Nutritional Support in the ICU

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ABSTRACT

Critical illness is a complex condition that can have a devastating impact on health and quality of life. Nutritional support is a crucial component of critical care that aims to maintain or restore nutritional status and muscle function. A one-size-fits-all approach to the components of nutritional support has not proven beneficial. Recent randomized controlled trials challenge the conventional strategy and support the safety and potential benefits of below-usual calorie and protein intakes at the early, acute phase of critical illness. Further research is needed to define optimal nutritional support throughout the intensive care unit stay. Individualized nutritional strategies relying on risk assessment tools or biomarkers deserve further investigation in rigorously designed, large, multicenter, randomized, controlled trials. Importantly, although nutritional support is crucial, it might not be sufficient to enhance the recovery of critically ill patients. Thus, achieving the greatest efficacy may require individualized nutritional support combined with early, prolonged physical rehabilitation within a multimodal, holistic care program throughout the patient's recovery journey.

Introduction

Critical illness is defined as vital organ dysfunction that is life threatening and requires intensive care unit (ICU) admission for life sustaining interventions, such as mechanical ventilation.[1] The critical illness itself and frequent need for sedation can lead to unconsciousness and immobilization. Severe critical illness is associated with inflammation, anorexia, gastrointestinal dysfunction, and metabolic disturbances, which generate pronounced catabolism responsible for protein loss, muscle wasting and weakness, and physical function impairments that can persist for years.[2-6] Many survivors experience post ICU syndrome, which variably combines ICU acquired weakness, cognitive dysfunction, musculoskeletal disorders, frailty, fatigue, endocrinopathies, and mood disturbances.[4] Critical illness is thus a time of extraordinary vulnerability, dependency, and change for patients and relatives (fig 1).

Nutritional support is an integral component of life sustaining strategies designed to counteract the detrimental effects of critical illness by providing energy and nutrients, preventing deficiencies in vitamins and trace elements necessary for protein synthesis, and minimizing the loss of protein and muscle mass.[7]

Knowledge of nutritional support of critically ill patients has relied on small randomized controlled trials (RCTs) and observational studies with low levels of evidence.[8] Recent RCTs challenge the traditional emphasis on early aggressive macronutrient provision for all patients.[9-11] Three themes have emerged. First, low calorie and protein intakes could improve outcomes, especially early during the acute phase of critical illness (ie, typically the first week in ICU) (fig 1).[12-14] Second, nutrition alone could be insufficient to restore muscle mass and function.[2 11] Third, pharmaconutrients have not shown benefits in patients with multiple organ failure (fig 2).[16-18]

The purpose of this review is to discuss current evidence on nutritional support during critical illness, to highlight new insights from recent studies, and to explore evolving concepts of nutrition and rehabilitation in critically ill patients. This review is intended for researchers and clinicians, including general internists, family practitioners, and ICU healthcare professionals.

Epidemiology

Of the millions of patients admitted to ICUs worldwide each year, most are unable to eat and therefore require nutritional support. The prevalence of malnutrition in those patients ranges from 38% to 78%.[19] Sarcopenia is common and associated with worse outcomes.[20] Among survivors of severe critical illness who require invasive mechanical ventilation and vasopressors, 25% to 100% have ICU acquired weakness with muscle wasting, functional impairments, delayed recovery, and poor quality of life, which may persist for months or years.[2 4 21 22] The efficacy of nutritional support in preventing and/or correcting the effects of stress catabolism remain unclear.[15]

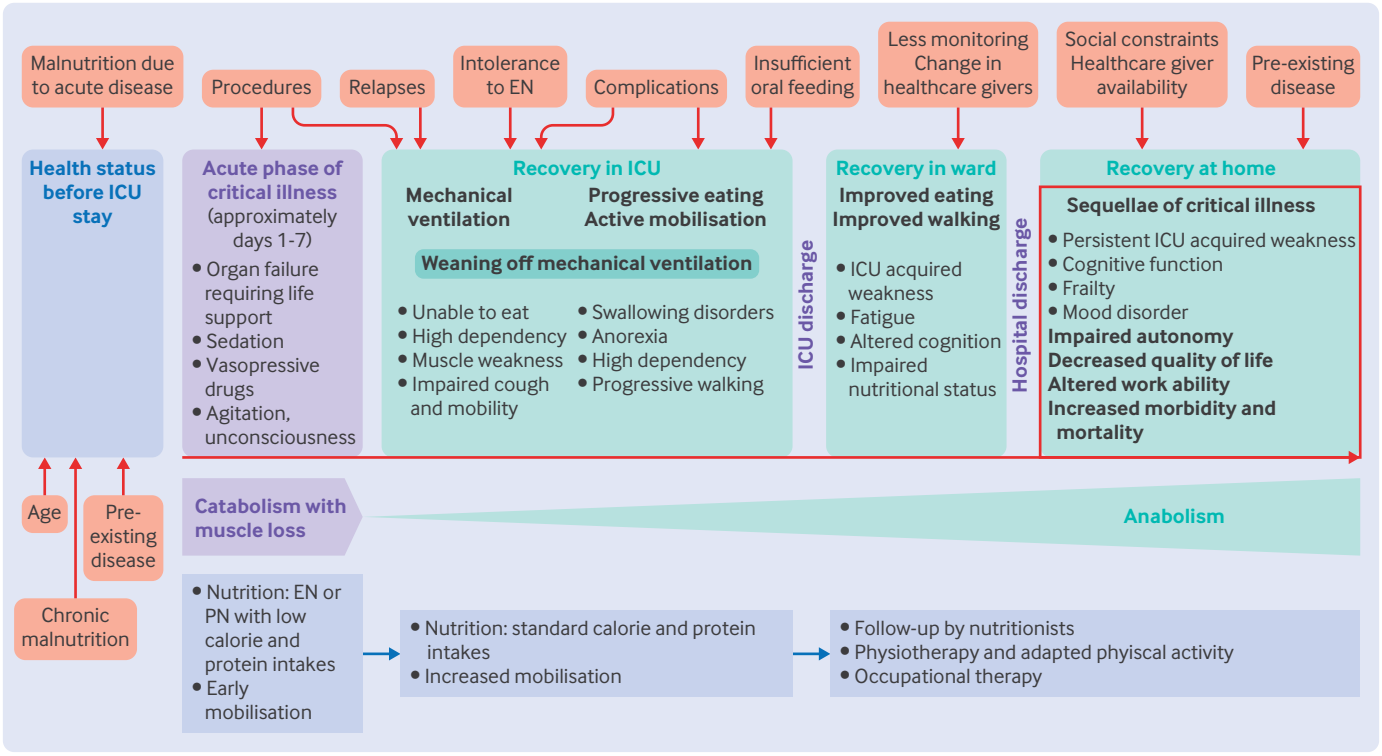

Fig 1 | The clinical trajectory of critically ill patients. EN=enteral nutrition; PN=parenteral nutrition; ICU=intensive care unit

Sources and selection criteria

We used PubMed database, the authors' libraries, and the reference lists of guidelines and landmark articles as sources of data for this review. We searched PubMed using keywords and keyword combinations to identify relevant articles on nutritional support in the ICU published from 2000 to 2023. Only English language articles published in peer-reviewed journals were selected. We used the following keywords: critical illness, critically ill, intensive care unit, intensive care, organ support, mechanical ventilation, enteral nutrition, enteral feeding, parenteral nutrition, parenteral feeding, nutritional assessment, malnutrition, energy need, calorie intake, energy intake, protein needs, protein intake, rehabilitation, ICU acquired weakness, gastric feeding, jejunal feeding, intolerance, micronutrients, and vitamins. We considered retrospective studies from large databases, prospective cohort studies, randomized trials, meta-analyses, systematic reviews, guidelines, and protocols. Given the high risk of bias in observational nutrition studies, we prioritized RCTs, which were adequately powered to assess treatment effectiveness on patient centered and publicly preregistered primary clinical outcomes, whenever available.[9] Key studies published before 2000 were also included if they were highly cited, helped to understand recent data or concepts, or were not followed by more recent studies on the same topic.

Assessing nutritional needs

Critical illness can be roughly divided into two phases: the acute phase and the recovery phase (fig 1). The acute phase is marked by catabolism and typically lasts until the end of the first week in ICU. By contrast, the recovery phase is characterized by anabolism with restoration of muscle mass and function. However, clinically or biologically relevant markers have not yet been identified to definitively identify the switch from the catabolic phase to the anabolic phase. Malnutrition with a negative energy balance has been associated with impaired wound healing, immune dysfunction, secondary infections, increased muscle loss, worse metabolic disturbances, and worse survival.[19 23-25] Delaying the provision of estimated nutritional requirements in patients unable to feed themselves for prolonged periods appears clinically counterintuitive and, in some sociocultural contexts, might be perceived as unacceptable. Nonetheless, the optimal nutritional supply during critical illness remains unclear.

Defining the energy and protein intakes required to minimize catabolism in the acute phase of critical illness

Protein and muscle loss occur quickly during critical illness.[26] A study involving serial femoral ultrasound scans demonstrated that cross sectional muscle mass decreased by 1% to 2% each day until at least day 10 in ICU.[2] Factors associated with worse muscle wasting were a greater number of failing organs, higher serum C reactive protein levels and, strikingly, higher protein intakes.[2 21] The extent to which protein

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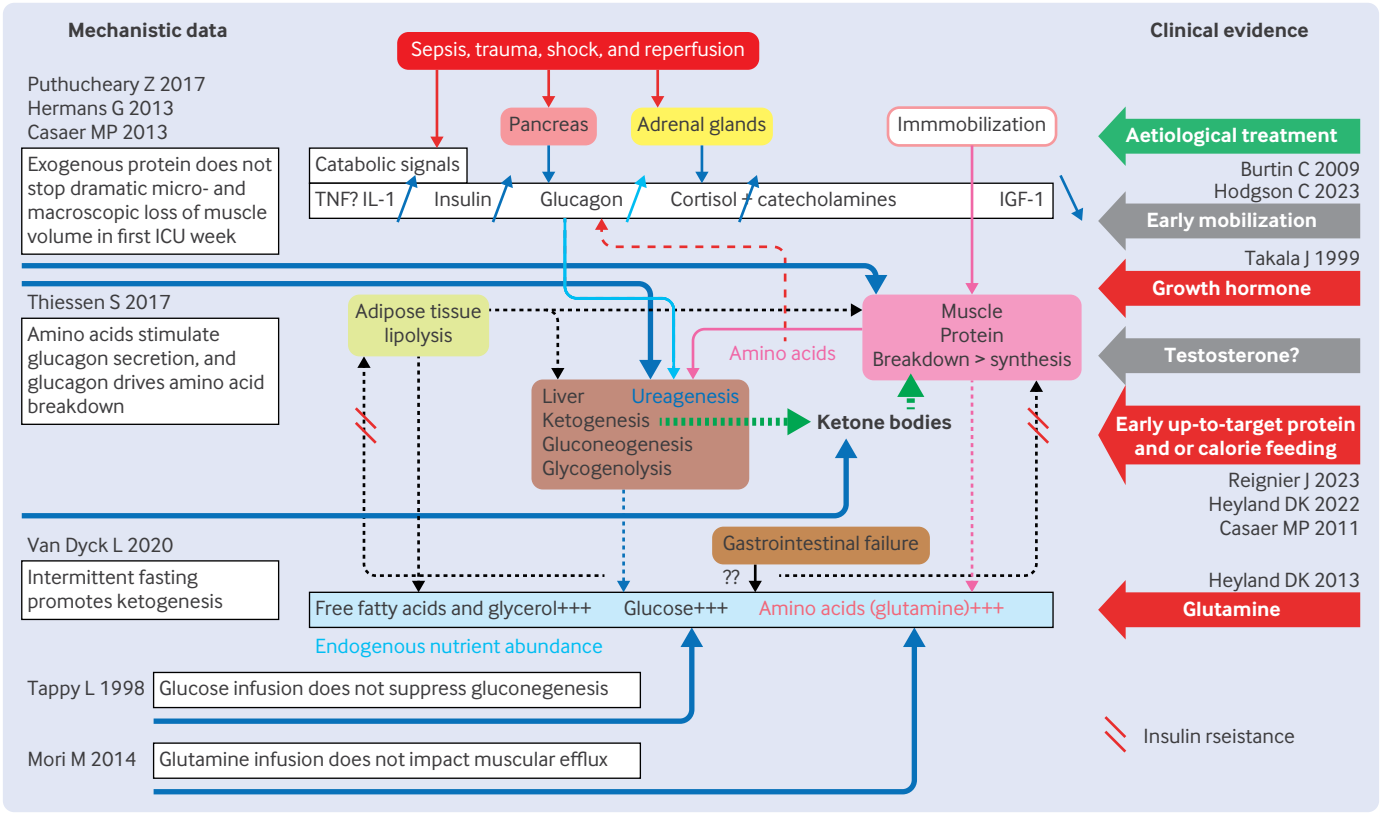
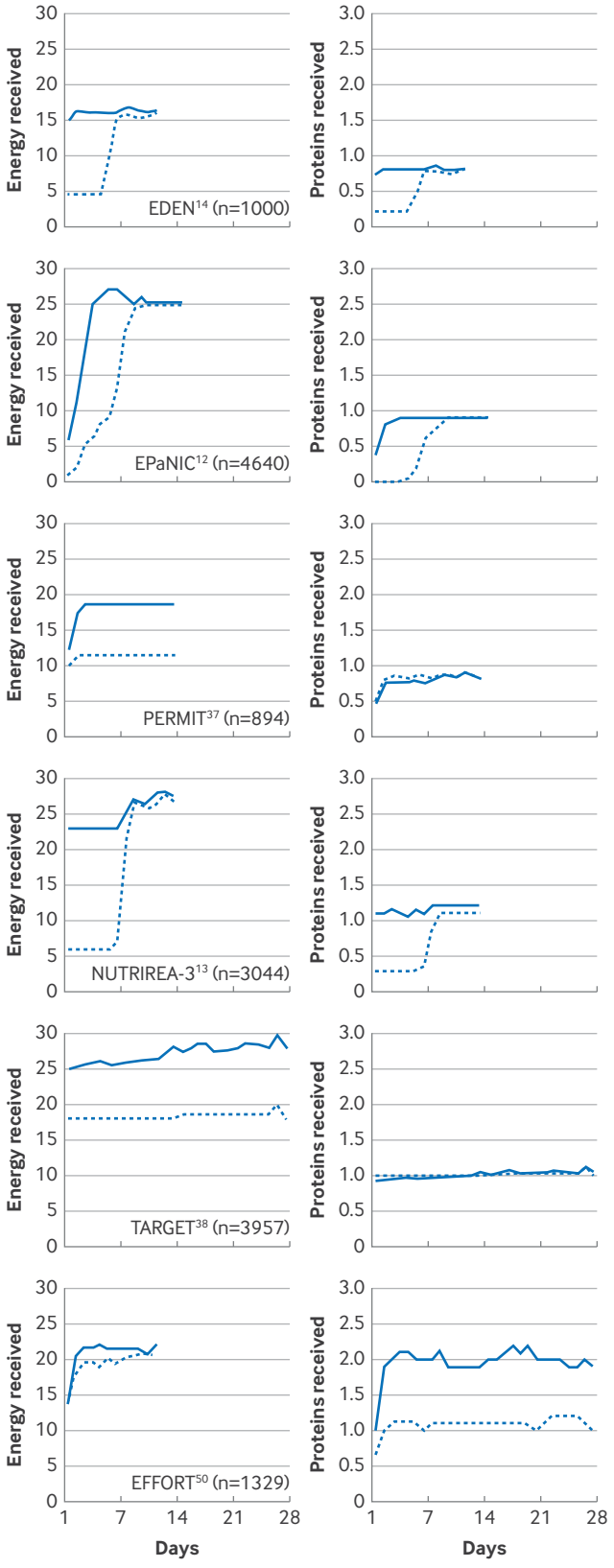


Fig 2 | Understanding the impact of nutritional interventions on early catabolism in critical illness. The main drivers of catabolism and abundant release of endogenous nutrients in critical illness appear to be increases in endogenous steroids, tumor necrosis factor, interleukins, cortisol, glucagon, and catecholamines; decreases in growth hormone and insulin levels; and immobilization (middle part of the figure). However, the contribution of immobilization during early critical illness remains unclear. The muscle volume decrease of about 1% per ICU day during the first 7 to 10 days is associated with the number of failing organs and is not suppressed by supplying exogenous protein or amino acids.[2 21 29] Higher serum amino acid levels increase hepatic protein breakdown and ureagenesis, probably by an increase in glucagon release.[188] Critically ill patients have long been considered unable to generate ketone bodies. However, intermittent fasting stimulates ketosis, which might protect muscle function.[11 188 189] Gluconeogenesis, early in critical illness, is not suppressed by dextrose administration, and exogenous glutamine infusion does not attenuate glutamine release by muscles (left panel).[190 191] The mechanisms described above might explain the failure of early mobilization to attenuate muscle wasting and the deleterious effects of anabolic interventions such as the administration of growth hormone, high energy and/or protein supplies, and glutamine, early during critical illness (right panel).[18 50 60 192] The potential impact of testosterone is under investigation. The green arrows indicate beneficial impact, red arrows potential harm, and gray arrows a neutral or unclear effect. ICU=intensive care unit; TNF=tumor necrosis factor; IL-1=interleukin-1; IGF-1=insulin growth factor-1

loss can be mitigated by nutritional intervention is unclear. A metabolic investigation in 16 critically ill patients found that intravenous glucose or lipid administration failed to suppress endogenous glucose production and protein oxidation during the first week in ICU.[27] A randomized crossover study of amino acid kinetics administered intravenous glutamine to 12 patients dependent on continuous veno-venous hemofiltration. Plasma concentrations of glutamine were restored but muscular glutamine release was not reduced, confirming the existence of anabolic resistance.[28] In a subgroup of 122 patients enrolled in the EPaNIC (evaluating Early versus late initiation of Parenteral Nutrition to supplement insufficient enteral nutrition In Critical illness) RCT, early supplemental intravenous protein, glucose, and lipids neither attenuated up regulated myofibrillar catabolic pathways nor suppressed synthesis, as assessed on femoral muscle biopsies after the first week in ICU (fig 2).[12 21] Thus, loss of microscopic myofiber size and macroscopic muscle volume was similar in patients with early as compared to late initiation of parenteral nutrition despite a between-group difference in cumulative energy debt exceeding 9000 kcal on average during the first week in ICU.[21 29] In summary, the available applied physiology data do not allow the determination of early nutritional needs in patients with critical illness, as they are rendered unreliable by anabolic resistance.

Epidemiological basis for determining nutritional needs early in critical illness

A large observational study of mechanically ventilated patients (n=2772) found that a higher energy intake was associated with lower day 60 mortality (odds ratio, 0.76; 95% confidence interval, 0.61 to 0.95; P=0.01 per 1000 kcal/day increment) and that a higher protein intake was associated with better survival (adjusted odds ratio 0.84; 95% confidence interval, 0.74 to 0.96; P=0.008 per 30



Intervention	Primary outcome	Other outcomes
480 kcal/d (5-6 kcal/kg/day; 0.2-0.4 g protein/kg/day) up to ICU D6, *v* 25-30 kcal/kg/day; 1.2-1.6 g protein/kg/day	No impact on ventilator-free days of trophic *v* standard feeding	No impact on infections, LOS, or D60 mortality of trophic *v* standard feeding
Early supplemental PN in patients intolerant to EN (goal: 25-30 kcal/kg/day) *v* no supplemental PN (low calorie low protein feeding) until D6	Shorter ICU LOS with low calorie/low protien feeding (no early supplemental PN) *v* early supplemental PN	• Fewer injections and shorter MV duration with low calorie/low protein feeding • No impact on mortality
Low calorie (40-60% of 25-30 kcal/kg/day) and standard protein intakes (1.2-1.6 g protein/kg/day) *v* standard intakes until ICU D14	No impact on D90 mortality of permissive low calorie *v* standard feeding	No impact on infections or LOS
Low calorie and protein intakes (6 kcal/kg/ day; 0.2-0.4 g/kg/day) *v* standard intakes 25 kcal/kg/day; 1.0-1.3 g/kg/day protein) until ICU D7	• Shorter time for ICU discharge with low *v* standard calorie and protein intakes • No impact on D90 mortality	• Less gut ischaemia and liver disfunction • Shorter MV duration with low *v* standard intakes
High calorie and standard protein intakes (36 kcal/kg/day; 1.4 g/kg/day) *v* standard calorie (24 kcal/kg/day) and protein intakes until ICU D28	No impact on D90 mortality of high calorie intakes *v* standard	No impact on infections or LOS
High protein (≥2.2 g/kg/day) and standard energy intakes *v* standard calorie and protein (≤1.2 g/kg/day) intakes until ICU D28	No impact on time to discharge alive from ICU of high protein intakes *v* standard	No impact on infections or mortality

Fig 3 | Energy (kcal/kg/day) and protein (g/kg/day) intakes and key findings in recent large randomized controlled trials (RCTs). The energy and protein intakes, intervention durations, and outcomes in recent large RCTs in critically ill patients are shown.[12-14 37 38 50] D=day; EN=enteral nutrition; PN=parenteral nutrition; ICU=intensive care unit; LOS=length of stay; MV=mechanical ventilation

g protein/day increment). For both calories and protein, the associations were strongest in patients whose body mass index (BMI) was <25 or ≥35 kg/m^2.[25] Overfeeding (36 *v* 31 kcal/kg/day), on the other hand, was associated with bloodstream infections (P=0.003) in a prospective longitudinal study of 200 patients in ICU receiving parenteral nutrition.[30] However, in reanalyses of several large RCTs based on various mathematical models, cumulative energy or protein doses were positively, negatively, or neutrally related to morbidity and mortality.[31] Moreover, in a post hoc analysis reanalysis of the EPaNIC trial, the observed thresholds for potential harm from energy and protein overfeeding were lower than 50% of the calculated targets.[32] Importantly, the interpretation of observational data is hindered by indication bias, as patients with greater illness severity and/or an unfavorable clinical course are often harder to feed or, conversely, are given more aggressive nutritional interventions. Moreover, immortal time bias can occur: as feeding improves over time in the ICU, an increased nutritional intake can be the consequence, rather than the cause, of a prolonged stay in ICU and higher ICU survival.[33] These biases could explain why treatment effects of nutritional support suggested by observational studies have not been confirmed by RCTs. Only RCTs can provide reliable guidance for clinical practice.[31 34-36]

Defining nutritional needs based on RCTs comparing different doses of energy, protein, or both

RCTs on energy doses

The PermiT (Permissive Underfeeding versus Target Enteral Feeding in Adult Critically Ill Patients) RCT in 894 medical ICU, surgical ICU, or trauma patients in ICU compared early, isonitrogenous energy restriction (permissive underfeeding) with standard feeding (835 ±297 *v* 1299 ±467 kcal/day, P<0.001; 46 ±14% *v* 71 ±22% of estimated calorie requirements, P<0.001) for up to 14 days.[37] Neither the primary outcome of day 90 mortality nor secondary clinical outcomes differed between the two arms. The TARGET (Augmented versus Routine Approach to Giving Energy) RCT compared isonitrogenous high calorie feeding by energy dense enteral nutrition (1.5 kcal/mL) with standard feeding for up to four weeks (1863 ±478 *v* 1262 ±313 kcal/day) and found no difference in survival or ICU dependency in 3957 mixed patients in ICU.[38] Neither quality of life nor function in daily life differed in six month survivors between the two arms.[39] In summary, isonitrogenous energy intakes of 40%, 70%, or 100% of estimated targets, starting at the early phase of critical illness and continuing for up to four weeks, did not improve survival in high quality RCTs. Thus, the evidence does not support early up-to-target feeding (fig 3).

Some experts attribute the above findings to energy targets in both study arms being estimated by calculations based on body weight, age, sex, and other clinical characteristics. Indirect calorimetry based on oxygen consumption, carbon dioxide production, and several physiological assumptions could provide a more accurate estimate of the true resting energy expenditure.[40 41] Indirect calorimetry can be difficult to perform and its results can be confounded by a high inspiratory oxygen fraction, presence of chest tubes with air leaks, intermachine variability, and other factors.[42 43] Data from a retrospective study in 1171 patients suggest that giving energy doses closer to the measured resting energy expenditure might improve outcomes.[41] However, the single center EAT-ICU (Early goal-directed nutrition in ICU) RCT, using indirect calorimetry and urine nitrogen measurements to guide macronutrient doses was not associated with significant improvement in the primary outcome, or physical functioning at six months, or in any of the secondary clinical outcomes.[44] Importantly, indirect calorimetry does not measure endogenous nutrient release, which is not suppressed by exogenous nutrients.[27] Moreover, even in experienced hands, routine implementation of indirect calorimetry in the ICU is challenging; the international Tight Calorie Control (TICACOS) RCT evaluating indirect calorimetry guided feeding was stopped prematurely after six years with only 417 patients enrolled in seven ICUs with indirect calorimetry experience (10 patients/center/year).[45 46] Nonetheless, given recent improvements in indirect calorimetry technology, the usefulness of indirect calorimetry for estimating energy requirements should be further investigated because it could prevent overfeeding during the acute phase and later on, and improve outcomes.

RCTs on protein doses

International guidelines recommend protein doses of 1.2–2.2 g/kg/day, although the supporting evidence is weak.[31 47-49] Of note, these protein/amino acid targets are rarely achievable with standard, commercially available enteral nutrition and parenteral nutrition preparations. The effect of higher protein doses was tested in 1301 critically ill patients at high nutritional risk (EFFORT-Protein RCT) by adding separate supplies of enteral protein or parenteral amino acids, or both until discharge from ICU or day 28 in ICU. Mean protein/amino acid intake was 1.6 ±0.5 *v* 0.9 ±0.3 g/kg/day (fig 3).[50] Neither the duration of ICU dependency nor day 60 survival differed between the two arms. The intervention could have increased mortality in patients with acute kidney injury, notably those not receiving renal replacement therapy (n=312).[51] The high protein/amino acid group had higher blood urea concentrations, suggesting greater protein catabolism, consistent with earlier RCTs.[12 18 44 52 53]

RCTs on energy and protein doses

In the EDEN RCT, trophic feeding with major energy and protein restriction (400 kcal and 0.3–0.4 g protein/kg/day, ie, about 25% of the standard targets) for up to six days in patients with acute lung injury resulted in similar clinical outcomes and less gastrointestinal intolerance compared with early full feeding (1300 kcal and 0.96–1.28 g protein/day, ie,

about 80% of the standard targets).[14] Importantly, detailed functional physical and cognitive testing after 6 and 12 months in 174 survivors and self-reported physical function (36-item Short Form (SF-36)) in 525 12 month survivors from this trial revealed neither harms nor benefits of trophic feeding.[5 6] By contrast, in 3044 mechanically ventilated patients requiring vasopressor support included in the NUTRIREA-3 RCT, energy and protein restriction (6 kcal/kg and 0.2–0.4 g/kg/day) versus 25 kcal/kg and 1.0–1.3 g/kg/day during the first week shortened ICU dependency and ventilator dependency and reduced the incidence of vomiting, diarrhea, and abdominal ischemia.[13] Similarly, in the EPaNIC RCT (n=4640), withholding early supplemental parenteral nutrition during the first week of critical illness enhanced recovery and decreased ICU acquired weakness and other morbidities. Inhibition of autophagy, a housekeeping mechanism crucial to preserving cell integrity and function, could explain the potentially detrimental effects of higher calorie and protein supplies early during critical illness. Loss of autophagy could cause the higher incidence of ICU acquired muscle weakness with early supplemental parenteral nutrition.[21 54-56] This hypothesis deserves further study. Anorexia during acute critical illness was suggested two decades ago as an adaptive mechanism, with early energy restriction possibly limiting the detrimental metabolic effects of the inflammatory response during the acute phase, and perhaps also impairing the growth of pathogenic microorganisms by decreasing the availability of micronutrients derived from food.[57] Early nutrient restriction could also promote ketogenesis, thereby avoiding excessive breakdown of amino acids.[9] Last, in patients not given early supplemental parenteral nutrition due to enteral nutrition intolerance during the first week of critical illness, tight glycemic control affected neither the duration of ICU dependency nor mortality, compared to liberal glucose control (TGC-Fast RCT, n=9230).[58] This result could be owing to the low calorie intake (400-800 kcal/day during the first week) and subsequent less severe hyperglycemia than previously reported.

In summary, moderate energy and protein restriction appears safe for several weeks in ICU, and emerging data show that restricting energy and protein to 6 kcal/kg/day and 0.3–0.4 g/kg/day, respectively, during the acute phase of critical illness could enhance recovery and decrease morbidity.

Vitamins, trace elements, and pharmaconutrients

During critical illness, serum levels of glutamine, growth hormone, vitamin D, selenium, and vitamin C are reduced. Despite strong associations linking these reductions to poor outcomes in observational studies and promising results of pilot clinical trials, corrective interventions were either not beneficial or detrimental in adequately powered RCTs.[18 59-62] These unexpected results suggest that either serum levels are unreliable for assessing deficiencies or the reduced levels are adaptive during the acute phase of critical illness. Other pharmaconutrients such as arginine, omega 3 fatty acids, and antioxidants have been suggested to modulate the immune response and dampen excessive inflammation, thereby preventing organ damage or promoting recovery.[63 64] However, RCTs in critically ill patients with multiple organ failure did not show benefits from supplying these nutrients.[16-18]

Evaluation of nutritional status and nutritional support effects

Tools for nutritional risk assessment include the Subjective Global Assessment, Mini Nutritional Assessment, Malnutrition Clinical Characteristics, and Malnutrition Universal Screening Tool.[65 66] The Nutrition Risk Screening 2002 (NRS-2002), developed and validated in patients not in ICU, incorporates age, food intake, weight loss, BMI, and illness severity.[67] It was developed by comparing disease severity, preadmission nutritional intake, and BMI in 8944 patients enrolled in RCTs. A score greater than five was associated with increased ICU mortality.[67 68] The Nutrition Risk in the Critically Ill (NUTRIC) score is based on observational data from 597 patients in ICU.[65] Higher scores were associated with higher day 28 mortality, but this association was weaker in patients who met calorie targets.[69] The modified NUTRIC (mNUTRIC) score omits the inflammation marker IL-6, whose inclusion does not improve predictive performance.[69] The mNUTRIC score relies on age, Acute Physiology and Chronic Health Evaluation II score, Sequential Organ Failure Assessment score, number of comorbidities, and number of days from hospital admission to ICU admission. These criteria are related to illness severity rather than nutritional status. A systematic review of studies that used different validated tools found that malnutrition was independently associated with longer stays in ICU, readmission to ICU, a higher incidence of infections, and higher hospital mortality.[19]

Various anthropometric parameters such as BMI, mid-upper arm circumference, and triceps skinfold thickness used to assess malnutrition have limited sensitivity and specificity. BMI, for example, does not reliably reflect cell mass and is affected by the fluid shifts seen during critical illness.[70] Serum biomarkers such as albumin, prealbumin (transthyretin), transferrin, and retinol binding protein are often taken as indicators of nutritional status. However, these biomarkers invariably decrease during acute infection or inflammation and can be affected by non-nutritional factors such as liver disease or protein-losing disease, making them unhelpful in guiding decisions on nutritional support.[71-73]

Recently, muscle mass assessed by ultrasound or computed tomography was investigated as a measure of nutritional status. In a systematic review, low skeletal muscle mass defined using computed tomography was present in 50.9% of patients in ICU and was associated with short term mortality.[74] Other measurement methods to measure body

composition, such as bioelectrical impedance, could have prognostic value in critically ill patients, but their role in guiding nutritional interventions remains unclear.[75]

Before being considered for clinical practice, nutritional biomarkers and risk scores will have to be shown in RCTs to discriminate between patients who respond to nutritional therapy and those who do not. A post hoc analysis of the PermiT RCT revealed, strikingly, that only low pre-albumin predicted a potential benefit from nutrient restriction.[76] This finding could indicate greater benefit of nutrient restriction in the most severely ill patients. The mNUTRIC-score, transferrin, phosphate, urinary urea nitrogen, nitrogen balance, and BMI do not identify patients with different responses to permissive versus standard feeding. Similarly, demographic characteristics previously associated with nutritional risk did not help to identify subgroups with different responses to nutritional interventions in the EPaNIC (BMI, NRS-2002, surgical *v* medical emergency admission, APACHE II scores, sepsis), EFFORT (BMI, mNUTRIC, sepsis), or TARGET (BMI) RCTs.[12 32 38 50] In critically ill patients in ICU randomized after stratification into high and lower nutritional risk groups (mNUTRIC ≥5, n=106 and mNUTRIC <5, n=44), no differences were demonstrated between trophic feeding and full feeding regarding day 14 and day 28 survival or ventilator, ICU, or hospital dependency.[77] Two year survival and SF-36 physical functioning in patients deemed at higher nutritional risk based on the NRS-2002, mNUTRIC or age above 70 years, was not compromised by withholding parenteral nutrition for one week in a large (n=3292) follow-up study of the EPaNIC RCT.[78]

In summary, we lack validated tools to guide nutritional support in critically ill patients. None of the currently available nutritional risk measures identifies patients known to benefit from an adaptive or individualized nutritional support strategy in the ICU. Whether the newly published SCREENIC score, which relies on six basic clinical characteristics, and the recently promoted Global Leadership Initiative on Malnutrition (GLIM) criteria perform differently remains to be investigated in RCTs before these tools can be used in ICUs.[79]

The importance of evaluating nutritional interventions using patient centered functional outcomes, as opposed to only mortality and ICU dependency, is welcomed.[5 6 21 39 78 80] The development of muscle weakness in the ICU, as assessed at the bedside in awake and cooperative patients by the Medical Research Council Sum Score, predicts long term morbidity.[81] Competing events, such as death or discharge from ICU, however, complicate such assessments. Providing 1.2 g/kg versus 0.8 g/kg of amino acids in 119 patients in ICU dependent on parenteral nutrition improved early handgrip strength.[82] However, after correction for the slightly lower mortality in the low protein group, probably due to chance, the handgrip strength gain was not significant.[83] Using biological responses for monitoring and nutrition guidance seems self-evident but is challenging to implement during RCTs, let alone in clinical practice, and carries a risk of interpretation errors. Table 1 lists key aspects.

Table 1 | Key features of nutritional support in patients treated with mechanical ventilation

Feature	Prescription	Expected benefits	Level of evidence*
Timing	Start early (within 24-48 hours after ICU admission)	Could reduce mortality, infectious morbidity and length of stay in hospital	Low
Route	Enteral or parenteral nutrition during acute phase† Enteral nutrition after acute phase† Parenteral nutrition in patients with persistent intolerance or contraindications to enteral nutrition	No difference in main outcomes between parenteral and enteral nutrition in randomized controlled trials	High
Dose in acute phase†	Low calorie, low protein	Shorter stay in ICU and fewer complications versus standard intakes Impaired outcomes with higher protein doses in acute kidney injury	High
Dose in recovery phase‡	25 kcal/kg/day and 1-1.2 g protein/kg/day	No benefit of higher doses in overall population	High
Continuous delivery over 24 hour cycle	Adjust flow rate to obtain required dose in 24 hours	Better tolerance of enteral nutrition, no impact on other outcomes	Low
Serum phosphate level monitoring	If serum phosphate <0.65 mmol/L, decrease calorie intake to 20 kcal/h for at least 48 hours	Could reduce mortality	Moderate
ICU team approach	Involve dietitians in follow-up of patients in ICU	Increased adequacy to nutritional needs	Low
Micronutrients	Supplemental micronutrients in patients receiving parenteral nutrition or <1500 kcal/day enteral nutrition	Decreased risk of deficiencies and subsequent complications	Low
Biological marker of nutritional status or efficacy of nutritional support	Not available to date	Decreased blood loss by sampling Lower workload	Moderate
Mobilization	Associate early and adapted mobilization	Shorter duration of mechanical ventilation and stay in ICU	Moderate

ICU=intensive care unit.
*Level of evidence was assigned based on highest quality study design included. High: at least one large, well designed randomized controlled trial. Moderate: one randomized controlled trial with methodological limitations, or well designed prospective observational studies with comparisons between groups. Low: observational and/or retrospective studies. All four authors agreed on which studies to select and on final assignment of evidence levels.
†Acute phase defined as first seven days after admission to ICU.
‡Recovery phase defined as period after seven days in ICU.

Table 2 | Ten recommendations to improve the delivery of enteral nutrition in patients in ICU

Recommendation	Benefits and drawbacks	Level of evidence,* studies referenced
Have a protocol for delivery of enteral nutrition and management of intolerance	Fewer errors, fewer periprocedural interruptions, increased standardization, increased enteral nutrition delivery No proven effect on patient outcomes	Low[113 160 193]
Prefer first line gastric to jejunal enteral nutrition	Shorter time to initiation of enteral nutrition and no difference in mortality or duration of mechanical ventilation Possibly more vomiting and pneumonia with gastric *v* jejunal feeding	High[106 107]
Do not routinely monitor residual gastric volume	Higher energy intake No increase in pneumonia Possibly increased incidence of vomiting	High[102]
Use prokinetic agents in case of vomiting	Reduces incidence of vomiting	Moderate[105]
Use trophic feeding (low calorie or low protein) during acute phase†	Better gut mucosa preservation, faster recovery, fewer digestive complications, fewer infections	High[12-14 194]
Use a small bore tube (no larger than 14 French gauge)	Decreases risk of sinusitis and mucosal injury	Moderate[85-87]
Perform routine chest radiography to check the tube tip is in the middle of the stomach	Avoids aspiration and pneumonia	Moderate[85-87]
Use iso-osmotic, isocaloric, normal protein polymeric formulas	Better tolerated than high calorie or high protein formulas, which have no benefit on outcomes	High[38 50]
Continue enteral nutrition in patients turned in prone position or treated with extracorporeal membrane oxygenation	Reduced intolerance and increased delivery of nutrients with adequate management of enteral nutrition	Low[114 115]
Fiber	Reduced incidence of diarrhea	Low[88]
Continue enteral nutrition until extubation	Non-inferior to 6 hour fasting for extubation failure, earlier extubation, and shorter stay in ICU	High[116]

ICU=intensive care unit.
*Level of evidence was assigned based on highest quality study design included. High: at least one large, well designed randomized controlled trial. Moderate: one randomized controlled trail with methodological limitations, or well designed prospective observational studies with comparisons between groups. Low: observational and/or retrospective studies. All four authors agreed on which studies to select and on the final assignment of evidence levels.
†Acute phase defined as first seven days after admission to ICU.

of nutritional support in patients on invasive mechanical ventilation.

Routes of nutritional support

Enteral nutrition in the ICU

Enteral nutrition is the preferred treatment for nutritional support in patients with a functioning gastrointestinal tract who are unable to eat.[34 47 49 84] Enteral nutrition is typically given continuously through a nasogastric tube, using a pump. A small-bore tube (no larger than 14 French) is preferred to minimize the risk of sinusitis and mucosal injury.[85] Tube placement with the tip in the middle of the stomach must be confirmed before starting delivery of enteral nutrition. The tube position can be checked by chest radiograph, air insufflation, end-tidal CO_2 measurement, pH testing, or ultrasonography. Chest radiography after blinded tube insertion is the most reliable method and remains the reference standard.[86 87] Iso-osmotic, isocaloric, normal protein polymeric formulas provide all the necessary nutrients and constitute the preferred option, at least during the first week of critical illness. A recent meta-analysis of observational and randomized studies in patients in ICU indicated that enteral nutrition solutions containing dietary fiber were associated with decreases in incidence and severity of diarrhea, without increases in other adverse events.[88] The strength of evidence was assessed as low or very low and all studies had small samples, therefore, this finding should be confirmed by adequately powered high quality RCTs of enteral nutrition formulations containing dietary fiber. Other preparations, such as formulations high in calories or protein, have not demonstrated clear benefits and may increase gastrointestinal complications (table 2).[38 50]

In most patients, enteral nutrition can be safely initiated at the flow rate required to achieve the prescribed energy intake.[89] Continuous enteral nutrition delivery using a feeding pump over a 24 hour cycle is a common practice.[90] Intermittent feeding is usually delivered over 20–60 minutes by an infusion pump or gravity drip every 4–6 hours and bolus feeding using a syringe or gravity drip usually over 5–10 minutes every 4–6 hours.[91] The aim of continuous feeding is to improve tolerance and decrease the risk of aspiration.[91] However, intermittent or bolus administration could be more physiologic and effective in delivering nutrients because it avoids the frequent interruptions encountered with continuous feeding. Intermittent enteral nutrition could also be more effective than continuous feeding in stimulating protein synthesis.[92 93] Compared with continuous feeding, intermittent feeding (and perhaps to an even greater extent intermittent fasting) helps reset the circadian rhythm and stimulates the secretion of postprandial gastrointestinal hormones that regulate gastrointestinal tract motility, gallbladder and pancreatic function, and nutrient absorption.[11 91 94] However, data from high quality RCTs about the best enteral nutrition time schedule remain limited. In a phase 2 single blind RCT (n=92), intermittent feeding was not associated with the preservation of muscle mass (the primary outcome) compared with continuous feeding, despite improved achievement of nutritional targets (25 kcal/kg/day and 1.2 g

protein/kg/day).[93] In a recent systematic review of observational and randomized studies in patients in ICU, continuous and intermittent enteral nutrition showed no clinically relevant differences for most of the outcomes.[95]

Complications

The most common complication of early enteral nutrition in critically ill patients is upper gastrointestinal intolerance, which is related to gastric hypokinesia and delayed gastric emptying, though definitions of enteral nutrition intolerance vary across studies.[96] Delayed gastric emptying can lead to increased gastric residual volume, gastroesophageal reflux, regurgitation of feed into the upper respiratory tract, and/or vomiting, occurring in up to 40% of patients on mechanical ventilation.[97 98] Not monitoring gastric residual volume did not increase the risk of ventilator associated pneumonia despite leading to more vomiting in an RCT, which indicates that the association between gastric residual volume and ventilator associated pneumonia is probably not causal.[99 100-102] Managing enteral nutrition intolerance could require discontinuing or substantially reducing the feed flow rate.[103 104] Prokinetic drugs such as metoclopramide or erythromycin have been shown to increase gastric emptying and reduce vomiting in critically ill patients with enteral nutrition intolerance, yet their use remains controversial due to the lack of high quality evidence.[97 105] Therefore, prokinetic drugs could be appropriate only after the acute phase in patients who are stable but exhibit persistent intolerance without evidence of gut obstruction.

Transpyloric or small bowel feeding has the theoretical advantage of bypassing the potentially hypokinetic stomach of critically ill patients. Two recent systematic reviews and meta-analyses of RCTs in patients in ICU suggested associations of transpyloric feeding with lower pneumonia rates and increased calorie delivery compared to gastric feeding but did not demonstrate benefits regarding other clinical outcomes such as invasive mechanical ventilation duration, length of stay in ICU, or mortality.[106 107] Moreover, transpyloric tubes can be difficult to insert, thus requiring specific expertise and equipment, and often delaying enteral nutrition initiation compared to gastric feeding. Therefore, transpyloric feeding is usually reserved for patients with persistent and proven intolerance to gastric feeding.

Prolonged feeding through a nasogastric or orogastric tube has been associated with several complications, including nosocomial sinusitis, nasal and esophageal ulceration, gastroesophageal reflux, and nosocomial pneumonia.[108] These complications might be less common with percutaneous gastrostomy, which has also been associated with lower rates of feeding interruption and improved patient comfort. As a result, percutaneous gastrostomy has been recommended for patients expected to require long term nutritional support (>30 days).[109] However, a systematic review of RCTs in adults with swallowing disturbances or dysphagia and indications for nutritional support found no difference in mortality, complications, pneumonia, or nutritional status between nasoenteric tube and percutaneous gastrostomy feeding.[110] In patients in ICU, no reliable studies have compared these two routes. Enteral feeding through a gastrostomy could be considered for critical illness survivors who experience discomfort and complications related to the nasoenteric tube, are unable to eat sufficiently and thus expected to require prolonged artificial nutrition, are at high nutritional risk, and are expected to be discharged to long term care facilities.[111] This strategy was used during the covid-19 pandemic.[112]

Periprocedural interruption of enteral nutrition is common, often unjustified, and can lead to underfeeding. A dedicated enteral nutrition protocol can help to minimize enteral nutrition discontinuation during procedures.[113] Previous observational studies evidenced a high prevalence of enteral nutrition intolerance among patients requiring prone positioning or extracorporeal membrane oxygenation.[114 115] However, these treatments are mainly used in the most severe forms of critical illness, which are associated with poored tolerance of enteral nutrition. To date, no high level evidence exists to definitively support a preference for enteral nutrition over parenteral nutrition in these patient populations. Before extubation, enteral nutrition is often stopped for 4–6 hours. However, this practice has been challenged by a recent cluster randomized trial demonstrating that continuing enteral nutrition until extubation was not inferior to fasting for six hours with continuous gastric tube suctioning regarding the seven day extubation failure rate.[116] Moreover, patients who received continued enteral nutrition in this trial were extubated earlier and had shorter stays in ICU.

Parenteral nutrition in the ICU

Parenteral nutrition is indicated in patients with prolonged (more than one week) gastrointestinal dysfunction, including after abdominal surgery. Commercially available ternary admixtures packaged in multichambered bags provide all three macronutrients and are increasingly used instead of compounded parenteral nutrition formulations. The theoretical advantage of compounded parenteral nutrition formulations is improved tailoring to individual patient needs. Ready to use ternary preparations have theoretical advantages of reduced manipulation, decreased workload, and decreased patient risks.[117] Standardized ternary parenteral nutrition products are available in formulations designed for both peripheral and central administration, with or without electrolytes. However, these solutions often lack vitamins and trace elements, which must be supplied separately according to the needs of each patient. In patients fed only by parenteral nutrition, providing a high calorie

and protein intake requires the use of hyperosmolar solutions, which should be administered via a central venous catheter or peripherally inserted central catheter to minimize the risk of venous damage and/or thrombosis.

Criteria for choosing the feeding route in patients in ICU

Experimental and observational clinical studies support beneficial effects of enteral nutrition on immune function and on the physical and functional integrity of the gastrointestinal tract.[118-123] Benefits might be optimal when enteral nutrition is started early, within 24–48 hours after admission to ICU. Early enteral nutrition has been associated with improved outcomes, including decreases in multiple organ failure and hospital acquired infection rates, lengths of stay in ICU and hospital, and mortality.[64 124-128] Numerous observational studies and meta-analyses providing low level evidence suggest beneficial effects of enteral nutrition compared with parenteral nutrition, including lower risks of hospital acquired infections, decreased costs and length of stays, and lower mortality. Supplemental parenteral nutrition prescribed to achieve 25–35 kcal/kg/day during the first week of critical illness in patients intolerant to enteral nutrition has been associated with longer stays in ICU and higher infection rates and should be avoided during the acute phase.[12] The interpretation of the results of the study was hindered because many patients in both arms received both enteral nutrition and parenteral nutrition. The early parenteral nutrition trial found no difference in the primary outcome of day 60 mortality when patients with a relative contraindication to enteral nutrition were randomized to either early parenteral nutrition or standard care.[129] The SPN trial evaluated parenteral nutrition guided by indirect calorimetry in 305 patients and found no impact on patient centered outcomes compared with enteral nutrition alone. The primary outcome was nosocomial infection from day 8 to day 28, with earlier infections not being considered, raising challenges in interpretation.[130 131]

Two recent large randomized trials, CALORIES and NUTRIREA-2, compared enteral nutrition with parenteral nutrition during the acute phase of critical illness and found no difference in the primary outcome of mortality or in the major secondary outcomes including secondary infections and length of stay.[132 133] NUTRIREA-2, which included patients given invasive mechanical ventilation and vasoactive drugs for shock, raised concern about an increased risk of gut ischemia with enteral nutrition.[132] As a result, recent US guidelines recommend either parenteral nutrition or enteral nutrition during the acute phase of critical illness, emphasizing the need for an individualized patient assessment and careful monitoring of outcomes.[31] Enteral nutrition is likely to be favored in most settings when physiological benefit, cost, availability, and experience are considered. After the acute phase (ie, when shock has resolved, as in the NUTRIREA-2 trial), enteral nutrition should be preferred over parenteral nutrition in patients without contraindications.

Irrespective of whether macronutrients are provided through parenteral nutrition or enteral nutrition, adequate doses of vitamins and trace elements at least equal to recommended daily allowances must be given, as was the case in the Refeeding-RCT, SPN trial, PermiT, EPaNIC and many other RCT's.[12 37 130 134] Higher doses might deserve consideration in patients receiving continuous renal replacement therapy, admitted for extended skin and soft tissue lesions, or having other factors associated with greater micronutrient losses.[135] Enteral nutrition supplying about 1500 kcal/day contains sufficient micronutrients to cover recommended daily allowances. Protocols for intravenous micronutrient administration in addition to parenteral nutrition should consider potential interactions among micronutrients, stability, and exposure to sunlight.[136]

Timing of nutritional support

Timing of enteral nutrition

Critical illness results in multiple structural and functional alterations in the gastrointestinal tract, including atrophic intestinal mucosal changes with increased permeability, intestinal immune function impairment, and decreased nutrient absorption. These changes allow the translocation of toxic mediators, which contribute to distant organ injury and multiple organ failure.[137 138] Animal models and, to a lesser degree, human studies indicate that these changes are more severe when enteral nutrition is delayed.[139 140] Also, early enteral nutrition could mitigate the nutritional deficiencies that accumulate rapidly during the first week in ICU.[47] Systematic reviews of RCTs indicate that early enteral nutrition (started within 24–48 hours after ICU admission) has beneficial effects on clinical outcomes. However, some of the included trials were considered at high risk for bias, and none addressed the optimal volume of early enteral nutrition.[141] Nevertheless, clinical practice guidelines suggest enteral nutrition initiation within 24–48 hours after ICU admission, despite the low or very low certainty of supporting evidence.[48 49 90] The expert consensus supports delaying enteral nutrition in patients with uncontrolled shock, severe upper gastrointestinal bleeding, bowel ischemia, or abdominal compartment syndrome.[47] Table 3 summarizes the recommendations for enteral nutrition initiation in special situations.

How quickly should energy and protein goals be achieved?

Multiple RCTs have challenged recommendations that energy and protein requirements should be met promptly during critical illness. Restricting the energy intake to 40% to 60% of the estimated target for up to 14 days or to 15% to 25% for up to six days resulted in similar outcomes compared to at-target energy intakes in multicenter RCTs.[14 37] The retrospective PROTINVENT (Timing of PROTein INtake and clinical outcomes of adult critically ill

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Table 3 | Recommendations for timing of enteral nutrition initiation in critically ill patients with no contraindication to enteral nutrition and unable to eat

Condition	Timing	Benefits	Level of evidence*
No gastrointestinal disease, injury, or dysfunction, and no hemodynamic instability			
General ICU patients, traumatic brain injury, stroke, malnutrition, obesity, prone positioning, extracorporeal membrane oxygenation	Within 24-48 hours	Decreases in mortality, stay in ICU, and incidence of new infections	Moderate
After major surgery	Within 24 hours		
Burns	Within 4-6 hours of injury		
Gastrointestinal disease, injury, or dysfunction			
Bowel ischemia, obstruction, or perforation	Withhold until gastrointestinal condition treated	Avoids additional harm by further compromising gut perfusion or by aggravating leakage of gastrointestinal content	Low
Abdominal compartment syndrome	Withhold until syndrome treated	Avoids additional increase in intra-abdominal pressure	Low
Severe upper gastrointestinal bleeding	Withhold until bleeding has stopped	Facilitates repeat endoscopy, angiography	Low
Severe acute pancreatitis	Within 24-48 hours	May decrease morbidity and mortality	Moderate
Abdominal trauma with intact or repaired gastrointestinal tract		Enhanced wound healing, reduced infectious complications	Low
Abdominal surgery, including aortic surgery, with no bowel injury			
Hemodynamic instability			
	Consider parenteral nutrition (low calorie, low protein doses until day 7) and start enteral nutrition as soon as hemodynamic stability is restored	Enteral nutrition may increase the risk of gut ischemia in patients treated for shock. No difference between early parenteral and early enteral nutrition for other outcomes	High

ICU=intensive care unit.
*Level of evidence was assigned based on highest quality study design included. High: at least one large, well designed randomized controlled trial. Moderate: one randomized controlled trial with methodological limitations, or well designed prospective observational studies with comparisons between groups. Low: observational and/or retrospective studies. All four authors agreed on which studies to select and on final assignment of evidence levels.

patients on prolonged mechanical VENTilation) study found a time dependent association linking protein intake to mortality: increasing the protein intake from less than 0.8 g/kg/day on days 1–2 to 0.8–1.2 g/kg/day on days 3–5 and more than 1.2 g/kg/day after day 5 was associated with the lowest six month mortality.[142] Another retrospective study, PROCASEPT (Association of PROtein and CAloric Intake and Clinical Outcomes in Adult SEPTic and Non-Septic ICU Patients on Prolonged Mechanical Ventilation), suggested that associations between macronutrient intakes and outcomes differed between patients with versus without sepsis.[143] In patients with sepsis, late (days 4–7) medium protein (0.8–1.2 g/kg/day) and late high (>110%) energy intakes were associated with better survival. For patients without sepsis, early (days 1-3) high protein intake (>1.2 g/kg/d)) was associated with higher six month mortality, while a medium or high protein intake (>0.8 g/kg/day) after day 3 was associated with better outcomes. Collectively, the existing data suggest a time dependent effect of the dose of macronutrients, which might be related to the time of anabolic switch occurrence. Furthermore, an RCT in mechanically ventilated patients without shock showed that immediate versus gradual achievement of the target enteral nutrition flow rate increased enteral nutrition delivery and was not associated with a higher incidence of serious adverse events, although prokinetic use was greater suggesting gastrointestinal intolerance.[89] In high risk patients, rapidly increasing enteral nutrition to the calorie target can lead to metabolic intolerance, which has been associated with worse long term outcomes.[134] Consequently, clinical practice guidelines suggest gradually increasing enteral nutrition volumes over the first few days, despite the absence of RCTs evaluating this strategy.[48 49] Thus, the optimal schedule for reaching macronutrient delivery goals remains uncertain and probably varies across patients. Markers indicating when to increase macronutrient delivery need to be identified.

When to stop enteral nutrition

Enteral nutrition is generally continued while the patient is intubated and is often maintained after extubation in patients who are expected to be unable to eat. After extubation, candidates for oral feeding should undergo a multi-step bedside assessment of swallowing function.[144] Enteral nutrition should be continued if swallowing is impaired or eating fails to provide more than 75% of nutritional needs.[145]

Specific subgroups of critically ill patients

Some subgroups of critically ill patients could benefit from special feeding strategies. A subgroup analysis of the EFFORT-PROTEIN trial suggested that protein restriction might improve outcomes in critically ill patients with acute renal failure but no renal replacement therapy.[146] Burn patients have very marked catabolism, and increasing protein and calorie targets has therefore been recommended, despite the lack of evidence that this improves outcomes.

For critically ill patients with severe or morbid obesity, American guidelines recommend low calorie and high protein targets, although the supporting evidence is limited. A recent reanalysis of the EFFORT-

PROTEIN trial found no benefits from higher protein intakes in obese patients.[147] The usual protein intake (≤1.2 g/kg/day) resulted in a shorter time to discharge alive than did the high protein intake (≥2.2 g/kg/day) (hazard ratio, 0.6; 95% confidence interval, 0.4 to 1.0).

Patients with poor feeding or significant weight loss before the critical illness are at risk for refeeding syndrome, a well described and potentially life threatening metabolic disorder that occurs when a patient accustomed over time to very low macronutrient intakes returns to usual or near-usual intakes. Manifestations include hypokalemia, hypophosphatemia, hypomagnesemia, hyperglycemia, insulin resistance, and water retention/edema. While the diagnostic criteria remain debated, at-risk patients who develop hypokalemia, hypophosphatemia, and/or edema while on full calorie feeding should be assumed to have refeeding syndrome. Protein and calorie intakes should be decreased to low levels for a few days or until serum potassium or phosphorus levels, or both, are restored. This strategy resulted in lower six month mortality in a multicenter, single blind, RCT in 339 adults at 13 ICUs in Australia and New Zealand. Calorie restriction in patients with hypophosphatemia did not increase the number of days alive after discharge from ICU but improved day 60 survival (91% *v* 78%, P=0.002) and overall survival time.[134]

Non-occlusive mesenteric ischemia affects up to 30% of patients in ICU with severe circulatory failure and can result in necrotizing enterocolitis, which carries a mortality rate of 70% to 100%.[148] The primary causative factors are organ failure (cardiogenic shock, septic shock, acute respiratory distress syndrome), patient characteristics (pre-existing cardiovascular disease, chronic renal failure), and medications (catecholamines, vasoconstrictors, cardiovascular drugs).[149 150] The potential role for enteral nutrition in the development of non-occlusive mesenteric ischemia remains controversial. In the NUTRIREA-2 trial, patients receiving 20–25 kcal/kg/day enterally had a fourfold increase in the risk of gut ischemia compared with those given only parenteral nutrition during the first seven days in ICU.[132] However, the overall rates were low with both feeding strategies, and the amount of enteral feed delivered daily could have influenced the outcomes. Further studies are needed to determine whether trophic dose enteral nutrition (≤500 kcal/day) could affect gut perfusion in patients receiving catecholamines for blood pressure support.

Multimodal and multidisciplinary care throughout the course of critical illness

Multidisciplinary and comprehensive approach to nutritional support

Nutritional support practices vary across ICUs, within the same hospital, and among healthcare providers within the same ICU.[104 151 152] In numerous ICUs, calorie and protein intakes are prescribed without consideration of patient-specific factors such as BMI, the status of critical illness, comorbidities, and ongoing organ dysfunctions.[153] Moreover, significant discrepancies between prescribed and actual nutrient intakes are common. These facts have been attributed to multiple factors including the lack of evidence about many aspects of nutritional support, the complexity of procedures, and the high number of healthcare providers involved. Furthermore, intolerance to enteral nutrition and its management often leads to interruptions and discontinuation of nutritional support. Also, interactions and conflicts with other ICU procedures such as prone positioning, transport outside the ICU, extracorporeal membrane oxygenation settings, and mobilization for physiotherapy often result in interruptions in feeding.[104 113] Key transitions such as extubation and ICU discharge have been associated with lower intakes than required or prescribed.[154-157] After extubation, the resumption of oral feeding raises concerns given the risk of swallowing disorders related to prolonged intubation and muscle weakness.[152 158 159] ICU discharge marks a break in the continuity of care, with changes in healthcare teams, habits, and protocols.

These challenges underscore the need for protocols reflecting a comprehensive and multidisciplinary, collaborative approach that involves ICU staff members from various disciplines, including physicians, nurses, dietitians, and physiotherapists, all closely involved in daily bedside care. Such an approach was feasible and improved nutrient delivery in patients in ICU (table 2).[160 161] In a multicenter, RCT in 1118 critically ill patients, energy goals were more often achieved with a multifaceted program based on guidelines than with standard care (mean, 6.10 *v* 5.02 days/10 fed days; difference, 1.07, 95% confidence interval 0.12 to 2.22; P=0.03), although neither mortality nor length of stay in ICU and hospital differed.[160] Dietitians play a central role in the nutritional management of critically ill patients.[162] Accurately quantifying dietary intake in patients in ICU remains challenging due to the lack of high quality evidence regarding the optimal approach.[163] The use of computer assisted decision support systems has been associated with enhanced monitoring, better standardization of nutritional prescriptions, and less discrepancy between intakes and prescriptions, compared with standard nutrition monitoring and prescription.[164] The Simple Evaluation of Food Intake scale has been found to be reliable for monitoring oral intakes after extubation and discharge from ICU (correlation between verbal analog Simple Evaluation of Food Intake scale and energy intake: Spearman's coefficient, 0.74; P<0.0001).[165 166] Strategies combining food intake monitoring and individualized nutritional support to achieve calorie and protein targets have been associated with improved outcomes outside of critical care. EFFORT (Effect of early nutritional support on Frailty, Functional Outcomes, and Recovery of malnourished medical inpatients Trial) compared

protocol guided individualized nutritional support with dietary consultation to standard care (no dietary consultation) in non-critically ill, medical ward patients at nutritional risk. The composite primary outcome of all cause mortality, ICU admission, non-elective hospital readmission, major complications, or functional status decline on day 30 was observed in 23% of 1015 intervention group patients versus 27% of 1013 control patients (adjusted odds ratio, 0.79; 95% confidence interval 0.64 to 0.97; P=0.023). Day 30 mortality was lower in the intervention group (0.65; 0.47 to 0.91; P=0.011).[167]

Long term rehabilitation including nutrition and mobilization

The goals of nutritional support in critically ill patients extend beyond immediate survival to long term survival, improved functional and cognitive status, and enhanced quality of life.[15] ICU acquired weakness has been associated with short term and long term complications, including a slow rate of functional improvement with impaired quality of life up to five years after discharge from ICU.[3 81] To date, none of the RCTs on interventions related to nutritional support in the ICU have demonstrated benefits on functional, cognitive, or quality of life outcomes in the long term.[12-14 16 37 38 44 50 129 132 160] Similarly, early mobilization was inconsistently associated with decreases in duration of invasive mechanical ventilation and length of stay in ICU and had no effect on mortality or long term physical outcomes.[168-172] An RCT evaluating combined early mobilization and occupational therapy versus usual care showed decreased rates of long term cognitive impairment (24% *v* 43%; absolute difference, −19.2%; 95% confidence interval −32.1 to −6.3; P=0.004) and ICU acquired weakness (0% *v* 14%; −14.1%; −21.0 to −7.3; P=0.0001) after one year.[173] However, the single center recruitment indicates a need for further evaluation. A large multicenter RCT failed to replicate the benefits of early mobilization, perhaps because the usual care patients received a relatively high amount of physical therapy.[174] It is concerning that adverse events were more common in the early mobilization arm.

ICU acquired weakness is a complex disorder of early muscle wasting ascribed to critical illness related nutritional deficiencies, immobilization, and inflammation.[2] ICU acquired weakness starts very early during critical illness and improves only very slowly after critical illness resolution, with inter-individual differences in severity and improvement rate. Given that the goal is rehabilitation in the long term, interventions limited to the stay in ICU or nutritional support strategies alone could be insufficient. To date, no published RCTs have evaluated nutritional strategies applied after discharge from ICU. Moreover, given the need for concurrent nutritional support and mobilization, these two interventions should probably be combined within a comprehensive and personalized approach.[4] In healthy but sarcopenic individuals, combined amino acid supplementation and physical exercise could improve muscle mass.[175] Thus, patients in ICU might need multifaceted rehabilitation programs that include nutritional support and interventions designed to promote mobility, optimize psychological wellbeing, facilitate a timely return to work, and minimize the impact of sequelae such as pain and cosmetic impairments.[4 15 176-178] These programs should be delivered continuously throughout the course of the illness and recovery (ie, successively in the ICU, in the discharge ward, in the rehabilitation center if relevant, and at home). Evaluations of such programs are ongoing.

Nutritional support of the critically ill in low and middle income countries

The available data on critical care nutrition come chiefly from high income countries and might not apply to low and middle income countries (LMICs), for which information is very limited.[179] Malnutrition is highly prevalent in LMICs and likely contributes to adverse outcomes in critically ill patients.[179-181] Of 335 South and East Asian ICUs, including some in LMICs, only 48% had dietitians on their staff.[182] A recent review highlighted the challenges in using available nutritional assessment tools (NUTRIC score, BMI) in LMICs and supported the feasibility of measuring the mid-upper arm circumference to detect malnutrition, although this observation requires further validation.[183] Access to commercial enteral nutrition products is also limited in LMICs, where locally sourced ingredients are often used to prepare low cost enteral nutrition preparations. Global quality and research initiatives to improve nutritional practices in LMICs are needed.

Emerging treatments

The last two decades have seen considerable advances in our understanding of optimal nutritional support for critically ill patients. Autophagy, anabolic resistance, and metabolic resistance are newly described phenomena whose pathophysiology and interactions with nutritional interventions deserve investigation.

New data indicate that using the same nutritional support strategy in all critically ill patients is unlikely to noticeably improve outcomes. Future strategies should be tailored to individual patients, notably regarding comorbidities, and modified over time as dictated by the course of the acute and subsequent critical illness, notably the presence and severity of organ failures. Better nutritional risk assessment tools and new biomarkers are needed to identify patients likely to benefit from nutritional support and determine the optimal nutritional strategy. Biomarkers for identifying patients most likely to benefit from lower amounts of macronutrients, while also identifying the different phases of critical illness, would be helpful.[10 184] Individualized nutritional support strategies potentially combined with physical therapy and anabolic adjuvant treatments should be rigorously compared with the current

QUESTIONS FOR FUTURE RESEARCH

- Can we identify biological markers of the catabolic and anabolic phases of critical illness?
- Can we elucidate the mechanisms associated with muscle wasting and recovery, and their interactions with nutrition and mobilization?
- Can we tailor nutritional strategies according to changes across the various phases and severity levels of critical illness, the underlying disease, and the nutritional status of the patient?
- Can anabolic agents improve muscular recovery after critical illness?
- Can individualized rehabilitation programs combining nutrition and mobilization help to improve recovery after critical illness?
- Can we define the most valid and reliable outcomes for assessing the effectiveness of nutritional strategies and rehabilitation programs?

standard of care in large, pragmatic, RCTs. The reasons underlying the differing effects of various macronutrient formulations in specific patient subgroups should be defined. Adding anabolic agents such as testosterone, β-hydroxy-β-methylbutyrate, and ketone esters might benefit muscle mass and function (ISRCTN13903536, NCT05825092).[185 186] Future RCTs should evaluate not only short term outcomes but also longer term outcomes including strength, cognition, and quality of life.

Guidelines

We examined guidelines from the American Society for Parenteral and Enteral Nutrition (ASPEN, USA), European Society for Clinical Nutrition and Metabolism (ESPEN), and European Society of Intensive Care Medicine (ESICM) for this review.[31 47-49 90] Substantial discrepancies exist between European and American guidelines on key points. European guidelines recommend enteral nutrition as the preferred treatment and American guidelines recommend either parenteral nutrition or enteral nutrition during the first week in ICU based on findings from two large RCTs.[132 133] For calorie target determination, European guidelines recommend using indirect calorimetry and American guidelines recommend using equations to estimate kilocalories/kilogram/day. Of note, the ESPEN acknowledges limited adherence to guidelines in daily practice.[187]

Conclusion

Nutritional support is a cornerstone of critical care with the premise that it helps to maintain or restore nutritional status; improve gut function; and prevent complications such as infection, muscle wasting, cognitive decline and weakness. However, the optimal nutritional strategy for achieving these goals remains unclear and more research is needed. The optimal route and type of nutritional support should probably be individualized according to the clinical condition, gastrointestinal function, and nutritional needs of each patient. Recent RCTs challenge the early aggressive feeding approach. A more conservative approach including low calorie and protein intakes has been shown to expedite recovery. Emerging evidence supports individualized programs incorporating early and prolonged physical rehabilitation with the goal of improving the long term quality of life in survivors of critical illness. Prospective studies to validate their efficacy and safety are needed.

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