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Review

How much underfeeding can the critically ill adult patient tolerate?

Oana A Tatucu-Babet [1], Emma J Ridley [1,2,*]

[1] Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Level 3, 553 St Kilda Road, Melbourne, VIC 3004, Australia
[2] Nutrition Department, Alfred Hospital, Alfred Health, Melbourne, VIC 3004, Australia

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ABSTRACT

Critical illness leads to significant metabolic alterations that should be considered when providing nutritional support. Findings from key randomized controlled trials (RCTs) indicate that underfeeding (<70% of energy expenditure [EE]) during the acute phase of critical illness (first 7 days of intensive care unit [ICU] admission) may not be harmful and could instead promote autophagy and prevent overfeeding in light of endogenous energy production. However, the optimal energy target during this period is unclear and full starvation is unlikely to be beneficial. There are limited data regarding the effects of prolonged underfeeding on clinical outcomes in critically ill patients, but recent studies show that oral food intake is suboptimal both in the ICU and following discharge to the acute care setting. It is hypothesized that provision of full nutrition (70–100% of EE) may be important in the recovery phase of critical illness (>7 days of ICU admission) for promoting recovery and rehabilitation; however, studies on nutritional intervention delivered from ICU admission through hospital discharge are needed. The aim of this review is to provide a narrative synthesis of the existing literature on metabolic alterations experienced during critical illness and the impact of underfeeding on clinical outcomes in the critically ill adult patient.

Introduction

Food shortages and famines have been described throughout history.[1] During starvation, adaptive processes are activated to reduce appetite, voluntary physical activity, and energy expenditure (EE) in order to preserve muscle mass and slow weight loss.[2] During stress starvation such as that experienced in critical illness, adaptive responses are overridden, contributing to altered nutrient metabolism and rapid and significant loss of muscle mass and body weight that may impact recovery.[2,3] The effects of nutrient provision on outcomes across different phases of critical illness are not well understood. The aim of this narrative review is to synthesize the existing literature on metabolic alterations experienced during simple *vs*. stress starvation, and to describe the impact of underfeeding on clinical outcomes across the different phases of critical illness.

Simple Starvation *vs*. Stress Starvation

Non-stress conditions: short- and long-term starvation

Famines have been described throughout history and remain prevalent.[1] Adaptive mechanisms increase chances of survival in response to short-term (<72 h) and long-term (>72 h) food shortages in non-stress conditions. These adaptations reduce appetite (anorexia) and encourage rest, helping to preserve macronutrient stores and muscle mass and reduce EE.[2,4] Although long periods of starvation can be tolerated in non-stress conditions, survival is unlikely when >40–50% body weight is lost or body mass index (BMI) decreases <13 in males and 11 in females.[5]

In short-term starvation, glucagon and catecholamine secretion is increased while insulin secretion is decreased, result-

* Corresponding author: Emma J Ridley, Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Level 3, 553 St Kilda Road, Melbourne, VIC 3004, Australia.
E-mail address: emma.ridley@monash.edu (E.J. Ridley).

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ing in increased breakdown of glycogen to glucose (glycogenolysis) and of triglycerides to glycerol and free fatty acids (lipolysis).[2,6,7] Glycogenolysis supplies the brain with glucose in the first 24 h, with gluconeogenesis providing essential glucose once glycogen stores are depleted.[2,8] Lipolysis occurs in adipose tissue, releasing glycerol and free fatty acids into the circulation as an energy source for skeletal and cardiac muscle, kidneys, and liver. Thus, EE is initially increased in short-term starvation.[2,7]

Insulin secretion further decreases during prolonged starvation. As glycogen becomes depleted, glucose to support brain function is supplied via gluconeogenesis using amino acids, lactate, and glycerol, which can result in considerable loss of muscle mass.[2,8] In order to slow this loss, EE is reduced through decreases in resting EE, diet-induced thermogenesis, and voluntary physical activity.[2,9,10] Decreases in muscle mass also contribute to a reduction in EE.[9,11] Increased β-oxidation of fatty acids in the liver and decreased glucose oxidation increase the production of ketone bodies during prolonged starvation, with the brain becoming less reliant on glucose and adapting to the use of ketones.[6,8,12] These adaptations help to reduce muscle mass loss by approximately two-thirds.[2]

Stress starvation

Adaptive responses to simple starvation that preserve muscle mass are completely overridden during stress conditions including critical illness (e.g., severe trauma, sepsis, and burns). Stress starvation is characterized by protein catabolism, increased EE, and glucose turnover, minimal ketosis, anorexia, hyperglycemia, insulin resistance, and salt and water retention.[2,3]

In critical illness, a new set of adaptive metabolic responses is activated that promotes survival through restoration of vital functions and homeostasis.[3,13] This mainly involves a neuroendocrine and immunologic response characterized by activation of the sympathetic nervous system, hypothalamic–pituitary axis, immune system, and an inflammatory response.[3,13] Hormones released from the gastrointestinal system (e.g., ghrelin) and adipose tissue (e.g., leptin) are also thought to play a role in the response to stress.[3]

The extent of metabolic alterations is proportional to the severity of stress.[13,14] The physiologic response to trauma was first described in 1942 as occurring in two distinct phases—namely, the “ebb” or early shock phase and “flow” or catabolic phase.[14] A third “anabolic” or recovery phase has since been described as part of a new concept of the phased response to metabolic stress.[3,13] These phases have been further defined as the early acute (day 1–2), late acute (day 3–7), and recovery (day >7–months) phases of critical illness in the recent 2019 European Society for Clinical Nutrition and Metabolism (ESPEN) critical care guidelines.[15] This terminology will be used hereinafter.

In the early acute phase of illness, which is characterized by hemodynamic instability and hormonal changes in response to the experienced stressors (e.g., early release of catecholamines), the body attempts to preserve homeostasis and tissue/organ function.[13] During this phase, EE is reduced and macronutrient metabolism is altered to provide fuel to vital tissues and organs.[3,13] The late acute phase is characterized by an “all or nothing” response in which there is a breakdown of tissue in order to provide substrates to preserve critical organ function and reduce the risk of bleeding and infection, along with increased oxygen consumption and EE.[3,13] In the recovery phase, metabolic responses normalize and protein and fat stores are gradually replenished.[13] An interesting adaptive response observed during illness is anorexia, which is increased by inflammation and may be exacerbated by decreased ghrelin (hunger hormone) and increased leptin (satiety hormone) secretion.[16–18] Although it may seem counterintuitive to reduce energy intake during periods of increased EE and catabolism, anorexia may play an important role in promoting recovery through activation of autophagy – a highly regulated cellular repair process—and by supporting immune function.[19] However, the exact role of anorexia in the different phases of critical illness remains to be elucidated.[4,16,20] The processes and consequences of the metabolic response to stress that are most relevant to nutrient provision are summarized in Table 1. At present, there is no clinical marker for the transition from catabolism to anabolism, which is likely to vary between patients.[3,16,21]

Table 1
Pathophysiology and metabolic consequences of critical illness over time.*[3,13,16,102]

Items	Early acute (day 1–2)	Late acute (day 3–7)	Recovery phases (> day 7 – months)
Anorexia	↑↑	↑	↑ or ↔
Autophagy	↑↑	↑	↔
Endogenous glucose production†	↑↑	↑	↔
Hyperglycaemia	↑↑	↑	↔
Refeeding risk‡	↑↑	↑	↔
Resting energy expenditure	↓	↑↑	↑

* Arrows indicate significant increases (↑↑), increases (↑), decreases (↓), or no difference (↔) in relation to baseline metabolism.
† Endogenous glucose production is not inhibited by an exogenous energy supply in the early acute phase of critical illness but can be partially inhibited in the late acute phase, and can be suppressed in the recovery phase.
‡ Risk according to pre-admission nutritional status and amount of energy provided.

Macronutrient metabolism during stress

During the acute phase of illness, the body’s ability to use macronutrients is altered and no longer depends on the timing and composition of exogenous nutrient provision.[3] Additionally, absorption of enteral macronutrients is thought to be reduced during critical illness.[22–24]

Carbohydrate metabolism

During stress, glucose is the preferred energy substrate in the acute phase of illness. Endogenous glucose production is increased, with two recent studies reporting levels of approximately 150–210 g/day on day 4 and 130–150 g/day on day 9–10 of intensive care unit (ICU) admission in patients receiving enteral nutrition (EN) and/or parenteral nutrition (PN).[25–27] Glucose turnover including glycogenolysis and gluconeogenesis in the liver, kidneys, and intestine is also increased during critical illness.[2,3] The production of lactate, which serves as a substrate for gluconeogenesis and as fuel for tissues and organs such as red blood cells, heart, and brain, is increased during stress. This is thought to be due to an increase in anaerobic glycolysis attributable to tissue hypoperfusion and/or hypoxia, although aer-

obic lactate production may also be increased.[3,28] Stress hyperglycemia is common with changes in glucose metabolism, and is further exacerbated by elevated levels of counter-regulatory hormones and cytokines that promote insulin resistance and hepatic glucose production.[3] Blood sugar variability including both low and high blood sugar levels has been linked to worse outcomes in critically ill patients.[3,29,30]

Lipid metabolism

The use of lipids is increased during the early phase of critical illness, but to a lesser extent than the use of carbohydrates. This is likely attributable to the large amount of oxygen and fully functioning mitochondria required for lipid oxidation as well as hormonal changes (such as hyperinsulinemia) that can inhibit lipid oxidation.[3,31] Lipolysis is accelerated in critical illness, resulting in increased levels of glycerol (a precursor for gluconeogenesis) and free fatty acid that can exceed energy requirements.[3,32,33] Increased lipolysis, together with reduced liver oxidation, leads to an elevation of free fatty acid levels over the first few days of critical illness, which may promote organ damage and inflammation.[3,34–36] Furthermore, derangement in circulating lipids is observed including hypertriglyceridemia, a decreased level of cholesterol, and decreases in high- and low-density lipoprotein levels, which have been linked to worse outcomes.[31,34]

Protein metabolism

In critical illness, the rate of protein breakdown is increased and exceeds that of protein synthesis. Stress metabolism is characterized by overactivation of the ubiquitin–proteasome pathway, which leads to excessive protein degradation and muscle wasting.[3] Along with glycerol, amino acids are the main substrates for gluconeogenesis in the liver and are used for the synthesis of acute phase proteins.[32,37] Critical illness can result in significant protein catabolism; as much as 20% of muscle mass may be lost over the first 10 days of ICU admission in severe cases.[38] Such loss contributes to ICU-acquired weakness, which is associated with increased morbidity and mortality following critical illness.[37,39,40]

Impact of Underfeeding in the ICU: What is the Evidence Telling Us?

When considering the impact of underfeeding on the critically ill patient, it is important to note that studies in this area have investigated exogenous supplies of nutrients and energy. This is due to the complexity of quantifying endogenous energy production, especially in the early acute phase of critical illness. Exploratory studies have been conducted to identify routinely available parameters and models that may aid in predicting endogenous glucose production in practice.[25]

Frequency of underfeeding

The latest ESPEN guidelines describe underfeeding as energy delivery that is <70% of estimated or measured EE.[15] Underfeeding is a common occurrence in the ICU, with approximately 50–60% of prescribed energy targets delivered in practice.[41,42] It is important to note that protein and micronutrient intake often follow energy intake; therefore, underfeeding can also lead to protein and micronutrient under provision. The most common reasons for interruption of EN feeding include intolerance (e.g., high gastric residual volumes), hemodynamic instability, and fasting prior to airway procedures and surgical interventions.[43–45] Underfeeding may be more pronounced or may go undetected in patients consuming an oral diet as compared to those receiving EN and/or PN.[46]

Observational energy provision studies between 2000 and 2010

In the past, nutritional support was provided with the aim of meeting 100% of estimated or measured EE throughout ICU admission, including in the early acute phase of critical illness. The results of observational studies conducted in the 2000s largely supported this practice [Table 2], with energy deficits associated with unfavorable outcomes such as increases in infections, duration of mechanical ventilation (MV), ICU admission, and mortality.[47–54] The largest of these studies, which enrolled 2722 mechanically ventilated patients, reported a reduction in overall 60-day mortality and increase in ventilator-free days (VFDs) for every 1000 kcal/day increase in energy provision. However, in a subgroup analysis of BMI categories, the association with survival was only observed for patients with a BMI <25 kg/m^{2}and between 35 kg/m^2 and 39 kg/m^2.[51] Moreover, some observational studies have reported inverse associations between nutritional adequacy and clinical outcomes such as ICU admission and hospital length of stay (LOS).[55,56]

Randomized controlled trials (RCTs)

Since 2011, five important and large randomized controlled trials (RCTs) have been published that have investigated the relationship between energy provision using EN and/or PN and outcomes in critically ill patients [Table 3].[35,57–60] The results of these trials have not supported the findings from observational work.

In three trials, patients in the intervention group were underfed to varying degrees (25–50% of estimated energy targets) compared to control patients (70–80% of estimated energy targets) for approximately 1 week after ICU admission.[35,57,58] The Early *vs.* Delayed Enteral Feeding to Treat People with Acute Lung Injury or Acute Respiratory Distress Syndrome (EDEN) and Permissive Underfeeding *vs.* Target Enteral Feeding in Adult Critically Ill Patients (PermiT) trials did not report any difference in the primary outcomes of VFDs to day 28 and 90-day mortality, respectively.[35,57] Patients receiving trophic EN in the EDEN trial experienced less regurgitation and elevated gastric residual volumes, but no differences were observed in frequency of diarrhea, aspiration, abdominal distention, and cramping.[35] In the PermiT trial, no differences in feeding intolerance were observed.[57] In the Early Parenteral Nutrition completing Enteral Nutrition in Adult Critically Ill Patients (EPaNIC) trial, patients initiated on late supplemental PN (≥day 8) after several days of intravenous glucose compared to early PN (within 48 h) had a 6.3% relative increase in the likelihood of being discharged alive and earlier from the ICU (hazard ratio: 1.06; 95% confidence interval: 1.00–1.13; P = 0.04). Furthermore, patients in the late PN initiation group had an increased likelihood of being discharged earlier from hospital and experienced

Table 2
Observational nutrition studies between 2000 and 2010.

Publication	Population	Duration	Energy delivery (kcal/day)	Key findings
Krishnan et al.[55]	187 MICU patients with ICU LOS ≥96 h	Up to ICU discharge	NR, median 51 (IQR 32–70)% energy adequacy	Energy adequacy of (1) 33–65% *vs.* 0–32% associated with ↑ likelihood of spontaneous ventilation prior to ICU discharge and (2) ≥66% *vs.* 0–32% with ↓ likelihood of hospital discharge alive and spontaneous ventilation prior to ICU discharge.
Rubinson et al.[53]	138 MICU patients without oral intake for ≥96 h	Up to ICU discharge	NR, 49% ± 29% energy adequacy	Energy adequacy of <25% *vs.* ≥25–49%, 50–74% and ≥75% was associated with ↑ risk of nosocomial bloodstream infections.
Villet et al.[47]	48 SICU patients staying ≥5 days in ICU	Up to 4 weeks	1090 ± 930	Cumulative energy balance (−12,600 ± 10,520 kcal) was associated with ↑ ICU LOS, complications, infections, days on antibiotics, length of MV.
Petros et al.[48]	61 MICU patients receiving EN for ≥ 7 days	Until ICU discharge or a maximum of 14 days	NR, 86% ± 30% energy adequacy	Patients who achieved a maximum feed volume of 2000 mL or 25 mL/kg by Day 4 (n = 46, 75%) compared to after Day 10 (n = 15, 25%) had a ↓ in ICU mortality.
Dvir et al.[49].	50 general ICU patients requiring MV ≥ 96 h	ICU admission	1512 (range 400–3210)	Maximum negative energy balance (−5805 [range: 0 to −17,274] kcal) was associated with ↑ ARDS, sepsis, renal failure, pressure sores, need for surgery, total complication rate.
Hise et al.[56]	77 SICU/MICU patients with LOS ≥ 5 days	Up to ICU discharge	SICU (n = 41): 991 ± 560 MICU (n = 36): 988 ± 373	Nutrition adequacy of <82% *vs.* ≥82% and <81% and ≥81% was associated with a ↓ ICU LOS and ↓ hospital LOS, respectively.
Alberda et al.[51]	2722 MV patients in the ICU for >72 h	Up to 12 days	1034 ± 514	Every 1000 kcal/day provided was associated with ↓ 60-day mortality and ↑ VFDs.
Faisy et al.[50]	38 MICU patients MV for at least 7 days	First 14 days of ICU	704 ± SEM 42	A mean energy deficit ≥ 1200 kcal per day of MV after ICU Day 14 was associated with ↑ ICU mortality rate.
Singh et al.[54]	93 respiratory ICU patients MV ≥24 h and ICU LOS ≥48 h	Up to ICU discharge	Survivors (n = 57): 1379 (IQR 1279–1563); non-survivors (n = 36): 1109 (IQR 765–1325)	Mean energy adequacy of ≤50% was associated with ↓ survival probability compared to >70–90% and >90% energy adequacy.
Strack van Schijndel et al.[52]	243 MICU/SICU patients enrolled Day 3–5 if expected to be in ICU for another ≥5–7 days	NR, LOV period used for energy and protein balance calculations	Males: 1730 ± 399 Females: 1536 ± 299	Achieving both energy and protein goals compared to not achieving both goals was associated with: Males: ↔ hazard ratio for ICU, 28-day and hospital mortality Females: ↓ hazard ratio for ICU, 28-day and hospital mortality

Articles were identified via Medline (Ovid) search combining "critical* ill* or Intensive Care Unit or ICU" terms with "energy or nutrition delivery".
Reported in mean ± standard deviation, unless otherwise stated. Values rounded to the nearest whole number.
↑: statistically significant increase in outcome; ↓: statistically significant decrease in outcome; ↔: no significantly statistical difference in outcome.
ARDS: Acute respiratory distress syndrome, EN: Enteral nutrition; ICU: Intensive care unit; IQR: Interquartile range; LOS: Length of stay; LOV: Length of ventilation; MV: Mechanical ventilation; MICU: Medical intensive care unit; NR: Not reported; OR: Odds ratio; SEM: Standard error of the mean; SICU: Surgical intensive care unit; VFDs: Ventilator-free days.

fewer ICU infections, while relative reductions were reported in the proportion of patients requiring MV for >2 days and renal replacement therapy.[58] Patients in the Early PN and the Augmented *vs.* Routine Approach to Giving Energy (TARGET) trial were not intentionally underfed, with the aims of meeting estimated energy targets in the intervention group and providing care that reflected usual practice in the control group.[59,60] No differences were reported in the primary outcomes of 60- and 90- day mortality, respectively.[59,60] However, it is difficult to draw conclusions from this trial regarding the impact of underfeeding on clinical outcomes as only a subset of patients (primarily in the control arms) were underfed.

The findings of these RCTs suggest that a degree of underfeeding (by design or as part of standard care) based on an estimated EE in the first week after ICU admission may not adversely affect outcomes compared to full nutrient provision, which may be harmful in some instances. The mode of nutrition (EN *vs.* PN) is also an important consideration but is outside the scope of this review.

Reasons for differences between observational studies and RCTs

A key explanation for the inconsistent results of observational studies and RCTs is the sample size and study design, with RCTs considered superior in terms of controlling for confounders. The above-mentioned RCTs had large sample sizes and were powered to detect differences in the primary outcome(s) of interest. However, nutrition trials are often underpowered to detect a difference in mortality, even with a large sample size. With the exception of two studies,[51,52] the observational studies had a sample size <200, making it highly unlikely that a true association between nutrition and clinical outcomes would be observed.[61,62] Another important point is that the observa-

Table 3
Summary of seminal RCTs exploring the impact of energy provision on clinical outcomes.

RCTs	Population	Duration	Intervention	Control	Primary outcome	Long-term follow-up
EPaNIC trial (2011)[58]	4640 adults with NRS ≥ 3	Up to day 16*	Late PN (≥day 8)	Early PN (within 48 h)	↑ Time to discharge alive from ICU	Yes
EDEN trial (2012)[35]	1000 adults within 48 h of ALI onset requiring MV	Up to day 12*	Trophic EN (Day 1–6)	Full EN	↔ VFDs to day 28	Yes
Early PN trial (2013)[59]	1372 adults with contraindications to early EN	NR; target achieved by study Day 3	Early PN (Day 1)	Standard care PN	↔ Day-60 mortality	Yes
PermiT trial (2015)[57]	894 medical, surgical or trauma ICU adult patients	Up to 14 days†	Permissive EN	Standard EN	↔ Day 90 mortality	No
TARGET trial (2018)[60]	3957 adult ICU patients undergoing MV	Up to 28 days‡	1.5 kcal EN	1.0 kcal EN	↔ 90-day mortality	Yes

RCTs were identified via a Medline (Ovid) search combining the terms "critical* ill* or Intensive Care Unit or ICU" with "energy or nutrition delivery". Articles were included if they enrolled ≥ 500 patients and were published in quartile 1 medicine journals such as *The New England Journal of Medicine* and *Journal of the American Medical Association.*

↑: statistically significant increase in outcome observed in the intervention compared to control; ↔: No statistically significant difference reported between the intervention and control.

ALI: Acute lung injury; EPaNIC: Early Parenteral Nutrition completing Enteral Nutrition in Adult Critically Ill Patients; EDEN: Early *vs.* Delayed Enteral Feeding to Treat People with Acute Lung Injury or Acute Respiratory Distress Syndrome; EN: Enteral nutrition; ICU: Intensive care unit; IQR: Interquartile range; MV: Mechanical ventilation; NR: Not reported; NRS: Nutrition risk screening; PN: Parenteral nutrition; PermiT: Permissive Underfeeding *vs.* Target Enteral Feeding in Adult Critically Ill Patients; RCTs: Randomized controlled trials; TARGET: Early PN and the Augmented *vs.* Routine Approach to Giving Energy; VFD: Ventilator-free day.

* Actual study duration: NR.

† mean 9 ± 5 days (intervention) and 9 ± 4 days (control).

‡ median 6 (IQR: 3–11) days in both groups.

tional studies did not always control for important confounders such as illness severity and survival bias.

Other explanations for the observed differences are that the RCTs did not limit recruitment to high nutritional risk ICU populations, and energy targets were based on estimated rather than measured EE. Critically ill patients that may benefit from full energy provision include malnourished and obese patients and those with prolonged MV and ICU admission.[50,51,63,64] Higher energy provision was found to be related to a reduction in overall 60-day mortality in patients with BMI <25 and ≥35–39 kg/m^2.[51] It has been suggested that patients with a Nutrition Risk in Critically Ill score ≥6 (out of 10) may benefit more from full energy and protein provision,[64,65] although this was not supported by post hoc analysis of PermiT trial data. The heterogeneous populations of key RCTs—which included predominantly young patients with few comorbidities, short mean ICU lengths of stay (e.g., median duration of ICU stay was <5 days in the EPaNIC trial), and BMI between 25 kg/m^2 and 34 kg/m^2[35,57–60]—may partly explain the inconsistencies. Additionally, given the associated challenges such as accessibility, cost, training requirements, and time needed to complete measurements, none of the above-mentioned RCTs used indirect calorimetry to guide energy provision, in contrast to four observational studies that used this technology.[47–49,52,66] This is a major limitation as discrepancies between estimated and actual EE are frequently observed in general and specific ICU populations.[67–69] As predictive equations are more prone to underestimating EE,[67,68] RCTs may compare different degrees of underfeeding between trial arms, making findings difficult to interpret. In a retrospective observational study of 1171 mechanically ventilated critically ill patients over a 12-year period (2003–2015), a nonlinear relationship between percent energy adequacy starting from day 3 of ICU admission (as determined using indirect calorimetry) and 60-day mortality was observed.[70] An energy adequacy of 70% was associated with decreased mortality, while higher values (in particular, >100% of EE [overfeeding]) were associated with increased mortality.[70] These results remain to be replicated in prospective work.

Most RCTs have focused only on the acute phase of critical illness but the timing and duration of nutritional support is likely to be important. Although some RCTs aimed to deliver nutritional interventions for longer durations (i.e., 28 days of ICU admission), this was not achieved in most patients [Table 3]. In keeping with our knowledge of metabolic changes across the different phases of illness, full provision of energy in the acute phase may not be beneficial (and may instead be harmful in some instances) because of the high endogenous energy production that cannot be suppressed.[3] Provision of exogenous energy during this period can thus promote overfeeding with the associated adverse consequences.[16,71] Autophagy is an important process that is activated during the acute phase of critical illness in response to various stimuli including inflammation, hypoxemia, and oxidative stress as a mechanism to promote organ recovery and survival.[19] Nutrient restriction is another important stimulator of autophagy while amino acids administered through PN suppress autophagy.[16,19,72,73] However, autophagy is difficult to measure and the precise effects of nutrient provision via EN and PN on autophagy throughout critical illness remain to be elucidated.[74]

Current clinical practice guidelines for the initiation of artificial nutritional support

Clinical practice guideline recommendations for the initiation of EN and PN in critically ill patients are summarized in Table 4. Early initiation (generally within 48 h) of EN is recommended in all three guidelines, given the potential benefits of trophic EN on gastrointestinal barrier function, alleviation

Table 4
Clinical practice guidelines for the initiation of EN and PN in critically ill patients.

Clinical Practice Guideline	Initiation of EN	Initiation of PN
Canadian Clinical Practice Guideline[76]	Early EN (within 24–48 h)	- Exclusive PN (when oral intake or EN contraindicated): should be considered early in nutritionally high-risk patients - Patients who are not malnourished, are tolerating some EN, or when PN is indicated for <10 days: low dose PN should be considered - Supplemental PN: should be considered on a case-by-case basis
ASPEN/SCCM[77]	Early EN (24–48 h) - Patients at high nutrition risk or severely malnourished: EN should advance to goal as quickly as tolerated over 24–48 h (while monitoring for refeeding) - Patients at low nutrition risk, well-nourished, and/or with low disease severity: Specialized nutrition therapy over the first week in ICU not required	Exclusive PN (when oral intake or EN contraindicated): - For patients at high nutrition risk or severely malnourished, start PN as soon as possible - For patients at low nutrition risk, withhold for the first 7 days Supplemental PN: should be considered after 7–10 days if unable to meet > 60% of energy and protein requirements by EN
ESPEN[15]	Early EN (within 48 h) - Early acute phase (ICU Day 1–3): Hypocaloric nutrition (< 70% of EE) - After Day 3: If using predictive equations, continue hypocaloric nutrition (< 70% of EE) for the first week If using indirect calorimetry, normocaloric nutrition (70–100% EE) can be progressively implemented	- Exclusive PN (when oral intake or EN contraindicated): within 3–7 days - For severely malnourished patients, consider early and progressive PN - Supplemental PN: should be considered on a case-by-case basis

ASPEN: American Society for Parenteral and Enteral Nutrition; EE: Energy expenditure; EN: Enteral nutrition; ESPEN: European Society for Clinical Nutrition and Metabolism; ICU: Intensive care unit; PN: Parenteral nutrition; SCCM: Society of Critical Care Medicine.

of catabolism, and mortality.[15,16,75–78] The most recently published ESPEN guidelines recommend the gradual introduction of EN in the acute phase of illness based on the findings of the above-mentioned RCTs. Hypocaloric nutrition (not exceeding 70% of estimated EE) is recommended over the first week of ICU admission. Where indirect calorimetry is used, hypocaloric nutrition is recommended for day 1–3 (<70%), followed by isocaloric nutrition from day 4–7 (70–100%).[15]

Nutrient provision during the recovery period of illness in the ICU and acute care ward

The importance of nutrition over the duration of hospital admission has become apparent with the increasing awareness of survivorship and quality of survival. Longer term nutritional interventions are critical, as the impact of deficit/excess on recovery is unlikely to be immediately observed owing to the nature of metabolic processes.[79] Data on nutrient intake in the late ICU and recovery periods of critical illness are emerging and concerning, with oral nutrition as the predominant type of nutrition.[80,81] In one of the earliest published reports, oral intake during the first 7 days following extubation in the ICU was examined in 50 patients.[82] The average daily energy and protein intake failed to exceed 50% of daily requirements on all 7 days for the entire population, with lack of appetite and nausea/vomiting as the most common barriers.[82] In a study of 32 patients from two centers in Australia and New Zealand, oral intake was assessed three times a week in the post-ICU period.[81] Intake varied markedly among individuals and according to the type of nutritional therapy that was provided; energy (37%, interquartile range [IQR]: 21–66%) and protein (48%, IQR: 13–63%) provision were lowest in patients who received no additional oral nutrition supplements.[81] In 19 patients followed for up to 14 days post extubation, a median of 47% (IQR: 29–66%) of energy and 27% (IQR: 15–41%) of protein targets was consumed when an oral diet was the sole source of nutrition, and a barrier to eating was reported in 79% of study days.[83] The issues associated with post-ICU nutrition are complex and multifactorial, and are related to individual patient factors following critical illness (reduced appetite, nausea, fatigue), clinician factors (belief of the importance of nutrition, knowledge, competing clinical priorities), and system factors (hospital food service and processes)[84,85] and ultimately contribute to ongoing nutritional inadequacy. It should be noted that the impact of prolonged nutrient deficits during the recovery period of illness is only hypothesized at this time as there are no definitive relevant data.

Long-term follow-up of critically ill patients

Long-term outcomes in ICU patients

In a seminal study on the long-term outcomes of 109 acute respiratory distress syndrome (ARDS) ICU survivors followed up for 3 months, 6 months, and 12 months, patients had lost a mean of 18% of their baseline body weight at the time of ICU discharge, with 71% of patients returning to their baseline body weight after 12 months.[86] As body composition measurements were not reported (NR), it is unclear whether fat-free mass returned to the baseline level. Functional limitations were reported 12 months after ICU discharge (n = 83) as determined based on the 6-min walk test and percentage of patients that returned to work (49%). Furthermore, quality of life domains were mostly lower than for age- and sex- matched controls.[86] Persistent functional impairments as well as reduced quality of life were reported in this same group of patients (n = 64) up to 5 years following ICU discharge.[87] Cognitive impairment has been observed following critical illness. In a recent systematic review of 46 studies examining cognition in patients from ICU discharge up to 13 years, the mean prevalence of cognitive impairment ranged from 35% to 81% at the 3-month follow-up,[88]

indicating that critically ill patients experience significant and varied disabilities that may persist over the lifetime.

Long-term follow-up within trials of nutritional interventions

It is perhaps unsurprising that the above-mentioned RCTs investigating the efficacy of short-term nutritional interventions have not demonstrated any effects on long-term outcomes.[58,59,89–91]

Impact of prolonged underfeeding in critically ill patients

Although anorexia is an adaptive process that may be beneficial in the early phase of illness, it is not known at what point it becomes detrimental to recovery by promoting underfeeding.

As prolonged underfeeding in the recovery phase of critical illness is unethical, our understanding of its impact can only be drawn from key starvation papers in noncritically ill populations. The results of the seminal Minnesota Starvation Study published in 1950 provide insight into the negative impact of prolonged semistarvation and refeeding.[79,92] In that study, 3200 kcal/day was provided (in conjunction with physical activity as well as laboratory and other tests including measures of cognition) to 36 conscientious objectors to World War II during the baseline period, followed by a 6-month semi-starvation period of 1800 kcal/day with 0.7–0.9 g•kg^{-1} • day^{-1} of protein.[92] Weight loss initially occurred too rapidly and energy and protein were increased. Subjects exhibited dramatic reductions in strength, mood, and cognitive function (including development of an obsession with food). In the final nutritional rehabilitation period, participants were provided 3000–4200 kcal/day but many did not gain weight at this level of intake and energy provision had to be further increased. For months afterward, participants consumed up to 5000 kcal/day at will in order to recover.[79,92]

In hospitalized patients, malnutrition is linked to increased morbidity, mortality, and healthcare costs.[93–95] Evidence outside of critical care demonstrates that the provision of nutritional support may be beneficial for a range of outcomes including anthropometric measures, hospital readmission, and survival.[96–100] A recent study conducted in 2088 patients at nutritional risk at eight centers in Switzerland reported a benefit of long-term, protocolized, and individualized nutritional interventions compared to a standard hospital diet.[96] There were fewer adverse outcomes (the primary outcome measure) and a lower rate of mortality in the intervention group compared to the control group and no increase in adverse events associated with nutritional support.[96] An RCT currently underway at 23 sites in Australia and New Zealand is investigating whether individualized nutritional intervention throughout ICU and hospital admission is advantageous for critically ill patients.[101]

Limitations

The main limitation of this work is the narrative rather than systematic review process that was used to identify and analyze studies, which may have impacted the conclusions. Nonetheless, our review is comprehensive and provides a valuable synthesis of published literature on the impact of underfeeding in different phases of critical illness while highlighting research gaps that should be addressed in future work.

Conclusions

Critically ill patients may be able to tolerate short periods of underfeeding without experiencing adverse outcomes. Nonetheless, the extent of underfeeding (trophic to 70% of EE) that should be targeted in the first week of critical illness has not been established and may differ for each patient. There is also limited information on the impact of underfeeding beyond the first week of critical illness. It is thought that prolonged underfeeding may negatively impact recovery, function, and cognition in the critically ill patient; RCTs conducted from ICU admission to hospital discharge are needed to confirm or refute this possibility. In the absence of definitive evidence, it is recommended that at least 70% of predicted or measured energy is targeted in the first week of illness based on the knowledge that far less is usually provided.

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Conflicts of Interest

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