN to prevent this. This is particularly true if patients have some initial intolerance to EN. Monitoring tolerance to EN is therefore essential to optimize delivery and should include the patient's overall clinical picture. Patients should be followed for intolerance based on physical exam findings, which may include abdominal distention, tenderness to palpation, and absence or reduced bowel sounds. ICU patients should additionally be followed for symptoms that suggest intolerance, ie, the presence or absence of flatus, stool, diarrhea, abdominal pain, and vomiting. Radiographs and other imaging may also be useful in some patients, particularly those who are heavily sedated or on mechanical ventilation.[1,110]

Although monitoring tolerance is an essential component of nutrition support, previous large trials have shown that overall EN is generally well tolerated in patients receiving mechanical ventilation. Both the EDEN and PERMIT trials reaffirm this. The EDEN trial fed 85% of patients enrolled via gastric tubes with few complications associated with this method. Feeding intolerance demonstrated by constipation, diarrhea, vomiting, and particularly aspiration were not common in either trial.[52,55] In addition, patients were fed while receiving vasopressors and various doses of sedative and narcotic medications during the EDEN trial.[52] The early initiation of EN for patients on mechanical ventilation in these trials was overall well tolerated. This highlights that clinicians may consider starting a standard formula as trophic feeds early in a patient's ICU admission as there is benefit to maintaining gut mucosa with trophic feeding and minimal patient risk.

Selection of Feeding Tube

Although studies are not conclusive, significant research has been previously done to determine the best route for delivery of enteral feeding and which method minimizes the risk of aspiration. There are studies that suggest that patients who are at elevated risk for aspiration may benefit from placement of a feeding tube in the small bowel.[111] A study of 474 patients by Methany et al found that there was 11.6% less aspiration (based on findings of pepsin-positive tracheal secretions) associated with a small-bowel tube compared with NG tubes. The study also noted less pneumonia from small-bowel feeding tubes compared with NG tubes ($P = 0.02$).[111] For patients at high risk for aspiration, the SCCM/ASPEN 2016 guidelines recommend a small-bowel feeding tube; however, the authors also recognize that gastric access is often easier to obtain and therefore often leads to less delay in initiating EN.[1] A meta-analysis of 13 trials did find less risk of pneumonia associated with small-bowel feeding, and in 6 of the included studies, there was actually improved delivery of EN.[1] However, a large randomized trial (n = 181) comparing gastric vs small-bowel feeding tubes in mechanically ventilated patients did not show any difference in total energy delivered or development of new episodes of pneumonia between the 2 groups.[112] Post-pyloric feeding tubes have been shown to have an increased risk of being accidentally placed in the lung, which may result in pneumothorax or pneumonitis when placed blindly.[110]

Gastric Residuals

High gastric residual volumes are commonly associated with a higher incidence of aspiration and/or pneumonia. However, more recent evidence has shown that high residuals are not linked to an increased risk of pneumonia. Several studies have demonstrated that changing the allowed gastric residual volume from <150 mL to >250 mL did not change the rate of pneumonia.[113,114] Additional studies have now also shown that mechanically ventilated patients tolerate no monitoring of gastric residuals without an increase in the rate of pneumonia. Some of the studies further showed an increase in the amount of EN patients received.[115,116] Based on this evidence, the SCCM/ASPEN 2016 guidelines no longer recommend monitoring gastric residual volumes as a marker of patient tolerance to EN. If gastric residuals are followed, EN should not be held for a volume <500 mL unless there are other signs of feeding intolerance.[1]

Prokinetic Agents

Patients with clinical evidence of EN intolerance and elevated gastric residual volumes may be considered for using a prokinetic agent to help improve the delivery of EN. A meta-analysis of 13 randomized trials (using erythromycin 250 mg IV and metoclopramide both 10 and 20 mg IV) showed these agents to be effective and overall safe for critically ill patients. Prokinetic agents in these studies were shown to significantly reduce gastric intolerance as well as reduce gastric residual volumes. There was no difference in rates of pneumonia, arrhythmia, diarrhea, or vomiting (although the quality of this evidence was not as robust as the evidence for improved gastric tolerance).[117] However, there remains some clinical concern for these agents as they do have adverse reactions and associated complications. Erythromycin may cause cardiac toxicity, tachyphylaxis, and potential bacterial resistance, and metoclopramide is associated with tardive dyskinesia and akathisia, although this is less commonly reported in critically ill patients.[118,119] ASPEN/SCCM Guidelines recommend prokinetic agent use only as needed in minimal-risk patients but suggest for patients who at are high risk for aspiration that a prokinetic agent may be started prophylactically to reduce possible adverse events and optimize EN.[1]

Conclusion

A significant amount of research focusing on EN in the ICU and mechanically ventilated patients has been published since early 2000s. This evidence has significantly changed and redefined the use of EN. EN certainly remains an important aspect of the mechanically ventilated patient's overall care. It is not simply caloric and protein support but is part of the patient's overall care and can provide both benefit as well as potential harm if not prescribed adequately. It is essential to treat each individual patient and situation as unique, as the growing medical evidence has shown that EN is no longer a one-size-fits-all therapy.

Statement of Authorship

K. Allen and L. Hoffman contributed to conception/design of the research; K. Allen and L. Hoffman contributed to acquisition, analysis, or interpretation of the data; K. Allen and L. Hoffman drafted the manuscript; K. Allen and L. Hoffman critically revised the manuscript; and K. Allen and L. Hoffman agree to be fully accountable for ensuring the integrity and accuracy of the work. All authors read and approved the final manuscript.

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