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REVIEW

Nutrition support for critically ill patients

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Abstract

Nutrition support is an important aspect of the management of critically ill patients. This review highlights the emerging evidence on critical care nutrition and focuses on the pathophysiologic interplay between critical illness, the gastrointestinal tract, and nutrition support and the evidence on the best route, dose, and timing of nutrition. Although indirect calorimetry is recommended to measure energy expenditure, predictive equations are commonly used but are limited by their inaccuracy in individual patients. The current evidence supports early enteral nutrition (EN) in most patients, with a gradual increase in the daily dose over the first week. Delayed EN is warranted in patients with severe shock. According to recent trials, parenteral nutrition seems to be as effective as EN and may be started if adequate EN is not achieved by the first week of critical illness. A high protein dose has been recommended, but the best timing is unclear. Immuno-nutrition should not be routinely provided to critically ill patients. Patients receiving artificial nutrition should be monitored for metabolic derangements. Additional adequately powered studies are still needed to resolve many unanswered questions.

KEYWORDS
calories, critical illness, enteral nutrition, NUTRIC score, protein

INTRODUCTION

Nutrition support in critically ill patients is essential to meet their metabolic needs and protect against the associated physiologic derangements. In the last decade, the evidence on critical care nutrition has grown significantly, thus changing clinical practice guidelines. Additionally, there are several ongoing trials in the field that will shape future clinical care. However, the delivery of nutrition to critically ill patients remains suboptimal.[1] In this review, we highlight the emerging evidence on critical care nutrition and present the interplay of the pathophysiologic changes between nutrition, gastrointestinal tract, and critical illness. We also discuss the different nutrition approaches for intensive care unit (ICU) patients. The following topics will be covered: (1) assessment of nutrition status, (2) determination of energy requirement, (3) parenteral nutrition (PN) vs enteral nutrition (EN), (4) timing of EN, (5) nutrition support in special situations, (6) specialized nutrition formulas, (7) immuno-nutrition and micronutrients, and (8) management of enteral feeding intolerance.

PATHOPHYSIOLOGY

Increasing evidence suggests that the gastrointestinal tract plays an important role in maintaining homeostasis during health and disease. During health, the gut transfers nutrients to the internal environment, plays an essential barrier function by segregating the intestinal microbiota from the host immune system and secretes important hormones that regulate multiple metabolic processes.[2,3] During critical illness, gut dysfunction is promoted by different mechanisms (Figure 1). Intestinal permeability and dysbiosis that lead to downstream migration of pancreatic enzymes, free fatty acids, and

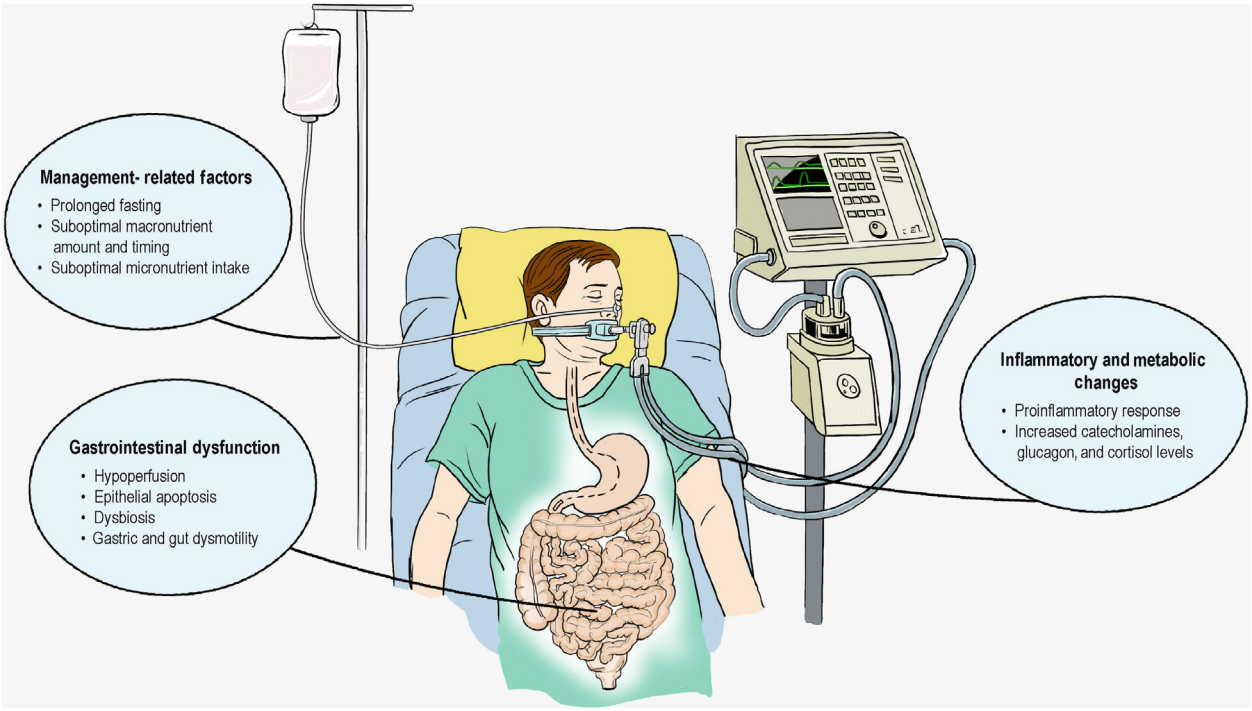

FIGURE 1 The interpaly of the pathophysiologic changes between nutrition, gastrointestinal tract and critical illness

proinflammatory cytokines into the systemic circulation can lead to organ failure.[4,5] As critically ill patients have inadequate nutrient intake confounded with impaired gastric emptying and intestinal dysmotility, they may quickly develop a state of malnutrition, which is associated with immunosuppression, poor wound healing, ICU-acquired muscle weakness, and other negative outcomes.[6,7] Moreover, prolonged unintentional fasting can promote these pathophysiologic changes and gut dysfunction in critically ill patients.

Nutrition support may promote recovery, which is mediated by different mechanisms. Nutrition support may mitigate the negative effects of macronutrient or micronutrient deficiencies that are prevalent in many ICU patients at baseline. The provision of exogenous nutrients may also mitigate the catabolic state and malnutrition.[6,7] EN has been shown to maintain or restore gastrointestinal integrity, thus reducing bacterial translocation[9]; support the diversity of the microbiome; and sustain the immune and metabolic responses of the gut.[10,11] These observations suggested that patients should receive full nutrition support from the onset of critical illness. This concept has been challenged because the catabolic state cannot be simply converted into an anabolic state by the provision of exogenous nutrients and because inappropriate nutrition, especially overfeeding, may suppress autophagy, a cellular repair process that is necessary to clear intracellular damage and essential for the immune response, which could be critical for recovery from organ failure.[12] Additionally, artificial nutrition is not without complications, such as hyperglycemia, liver steatosis, aspiration, bloodstream infections, intestinal ischemia, and refeeding syndrome.

ASSESSMENT OF NUTRITION STATUS

Malnutrition is common in critically ill patients. A systematic review of studies found that the prevalence of malnutrition in critically ill patients ranged from 38% to 78% and that malnutrition was independently associated with increased ICU stay, ICU readmission, incidence of infections, and hospital mortality.[13]

There is no gold-standard test for the assessment of nutrition status in critically ill patients. Commonly used tools include clinical and anthropometric parameters as well as serum biomarkers. All these variables have limitations in terms of sensitivity and specificity. For example, fluid shifts that occur in critically ill patients alter the reliability of anthropometric indicators, such as the skinfold measurement, and the hepatic synthesis of serum biomarkers—such as albumin, prealbumin (transthyretin), and transferrin—decreases during acute infection or inflammation. The Nutrition Risk Screening 2002 (NRS 2002), which incorporates age, food intake, weight loss, body mass index, and illness severity, is used to identify ICU patients at high nutrition risk.[14] It has been mainly validated in hospitalized patients.[15] Additionally, a score of >5 on admission has been shown to predict ICU mortality.[14] The Nutrition Risk in Critically Ill (NUTRIC) score is composed of points for age, Acute Physiology and Chronic Health Evaluation II score, Sequential Organ Failure Assessment (SOFA) score, number of comorbidities, and days from hospital admission to ICU admission, but it does not include direct nutrition measures.[16] In one study, each 1-point increment in NUTRIC score has been associated with a 49-g higher protein deficit and a 752-kcal higher energy deficit, and NUTRIC

scores >4 had over twice the odds of having protein deficits ≥300 g and energy deficits ≥6000 kcal compared with NUTRIC scores ≤4.[16] The clinical utility of NUTRIC score was demonstrated in several observational studies. In a multicenter, multinational observational study of mechanically ventilated patients, increased nutrition intake was associated with faster time to discharge alive and lower mortality among patients with high NUTRIC scores (malnutrition), but not among those with low NUTRIC scores.[17] However, a post hoc analysis of the Permissive Underfeeding Versus Target Enteral Feeding in Adult Critically Ill Patients (PermiT) trial, which compared permissive underfeeding (40%–60% of energy requirement) with standard feeding (70%–100% of requirement), found no association between the feeding strategy and mortality in the group with a high NUTRIC score (>4) or the group with a low NUTRIC score (≤4).[18] NUTRIC and NRS 2002 scores seem to perform differently in the ICU setting and are not equivalent.[16]

DETERMINATION OF ENERGY REQUIREMENT

Measuring the resting energy expenditure via indirect calorimetry for critically ill patients provides the most accurate estimate of energy requirements.[19] Indirect calorimetry measures oxygen consumption (VO_2) and carbon dioxide production (VCO_2); then, energy expenditure is calculated using the Weir formula: Energy expenditure (kcal/day) = $3.941 \times VO_2$ (L/min) + $1.11 \times VCO_2$ (L/min) × 1440.

The premise of accurate estimation of energy expenditure is to help to avoid underfeeding and overfeeding, both of which are associated with worse outcomes. However, strong evidence for the clinical benefit of indirect calorimetry is lacking. In the Early Goal-Directed Nutrition in ICU Patients (EAT-ICU) trial, ventilated patients were randomized to early goal-directed nutrition, which was guided by indirect calorimetry and 24-h urinary urea, aiming at 100% of requirements from day 1 using EN and PN, or were randomized to standard nutrition, which aimed at providing 25 kcal/kg/day by EN.[20] The primary outcome (physical quality of life at 6 months) and other important outcomes did not differ between the two groups.[20] Of note, there was no significant difference between indirect calorimetry and equation-derived energy requirements in the trial.[20] The results of indirect calorimetry should also be interpreted cautiously in certain clinical situations, such as physical agitation, unstable body temperature or pH, need for a high fraction of inspired oxygen (>60%), and use of renal replacement therapy or extracorporeal membrane oxygenation (ECMO).[21]

Hence, predictive equations are frequently used instead. However, the ability of these predictive equations to accurately predict resting energy expenditure has also been questioned because of differences in the metabolic rates of individual ICU patients. A systematic review showed that when compared with indirect calorimetry measurements, 38% of the 13 studied predictive equations underestimated and 12% overestimated energy expenditure by >10% at a group level.[22] On an individual patient level, predictive equations underestimated and overestimated energy expenditure in 13%–90% and 0%–88% of patients, respectively.[22] Limited evidence suggests that certain equations are more specific for certain ICU populations. For example, the Penn State equations are considered by some experts as the most appropriate for critically ill patients on mechanical ventilation.[23]

Some ventilators have mainstream CO_2 sensors connected to the airway adapter that measure end-tidal CO_2, allowing the estimation of VCO_2 and resting energy expenditure with better accuracy than the predictive equations. A study found that the energy expenditure from ventilator-derived VCO_2 was accurate and suggested that it can be calculated at the bedside using a simple formula (energy expenditure = $8.19 \times VCO_2$ [ml/min]).[24] Further studies are needed to improve the accuracy of VCO_2 measurement, detect sources of error, and demonstrate clinical benefit.

The clinical practice guidelines of the American Society for Parenteral and Enteral Nutrition and the Society of Critical Care Medicine (ASPEN/SCCM) suggested the use of predictive equations or a weight-based equation (25–30 kcal/kg/day) to estimate energy requirements in the absence of indirect calorimetry.[25] For intubated patients, the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend indirect calorimetry to estimate energy expenditure and, if calorimetry is not available, using VO_2 from pulmonary arterial catheter or VCO_2 derived from the ventilator.[19]

QUANTITY OF NUTRITION IN CRITICAL ILLNESS

The critical illness usually passes through two main phases: an acute phase and a recovery phase.[19] The acute phase occurs generally in the first week of illness and is characterized by hypercatabolism and metabolic and hemodynamic instability.[19] It is further divided into early (days 1–2) and late acute phase (days 3–7).[19] In the acute phase, especially early on, there is an activation of hormonal, inflammatory, and immune pathways, leading to severe metabolic derangements characterized by endogenous energy production, glycogenolysis, gluconeogenesis, insulin resistance, protein catabolism, and anabolic resistance.[19] The late phase is characterized by substantial muscle wasting and stabilization of the metabolic disturbances.[19] In the recovery phase, these derangements begin to stabilize, and the metabolic state switches to an anabolic phase that may extend over several weeks or months.[19] The energy goals of nutrition support in critically ill patients have been long debated and should probably depend on the stage of critical illness. In the early phase, full feeding may cause overfeeding and refeeding syndrome. By contrast, underfeeding (<50% of energy requirement) may deplete energy reserves, reduce lean body mass, and increase infectious complications.[26]

Several randomized controlled trials (RCTs) have addressed the nutrient target of early nutrition. The PermiT trial randomized patients within 48 h after ICU admission to permissive underfeeding (40%–60% of energy requirement) or standard feeding (70%–100%) for up to 14 days, with similar targets of protein intake in both groups.[27] The trial found no difference in the primary end point of 90-day mortality between the two groups.[27] The EDEN trial compared early trophic (15%–25% of energy requirements) vs full EN for the first 6 days in patients with acute lung injury/acute respiratory distress syndrome (ARDS) and found no difference between the two groups in

ventilator-free days, 60-day mortality, or infectious complications.[28] Similarly, another RCT comparing hypocaloric (15 kcal/kg/day) with normocaloric (25 kcal/kg/day) EN, with both patient groups having hyperproteic intake (1.7 g/kg/day protein) for up to 7 days, found no difference in outcomes between the two groups.[29] The double-anonymized Augmented Versus Routine Approach to Giving Energy Trial (TARGET), which evaluated energy-dense (1.5 kcal/ml) vs routine (1.0 kcal/ml) EN given at 1 ml/kg/h for up to 28 days in 3957 patients, found no differences in 90-day mortality (primary outcome), survival time, organ support, number of days alive and out of the ICU and hospital or free of organ support, and incidence of infective complications or adverse events.[30] Several systematic reviews found no difference in mortality between lower vs higher energy intake,[31–33] but they differed in their methodologies and in the trials included in the review. Lower rates of bloodstream infections and incident renal replacement therapy and decreased mechanical ventilation duration were observed with lower energy intake in two reviews.[32,34]

The 2016 ASPEN/SCCM guidelines recommended a gradual increase of EN to reach the energy target over the first week of ICU stay for patients with low nutrition risk and within 72 h for those with high nutrition risk.[25] The 2018 ESPEN guideline preferred hypocaloric over isocaloric nutrition for the first week of ICU stay when predictive equations are used to estimate the energy need.[19]

THE PROTEIN DOSE

Several observational studies demonstrated better outcomes with higher protein intake in different types of ICU patients.[35,36] However, higher protein intake may be detrimental, possibly through increasing urea production,[37] inducing glucagon secretion,[38] and inhibiting autophagy, a cellular repair process that is necessary to clear intracellular damage.[39] A preplanned analysis of the Paediatric Early Versus Late Parenteral Nutrition In Critical Illness (PEPaNIC) trial found that higher protein intake in the first week of critical illness was associated with a higher risk of infections and lower risk of earlier live weaning from mechanical ventilation and earlier live ICU discharge.[40] A retrospective study found that higher protein intake during the first 3–5 ICU days was associated with increased long-term mortality.[41] A prospective observational study conducted among adult ventilated patients showed that the provision of energy and protein at greater than or equal to two-thirds of the prescribed amount, compared with less than two-thirds of the prescribed amount, was associated with a trend toward increased 60-day mortality (adjusted odds ratio [OR], 2.23; 95% CI, 0.92–5.38), which was more significant in the group with low nutrition risk.[42] Moreover, a post hoc analysis of the PermiT trial demonstrated no difference in outcomes among patients who received lower (0.6 ± 0.2 g/kg/day) vs higher protein intake (1.0 ± 0.2 g/kg/day), although the difference in protein between the two groups was moderate.[43]

RCTs that directly compared higher vs lower protein intake in ICU patients are scarce and are characterized by small differences in protein intake, as the actual protein dose is frequently less than the prescribed dose. One RCT randomized 474 adult ICU patients to receive supplemental parenteral amino acids (up to 100 g/day) or standard care and found no differences in the primary outcome (mean duration of renal dysfunction) and mortality.[44] When hyperproteic (1.4 g/kg/day), hypocaloric EN was compared with isocaloric (0.76 g/kg/day protein) EN in an RCT, a significant improvement in SOFA scores at 48 h in the hyperproteic group was noted.[45] When 1.7 g/kg/day protein was provided with a normocaloric vs hypocaloric regimen, no significant differences between the two groups were observed.[46] Another trial randomized 120 mechanically ventilated adult patients to higher protein intake (2.0–2.2 g/kg/day) or standard protein (1.4–1.5 g/kg/day). The physical component summary score of the SF-36 tool at 3 and 6 months was similar between the two groups.[47] However, after adjusting for covariates, a negative delta protein (protein received minus protein required) was associated with a lower physical component summary score at 3 and 6 months.[47] A meta-analysis assessed the risk of mortality with protein intake (14 trials investigating various interventions and routes of nutrition in 3238 patients).[48] Less protein did not influence mortality risk (pooled OR, 0.94; 95% CI, 0.72–1.22; $I^2 = 48.2\%$).[48] Another systematic review that examined the association of energy and/or protein provision on changes in skeletal muscle mass in critically ill patients found no association between energy and protein delivery and changes in skeletal muscle mass.[49] The EAT-ICU trial randomized ventilated patients to early goal-directed nutrition guided by indirect calorimetry and 24-h urinary urea, aiming at 100% of requirements from day 1 using EN and PN or standard nutrition, and found no differences in the physical quality of life at 6 months and other important outcomes.[20]

Protein catabolism is highest early in critical illness and subsides gradually, but the optimal timing of protein intake remains unclear. A retrospective study found that early protein intake ≥1.2 g/kg at day 4 was associated with better survival in non-overfed, nonseptic, ventilated patients.[50] A large retrospective cohort study of mixed ICU patients receiving EN or PN found that early protein intake was independently associated with increased survival.[51] A retrospective study suggested that although an overall low protein intake was associated with the highest mortality risk, high protein intake during the first 3–5 ICU days was associated with increased long-term mortality.[52] The lowest 6-month mortality was found with increasing protein intake from <0.8 g/kg/day on days 1–2 to 0.8–1.2 g/kg/day on days 3–5 and >1.2 g/kg/day after day 5.[52] Another retrospective study evaluated 423 patients with prolonged mechanical ventilation and found that in those with sepsis (n = 297), medium protein intake (0.8–1.2 g/kg/day) at days 4–7 was associated with lower 6-month mortality (hazard ratio, 0.65; 95% CI, 0.42--0.99) compared with high intake (>1.2 g/kg/day).[53] In the non-sepsis group, early high and late low (<0.8 g/kg/day) protein intake was associated with higher 6-month mortality compared with low and high protein intake.[53]

Therefore, the optimal amount and timing of protein intake in critically ill patients remain largely unclear. Recent clinical practice guidelines have generally recommended higher protein intake (>1.2 g per kilogram of actual body weight per day) in critically ill patients than in healthy individuals. In general, high protein provision is advocated in

the late phase of critical illness.[54] However, this is controversial in the early phase.[54] At present, protein dose is being studied in several trials.

EXCLUSIVE PN VS EN

The use of PN has decreased over time because of the limited evidence for routine use, higher cost compared with EN, requirement for a central venous catheter (thus increasing the risk of complications), and the possibility of overfeeding and significant metabolic derangements with its use. As PN bypasses the gut, the beneficial effects of EN on the gastrointestinal mucosa and the associated effects on the inflammatory response are lost.

Several trials evaluated PN in critically ill patients. An early meta-analysis showed a significant reduction of mortality in favor of PN compared with EN started after 24 h (OR, 0.29; 95% CI, 0.12–0.70), but not with earlier EN.[55] A more recent systematic review and meta-analysis of 18 trials that compared EN with PN regardless of timing found no difference in mortality, but EN was associated with fewer infectious complications (risk ratio, 0.64; 95% CI, 0.48–0.87; $I^2 = 47\%$) and shorter ICU length of stay.[56] The difference in infectious complications was not observed when the energy administered by PN and EN were similar, as is the case with the recent trials.[56] Improved glucose control, better care of central lines, and avoidance of overfeeding have made PN safer than it was previously.

The routes of nutrition support have been compared in recent RCTs. The Early Administration of Enteral or Parenteral Nutrition to Critically Ill Adults (CALORIES) trial, in which patients who could be fed enterally or parenterally were randomized to either early EN or early PN within 36 h after admission, found no differences in the primary outcome of 30-day mortality, infectious complications, and adverse events.[57] In the Enteral Versus Parenteral Early Nutrition in Ventilated Adults With Shock (NUTRIREA-2) trial, patients in shock were randomized to receive EN or PN within 24 h after endotracheal intubation to achieve energy target on day 1.[58] The study found no difference in the primary outcome of 28-day mortality.[58] However, early EN was associated with a fourfold increase in ischemic bowel and colonic pseudo-obstruction compared with early PN.[58]

SUPPLEMENTAL PN IN THE ICU

Supplemental PN is often used when EN alone is not sufficient. The Swiss supplemental PN study demonstrated that combining EN with supplemental PN to optimize energy provision reduced nosocomial infections in critically ill adults who fail to achieve targeted energy delivery with EN alone.[59] However, the Impact of Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients (EPaNIC) trial compared early PN (within 48 h 2312 patients) with late PN (after day 7; 2328 patients) to supplement insufficient EN.[60] Patients receiving late PN were more likely to be discharged alive earlier from the ICU and hospital and had fewer ICU infections, lower incidence of cholestasis, and shorter duration of mechanical ventilation and renal replacement therapy.[60] The differences in outcomes may have been due to lower nutrients received in the first week, rather than differences in nutrition route per se. Similarly, the PEPaNIC trial randomized 1440 pediatric medical-surgical ICU patients who received PN supplemental to EN either early within 24 h after ICU admission or late PN starting day 8.[61] Compared with the early PN group, the late PN group had fewer new infections and shorter ICU stay.[61] The EAT-ICU trial showed no difference in 6-month physical function between the EN group and early-goal-directed nutrition group, which included supplemental PN to achieve estimated energy requirement during the first week of critical illness.[20] A systematic review and meta-analysis of eight RCTs (5360 patients) found that EN alone (compared with combined PN and EN) resulted in fewer respiratory infections (risk ratio, 1.13; 95% CI, 1.01–1.25) and shorter hospital length of stay.[62] However, another meta-analysis of five RCTs showed that compared with EN alone, supplemental PN to EN decreased the risk of nosocomial infections (relative risk, 0.73; 95% CI, 0.55–0.97) and ICU mortality (relative risk, 0.57; 95% CI, 0.34–0.95).[63]

The 2016 ASPEN/SCCM guidelines recommended postponing the initiation of PN until after the first week of ICU admission and after implementing all strategies to maximize EN.[25] The 2018 ESPEN guidelines recommended the initiation of PN within 3–7 days in case of contraindications to oral nutrition and EN.[19] Earlier PN supplementation may benefit some patients (eg, those who do not tolerate full EN and after the early acute phase of critical illness). More data are needed to identify these patients.

TIMING OF EN

Early EN has been recommended to reduce the cumulative nutrition deficits, which is common in ICU patients. Several systematic reviews demonstrated the benefits of early EN (started within 24–48 h from hospitalization, resuscitation, surgery, or ICU admission) on the clinical outcomes of critically ill patients. A recent systematic review of RCTs compared early EN within 24 h of ICU admission with other forms of nutrition support and showed no significant difference in mortality between early EN and all other forms of nutrition support.[64] A priori planned subgroup analysis revealed that early vs delayed EN significantly reduced mortality.[64] Systematic reviews of early EN vs standard therapy in elective surgery, surgical critical care, and acute pancreatitis similarly showed that early EN (ie, initiated the day after the operation) leads to reductions in infection, hospital length of stay, and mortality.[65,66]

Current clinical practice guidelines have suggested early (24–48 h) EN initiation for most ICU patients rather than EN delay.[25,67] However, EN should be delayed in certain patients (Table 1).

ACCESS FOR EN

Feeding tubes inserted nasally or orally are mainly used for short-term enteral feeding (4–6 weeks). pH measurement of gastric aspirate (pH

TABLE 1 Recommendations for the initiation of feeding in special situations

Situation	Recommendation
Noninvasive ventilation	Delayed EN is suggested if continuous noninvasive ventilation is needed.[107] High-flow nasal cannula in between treatment sessions to allow intermittent EN is suggested.
Prone position for acute respiratory distress syndrome	EN can be initiated during the prone position, and the use of hypocaloric or dense EN is suggested.[78] The bed should be tilted to a maximum of 30°. The routine use of prokinetics should be considered, and feeding intolerance should be closely monitored.[78]
Infusion of neuromuscular blockers	Early EN is generally safe in patients on an infusion of neuromuscular blockers without severe gastrointestinal dysfunction.[78]
Severe COVID-19	Early EN at trophic doses and advancement as tolerated are recommended.[108]
Upper gastrointestinal bleeding	EN can be started when the bleeding has stopped and no signs of rebleeding are present.[19]
Severe acute pancreatitis	EN (nasogastric and nasojejunal) may be preferred therapies over parenteral nutrition.[66] Early EN is preferred over delayed nutrition.[19,67]
Bowel ischemia	EN should be held.[19,67]
Bowel obstruction	EN should be held.[19,67]
Open abdomen	Early EN is recommended.[19,67]
Traumatic brain injury	Early EN is recommended.[19,67]
Abdominal trauma with the gastrointestinal tract maintained or restored	Early EN is recommended.[19,67]
Abdominal surgery	Early EN is recommended.[19,67] In case of complications, EN is preferred over parenteral nutrition unless there is discontinuity or obstruction of the gastrointestinal tract or abdominal compartment syndrome.[19]

Abbreviations: COVID-19, coronavirus disease 2019; EN, enteral nutrition.

≤ 5.5) is a reliable method for verification of gastric tube placement, but radiographic confirmation remains the gold standard.[68] Postpyloric vs gastric feeding has been debated for a long time. A meta-analysis of 17 RCTs showed that postpyloric tube feeding could deliver higher proportions of estimated energy requirement and reduce the gastric residual volume (GRV).[69] However, there was no benefit on mortality, new-onset pneumonia (OR, 0.77; 95% CI, 0.53–1.13), and aspiration (OR, 1.20; 95% CI, 0.64–2.25).[69] In cases of increased risk of aspiration, gastroduodenal inflammation, or proximal enteric fistula, postpyloric feeding may be indicated. A meta-analysis of 14 clinical trials (753 adult patients) demonstrated that prokinetic agents compared with the standard technique (OR, 2.26; 95% CI, 1.14–4.49) and gastric air insufflation compared with prokinetic agents (OR, 3.46; 95% CI, 1.63–7.35) increased the success rate of postpyloric placement.[63] Bedside electromagnetic-guided placement has been increasingly used for the placement of nasoenteral tubes with a success rate of around 85%.[64] Jejunal tube feeding is discouraged in patients on high doses of vasopressors, as data from small case series suggested an increased risk of bowel ischemia (up to 8.5%) and mortality (46%–100%).[70]

Continuous EN is preferred by most ICUs and is associated with quicker attainment of nutrition goals than bolus feeding and possibly with less risk of aspiration.[71] By contrast, intermittent or bolus feeding has been considered more physiologic and to be associated with a more positive effect on muscle protein synthesis and gastrointestinal hormone secretion than continuous EN in critically ill patients.[71] However, there is no evidence that any particular feeding method is superior clinically to others.[71] A phase 2 trial in mechanically ventilated patients found similar muscle loss in intermittent EN or standard continuous enteral feeding groups with higher glycemic variability with intermittent EN.[72]

NUTRITION SUPPORT IN SPECIAL SITUATIONS

Nutrition for patients with high nutrition risk

Full nutrition support is believed to be most beneficial in patients with high nutrition risk. However, this has not been demonstrated in RCTs. A post hoc analysis of the PermiT trial showed that permissive underfeeding was associated with similar mortality compared with standard feeding in patients with high and low nutrition risk as assessed by the NUTRIC score and by several other nutrition risk tools, including body mass index, transferrin, phosphate, urinary urea nitrogen, and nitrogen balance.[73] On the contrary, there is evidence that patients with high nutrition risk may be harmed by higher energy and/or protein intakes in the acute phase of critical illness. In an RCT of patients with refeeding syndrome, defined as hypophosphatemia occurring within 72 h of EN initiation, restricted energy intake vs standard intake resulted in no difference in the primary end point of the number of days alive after ICU discharge, but with higher 60-day survival.[74] Post hoc analysis of the PermiT trial suggested that patients with low serum prealbumin

levels might have lower mortality with permissive underfeeding compared with standard feeding.[73] The PEPaNIC trial suggested that delayed PN might be associated with lower infection risk and with a higher likelihood of an earlier discharge alive in children at increased nutrition risk.[61] Therefore, it is unclear what is the best approach to identify patients at high nutrition risk and whether full nutrition support is beneficial or harmful in them.

Nutrition during shock and acute gastrointestinal injury

Patients with shock who require high-dose vasopressors or with high-grade acute gastrointestinal injury (ie, severe ileus accompanied by vomiting, high GRV, and intra-abdominal hypertension) may be harmed by EN. In the NUTRIREA-2 trial, which compared early EN with early PN (both targeting 20–25 kcal/kg/day within 24 h after intubation) in ventilated adults with shock who required vasopressors, showed a higher incidence of vomiting, diarrhea, bowel ischemia (2% vs <1%; hazard ratio, 3.84; 95% CI, 1.43–10.3), and acute colonic pseudo-obstruction (1% vs <1%; hazard ratio, 3.7; 95% CI, 1. 03–13.2).[58] However, several observational studies showed potential benefit with early EN in shock. Using a Japanese inpatient database and propensity matching, a retrospective study evaluated 52,563 patients grouped by their norepinephrine doses (low dose: <0.1 mcg/kg/min, medium dose: 0.1–0.3 mcg/kg/min, and high dose: ≥0.3 mcg/kg/min).[74] The study found that early EN was associated with lower 28-day mortality in the low- and medium-dose groups compared with late EN.[74] In the high-dose group, 28-day mortality did not differ significantly between the early and late EN groups.[74] The optimal dose of EN in shock has not been determined. The European Society of Intensive Care Medicine (ESICM) clinical practice guidelines suggest delaying EN in uncontrolled shock, such as those on escalating or high doses of vasopressors.[67]

Nutrition during ECMO

Indirect calorimetry is influenced by the effects of ECMO on O_2 and CO_2 exchange. Hence, a modified protocol is needed to measure energy requirement in these patients.[75] Predictive equations may overestimate and underestimate energy needs during ECMO.[75] Observational studies suggest that EN during ECMO is safe and may be associated with reduced mortality.[76,77] Using data from a Japanese national database, early EN was associated with reduced mortality compared with delayed EN, with no difference in the incidence of acute mesenteric ischemia and nosocomial pneumonia.[76] Another study of 150 patients undergoing venoarterial ECMO observed that early EN was negatively associated with acute mesenteric ischemia (OR, 0.15; 95% CI, 0.03–0.69; $P = .02$).[77] A weight-based formula, rather than indirect calorimetry, to determine the energy target and a stepwise EN advancement are suggested in patients on venovenous or venoarterial ECMO.[78]

In addition, the nutrition support for other subgroups of critically ill patients and those undergoing certain treatments are outlined in Table 1.

SPECIALIZED NUTRITION FORMULAS, IMMUNO-NUTRITION, AND MICRONUTRIENTS

Specialized formulas

Several EN formula categories exist and are generally classified as standard, peptide based (elemental or semielemental), immune modulating, disease specific, and food based. The standard EN formulas are designed to meet the basic macronutrient and micronutrient (vitamins and trace elements) requirements and are given for most ICU patients.

Diabetes-specific formulas are commonly used in the ICU because of the high prevalence of hyperglycemia and diabetes. An RCT that evaluated two diabetes-specific formulas in ventilated patients with hyperglycemia found that they reduced insulin needs and glucose variability, improved glycemic control, and reduced ICU-acquired infection (tracheobronchitis and pneumonia) compared with standard control formulas.[79] In patients with acute kidney injury, specialized formulas that are low in potassium and phosphate are recommended in the presence of significant electrolyte abnormalities.[25] In patients with hepatic encephalopathy, EN rich in branched-chain amino acids (valine, leucine, and isoleucine) may be used, as these amino acids have a stimulatory effect on ammonia detoxification to glutamine and decreased concentrations in liver cirrhosis. However, the evidence for clinical benefit is lacking.

As gastrointestinal intolerance is common in critically ill patients, elemental/semielemental formulas are frequently considered. Evidence on their effectiveness is controversial. A retrospective study in abdominal surgery patients showed that the GRV of patients receiving semielemental EN was significantly lower than that of patients receiving standard EN.[80] A trial that compared the effects of hydrolyzed protein EN and isocaloric control polymeric whole-protein feed found no differences in diarrhea-free days and the number of diarrhea events.[81] Elemental or peptide formulas may be advised in patients with shock who require vasopressors.[82]

Immuno-nutrition

Several specialized enteral and parenteral formulas with immunonutrients are currently available on the market. These formulas usually consist of a combination of antioxidants, trace elements, essential amino acids (glutamine, arginine), or essential fatty acids, such as ω-3 fatty acids.

Arginine plays an important role during periods of metabolic or traumatic stress and serves as a substrate for nitric oxide production and as a potent immune function modulator. Despite theoretical benefit, the evidence does not favor the use of an arginine-enriched diet in patients with sepsis, especially septic shock.[83] An RCT of either total PN or EN

containing extra L-arginine, ω-3 fatty acids, vitamin E, beta carotene, zinc, and selenium found higher mortality in the subgroup of patients with severe sepsis or septic shock.[84] However, one recent RCT found that a 72-h intravenous infusion of L-arginine in septic shock was safe and did not result in significant improvement in organ function and global hemodynamics.[87]

Glutamine, an important energy and nitrogen source for nucleotide synthesis in rapidly dividing cells such as enterocytes and immune cells, thus contributing to immune cell and gut barrier functions,[83] has been the subject of several studies with variable results. The multicenter Reducing Deaths Due to Oxidative Stress (REDOXS) trial showed an increase in mortality with high doses of enteral and parenteral glutamine (0.6 g/kg/day) in ICU patients with multiorgan failure.[85] A meta-analysis of RCTs (1980–2014) showed that enteral glutamine supplementation was not associated with reduced mortality in critically ill patients (risk ratio, 0.94; 95% CI, 0.65–1.36).[86] However, in patients with severe burns, enteral glutamine supplementation was associated with decreased hospital mortality and hospital stay.[86] Another meta-analysis in patients with burns showed that glutamine supplementation was associated with lower infectious complications and mortality due to bacteremia.[88] In trauma patients with delayed wound healing, oral glutamine reduced time to wound closure (22 vs 35 days in controls; $P < .01$).[89]

Supplementation of ω-3 fatty acids, whose anti-inflammatory and immunomodulatory properties may improve the clinical outcomes of critically ill patients, has been studied in different conditions. The Enteral Omega-3 Fatty Acid, Gamma-Linolenic Acid, and Antioxidant Supplementation in Acute Lung Injury (OMEGA) trial was stopped early, as it showed that enteral supplementation of ω-3 fatty acids, γ-linolenic acid, and antioxidants in patients with acute lung injury did not improve outcomes and might be harmful.[90] Two meta-analyses suggested that enteral supplementation of ω-3 fatty acids benefits patients with ARDS in terms of oxygenation, length of mechanical ventilation, and length of ICU stay, but not mortality.[91] Another meta-analysis (17 RCTs, 1239 patients) on parenteral or enteral ω-3 fatty acids in adult critically ill patients with sepsis or septic shock showed that ω-3 supplementation compared with no supplementation or placebo had no significant effect on mortality (relative risk, 0.85; 95% CI, 0.71–1.03; $I^2 = 0\%$; moderate quality) but significantly reduced ICU length of stay ($I^2 = 82\%$; very low quality) and duration of mechanical ventilation ($I^2 = 60\%$).[92] Of note, the administration of enteral fish oil has been associated with negative outcomes when administered as a bolus and with a low-protein regimen.[93]

The Glutamine, Fish Oil, and Antioxidants in Critical Illness (MetaPlus) RCT compared high-protein EN enriched with immune-modulating nutrients (glutamine, fish oil, and antioxidant-enriched) with standard high-protein EN in ventilated patients and found no statistically significant difference in the incidence of new infections.[94] There was a higher 6-month mortality rate in the medical subgroup with immune-modulating nutrients (adjusted hazard ratio, 1.57; 95% CI, 1.03–2.39; $P = .04$).[94]

The 2016 ASPEN/SCCM guidelines suggest that immune-modulating feeding formulas should be reserved for certain populations such as patients with traumatic brain injury and perioperative patients.[25] Arginine supplementation in sepsis is not recommended, because of a lack of consistent benefit.[25] The 2018 ESPEN guidelines recommend that additional enteral glutamine and high-dose ω-3–enriched enteral formulas should not be given on a routine basis to critically ill patients (except for trauma and burn [>20% surface area] patients for glutamine).[19]

Micronutrients and antioxidants

Because of oxidative stress–mediated cell damage during critical illnesses and frequent deficiencies, the supplementation of trace elements (selenium, copper, manganese, zinc, and iron) and vitamins (thiamin, E, C, and beta carotene) in pharmacologic doses has been advocated and frequently practiced. Despite encouraging results from early studies, recent trials showed no significant benefit. In the REDOXS trial, antioxidants did not affect 28-day mortality or any other secondary end point.[85] In a meta-analysis of 21 RCTs comparing intravenous selenium as a single or combined therapy with placebo, selenium did not affect mortality, infections, ICU and hospital length of stay, renal function, or ventilator days.[95] A meta-analysis of 17 studies (3133 patients) showed no mortality reduction in patients treated with intravenous vitamin C (alone or combined with hydrocortisone/thiamin) when compared with the reference (risk difference, −0.05; 95% CI, −0.11 to 0.01; $P = .08$; $I^2 = 56\%$).[96] The Vitamin D to Improve Outcomes by Leveraging Early Treatment (VIOLET) trial indicated that high-dose enteral vitamin D_3 did not improve 90-day mortality and other secondary outcomes in critically ill, vitamin D–deficient patients.[97] Critically ill patients at risk for thiamin deficiency, such as those with malnutrition, alcohol use disorders, and severe metabolic stress, may benefit from thiamin supplementation.[98] Zinc deficiency can be exacerbated during critical illness, such as sepsis. However, it is unclear whether zinc supplementation benefits critically ill patients.[99]

The 2016 ASPEN/SCCM guidelines could not make a recommendation regarding selenium, zinc, and antioxidant supplementation in sepsis, because of conflicting results.[25] The 2018 ESPEN guidelines stated that high-dose antioxidants, such as copper, selenium, zinc, and vitamins E and C, should not be administered in the absence of confirmed deficiency.[19]

MANAGEMENT OF ENTERAL FEEDING INTOLERANCE

Gastric emptying is often impaired during critical illness, which may result in large GRVs during EN. Because of aspiration risk, EN is often discontinued when GRVs are large. There is no agreement on the definition of enteral feeding intolerance; however, GRV has been considered its surrogate.[100] Its other manifestations include diarrhea, vomiting, and ileus. A systematic review of 72 studies estimated that the prevalence of enteral feeding intolerance at 38% (95% CI, 31%–46%).[100] The median volume defining a large GRV was 250 ml (range,

TABLE 2 Monitoring of patients receiving artificial nutrition

What to monitor	Recommendation
Determination of energy requirement	Detremine on ICU admission. Reevaluate at least once weekly thereafter.
Gastric residual volume	Routine monitoring of gastric residual volume is not recommended. Holding enteral nutrition is not recommended unless the gastric residual volume is >500 ml or there are significant signs of feeding intolerance.[25]
Blood glucose	4- to 6-hourly monitoring is recommended for most patients, especially in the early period of critical illness. Less frequent monitoring is warranted when blood glucose levels become stable. Target blood glucose of <10 mmol/L in most patients.
Serum electrolytes (such as sodium, potassium, chloride, phosphate, and magnesium)	The optimal frequency of monitoring is unknown. Daily monitoring is suggested for most patients, especially in the early period of critical illness. In patients at risk for refeeding syndrome, phosphate and potassium should be checked twice daily during the first 48 h of feeding.
Serum zinc	The optimal frequency of monitoring is unknown. Routine monitoring is not indicated.
Serum liver enzymes	The optimal frequency of routine monitoring is unknown for patients receiving enteral nutrition. Once weekly is suggested in patients receiving parenteral nutrition. More-frequent monitoring may be indicated in patients with abnormal levels.
Serum triglycerides	The optimal frequency of monitoring is unknown for patients receiving enteral nutrition. Once weekly is suggested in patients receiving parenteral nutrition.

Abbreviation: ICU, intensive care unit.

75–500 ml).[100] Enteral feeding intolerance has been associated with increased mortality and longer ICU stay.[100]

The 2016 ASPEN/SCCM guideline suggested not using GRVs as part of routine care to monitor ICU patients receiving EN and avoiding holding EN if GRV <500 ml in the absence of other signs of intolerance.[25] An RCT compared EN with and without measuring GRV and showed no difference in the incidence of ventilator-associated pneumonia.[101] A recent meta-analysis found that not monitoring vs monitoring GRV decreased the rate of feeding intolerance in critically ill patients and did not increase mortality or ventilator-associated pneumonia (risk ratio, 1.03; 95% CI, 0.74–1.44).[102]

Prokinetic agents are frequently used to treat enteral feeding intolerance. A systematic review of 13 RCTs (341 critically ill patients) that compared a prokinetic agent (metoclopramide, erythromycin, and domperidone) with placebo found that prokinetics reduced GRVs (risk ratio, 0.69; 95% CI, 0.52–0.91) and enteral feeding intolerance with no difference in vomiting, diarrhea, pneumonia, or mortality.[103] The multicenter PROMOTE trial, in which 120 critically ill patients with enteral feeding intolerance received either ulimorelin, a ghrelin agonist, or metoclopramide, found no difference in the daily protein intake over the 5 days of treatment.[104]

Feeding protocols may help improve energy and protein intake. In a quality-improvement initiative, eight Canadian ICUs implemented the Enhanced Protein-Energy Provision via the Enteral Route Feeding (PEP uP) protocol, and 16 ICUs served as control sites.[105] Patients at PEP uP sites received more energy (60.1% vs 49.9% of the prescribed requirement; $P = .02$) and more protein from EN (61.0% vs 49.7% of prescribed amounts; $P = .01$) compared with patients in control hospitals.[105] Studies that attempted to increase nutrient delivery through feeding protocols did not demonstrate differences in mortality.[106]

Patients receiving artificial nutrition should be closely monitored, especially in the early period of nutrition support, during which patients may develop harmful metabolic responses, such as the refeeding syndrome. Table 2 suggests the elements that should be monitored during artificial feeding.

CONCLUSIONS

Nutrition support in critically ill patients is an essential therapy, as its timing, route, and amounts of macronutrients and micronutrients affect the course of the disease and its outcomes. It has evolved significantly in the last two decades, as several well-done studies have been conducted and have clarified many aspects of critical care nutrition. Based on the current evidence, the nutrition status of critically ill patients should be assessed on admission and periodically; EN is preferred over PN in general, should be started early (within 24–48 h), and should be gradually increased to goal over at least a few days; in certain patients, such as those with severe shock, EN may be delayed to avoid mesenteric ischemia; supplemental PN is indicated if EN is inadequate in the first week; a full dose of enteral protein is probably more appropriate in the late phase of critical illness, when catabolism ceases and anabolism becomes more active; immune-enhancing enteral formulas and supplementation of micronutrients and antioxidants should not be provided on a routine basis. Although patients receiving artificial nutrition should be closely monitored for enteral feeding

intolerance and metabolic derangements, routine GRV measurement is not needed.

However, many questions remain unanswered, and several challenges need to be addressed in future properly conducted and adequately powered studies. These studies should integrate nutrition interventions with the different physiologic changes that occur during the different phases of critical illness and should also target the appropriate population.

CONFLICT OF INTEREST

Yaseen M. Arabi is the principal investigator (PI) and Hasan M. Al-Dorzi is the co-investigator in the PI-initiated ongoing clinical trial "Replacing Protein via EN in a Stepwise Approach in Critically Ill Patients Randomized Controlled Trial-REPLENISH Trial" (ClinicalTrials.gov identifier: NCT04475666) sponsored by King Abdullah International Medical Research Center (KAIMRC).

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AUTHOR CONTRIBUTIONS

Hasan M. Al-Dorzi and Yaseen M. Arabi equally contributed to the conception and design of the research; Hasan M. Al-Dorzi and Yaseen M. Arabi contributed to the acquisition and analysis of the data; Hasan M. Al-Dorzi and Yaseen M. Arabi contributed to the interpretation of the data; and Hasan M. Al-Dorzi and Yaseen M. Arabi drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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