Review Article

(Mal)nutrition in critical illness and beyond: a narrative review

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Summary

Close liaison with ICU-trained dietitians and early initiation of nutrition is a fundamental principle of care of critically ill patients– this should be done while monitoring closely for refeeding syndrome. Enteral nutrition delivered by volumetric pumps should be used where possible, though parenteral nutrition should be started early in patients with high nutritional risk factors. Malnutrition and loss of muscle mass are common in patients who are admitted to ICUs and are prognostic for patient-centred outcomes including complications and mortality. Obesity is part of that story, and isocaloric and high-protein provision of nutrition is important in this group of patients who comprise a growing proportion of people treated. Assessing protein stores and appropriate dosing is, however, challenging in all groups of patients. It would be beneficial to develop strategies to reduce muscle wasting as well; various strategies including amino acid supplementation, ketogenic nutrition and exercise have been trialled, but the quality of data has been inadequate to address this phenomenon. Nutritional targets are rarely achieved in practice, and all ICUs should incorporate clear guidelines to help address this. These should include local nutritional and fasting guidelines and for the management of feed intolerance, early access to post-pyloric feeding and a multidisciplinary framework to support the importance of nutritional education.

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Introduction

Critical illness results in hypermetabolism and hypercatabolism, putting patients in the ICU at high risk of malnutrition [1]. The metabolic and hormonal changes in critical illness result in muscle wasting and associated ICU-acquired weakness which can persist for years [2]. With adverse outcomes associated with both under- and overfeeding in the ICU [3], the timing, avenue and quantity of nutrition provision continue to be of great interest. With optimal nutrition delivery required throughout the ICU stay and in the recovery phase to improve functional outcomes [4], a tailored and individualised approach to nutrition therapy is essential. However, the lack of high-quality evidence and large randomised controlled trials continues to leave many questions unanswered. We aim to discuss the current evidence for nutrition during and after critical illness and highlight relevant unanswered questions in the field (Fig. 1).

Distinct metabolic phases occur after injury or illness, with each phase having different nutrient metabolism. The `ebb, flow and recovery´ phases of the stress response are widely referenced. The ebb phase is characterised as a period of reduced energy expenditure and an increase in endogenous glucose production which cannot be abolished by exogenous energy sources [5]. The ensuing flow phase sees a period of hypermetabolism and breakdown of lean tissue regardless of the presence of exogenous substrate. The recovery phase is where anabolism is likely to occur and repair and recovery can take place [5]. There are currently no biomarkers to identify when patients shift from one phase to another [6], yet international guidelines recommend feeding according to these phases of illness. We will further explore patient and other factors that influence the assessment of nutritional needs, as well as how they may also influence prognostication and outcomes.

Malnutrition

Malnutrition is a prognostic risk factor for patients in ICU and influences clinical outcomes such as length of stay, mechanical ventilation days, infection risk and mortality [7]. A meta-analysis of 20 studies identified the prevalence of malnutrition to be between 38% and 78% in the ICU [8]. Patients in the ICU are at high nutritional risk which increases during a prolonged stay [9]. With no validated nutrition risk-screening tools in critical illness, the Nutrition Risk in Critically Ill (NUTRIC) score was developed and validated as a nutritional risk assessment tool for patients in the ICU [10]. A recent systematic review showed that the NUTRIC score was related to clinical outcomes, length of stay and was appropriate for use in the ICU [11]. However, its use and

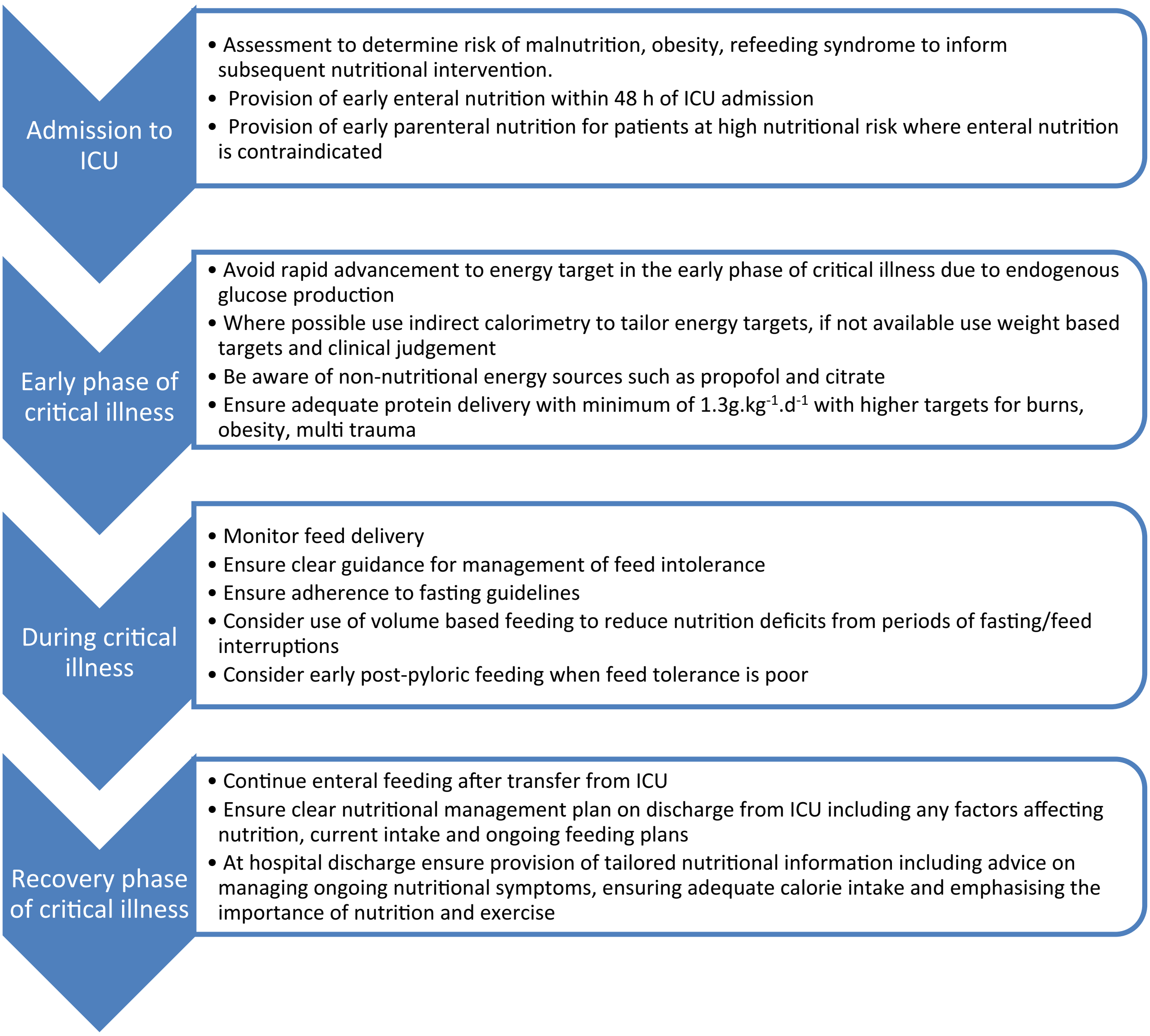

Figure 1 Flow chart highlighting best practice during each stage of the critical illness journey.

functionality in the clinical setting is unclear. The Global Leadership Initiative on Malnutrition tool has been proposed by the European Society of Enteral and Parenteral Nutrition as a method for diagnosing malnutrition in clinical settings [12]; it is, however, not validated for use in patients in the ICU. It remains a crucial role of the ICU dietitian to identify malnourished patients on admission and minimise the risk of patients developing malnutrition during their stay.

Obesity

Increases in obesity rates worldwide are reflected in the ICU population, with a global prevalence of around 20% [13]. Patients classified as obese (BMI > 30 kg.m^{-2}) have large variations in lean body mass, ranging from high muscle mass or sarcopenic obesity. Predictive equations commonly used to estimate energy requirements were developed in non-obese populations with very different body compositions. This makes estimating the nutrition needs of the obese population particularly challenging. The European Society of Enteral and Parenteral Nutrition recommends isocaloric and high-protein provision for obese patients. The use of an adjusted body weight (20–25%) to estimate energy needs (to account for differences in metabolic demand of adipose tissue and muscle) is recommended, with actual body weight used to estimate protein targets [5]. The energy targets proposed in the 2016 American Society for Parenteral and Enteral Nutrition/Society for Critical Care Medicine guidelines demonstrated significant variation to measuring energy expenditure [14]. The more recently published 2022 updated guideline removed these proposed energy targets due to a lack of randomised controlled trial data [15]. Despite the limited evidence, it is important not to assume adequate energy stores in obese patients. These patients should be assessed and fed appropriately to limit loss of lean body mass and reduce their rehabilitation burden. While patients are critically ill, it is not appropriate to consider weight loss strategies as most of this loss is of muscle.

Assessment of protein stores

The metabolic response to critical illness results in early and rapid loss of muscle mass as proteins are used to support immune function and in the synthesis of acute phase proteins. Muscle mass at ICU admission has been correlated with ICU survival [16]. Muscle mass loss has been reported up to 2% per day in critically ill patients [6] or 1 kg per day over the first 10 days [17]. Loss of muscle area as judged by CT has been shown to occur irrespective of energy and protein provision [18].

Methods of body composition assessment such as bioelectrical impedance or skin fold measurements, used in other patient populations, should be interpreted with caution due to significant daily fluid shifts in ICU patients. Phase angle has been used in bioelectrical impedance to predict 90-day mortality. In this case, phase angle is used to represent cellular health, and bioelectrical impedance is not used for body composition [19]. Clinical assessments are therefore limited to basic assessments of weight, height, BMI and a clinical examination of muscle stores. Research tools to determine components of body composition have

Table 1 Body composition assessment in ICU; skeletal muscle and protein turnover [6, 20–22].

Method	Abdominal CT	Muscle ultrasound	Stable isotopes
Location	Abdominal CT at L3	Multiple potential sites: e.g., quadriceps, forearm, bicep	Whole body (or leg)
What is measured?	Skeletal muscle: area (cm^{-2}) Quality/density (Hounsfield units) Skeletal muscle index (cm^{-2}.m^{-2})	Skeletal muscle: Depth (cm) Area (cm^{-2}) Quality (echogenicity) Pennate angle (force)	Whole body protein turnover (or leg)
Frequency	Usually one-off	Serial	Serial
Strengths	Accuracy Published cut-off for sarcopenia Skeletal muscle index predicts ICU acquired wasting	Easily accessible Not ionising Potential to use muscle glycogen `score´ for recovery	Accuracy Identifies patient in positive or negative protein balance
Limitations	Ionising Selection bias Serial measurements less likely Cost Specialist training required	No agreed procedure No clinical cut-off Subjective Reduced interobserver reliability Specialist training required	Costly Time consuming Specialist training required

CT, computed tomography.

emerged over the last few decades, although these methods have not yet translated into clinical practice. A summary of the different research tools is presented in Table 1.

Refeeding syndrome

Refeeding syndrome is classified as a measurable reduction in phosphorus, potassium, and/or magnesium, or the manifestation of thiamine deficiency, in response to calorie provision after a period of reduced or absent calorie intake [23]. At-risk patient groups in critical care include those with prolonged fasting/minimal nutrition, those with backgrounds of substance abuse and patients malnourished on admission. Nutrition targets should be met early in patients who are malnourished while monitoring for refeeding syndrome [5].

New guidelines recommend that nutrition be initiated with intravenous dextrose 100–150 g or 10–20 kcal.kg^{-1} for the first 24 h before advancing by 33% of goal energy every 2–3 days [23]. However, this is often done more rapidly in the ICU due to the enhanced ability to monitor and supplement electrolytes. Electrolyte replacement before initiating nutrition should be considered for patients at moderate or high risk of refeeding syndrome with low electrolytes. This recent guideline supports a more aggressive nutrition introduction than previous guidelines [24]. Clear guidance on thiamine and multivitamin supplementation in patients with or at risk of refeeding syndrome is also provided.

Timing and delivery of enteral and parenteral nutrition

A principle common to all nutritional guidelines is that enteral nutrition should be commenced within 48 h of ICU admission in patients whose lungs are being mechanically ventilated [5, 25, 26]. Patients at high nutritional risk should achieve their nutrition goals early (within 24–48 h) if tolerated, while monitoring for refeeding syndrome [25]. Enteral nutrition is contraindicated in patients with uncontrolled shock; uncontrolled hypoxemia and acidosis; uncontrolled upper gastro-intestinal bleeding; gastric aspirates $>$ 500 ml.6 h^{-1}; bowel ischemia; bowel obstruction; abdominal compartment syndrome; and high-output fistulae without distal feeding access [5, 27].

Exclusive parenteral nutrition should be started early for patients at high nutritional risk [5, 25, 26]. Guidance for starting parenteral nutrition in patients at low nutritional risk varies in international guidelines from 3 to 10 days [5, 25, 26]. The use of supplemental parenteral nutrition should be assessed on a case-by-case basis [5, 26], or if $<$ 60% of energy and protein targets have been met in 7–10 days. A recent systematic review and meta-analysis showed that when enteral nutrition targets cannot be reached, supplemental parenteral nutrition was of benefit in increasing energy and protein provision without adverse complications [28].

The recommended method for the delivery of continuous enteral nutrition is to use a volumetric pump to accurately deliver the correct calculated hourly volume at a controlled rate [5] The aim of this is to feed safely and minimise the potential risks of complications. Nutrition targets are often poorly met in the ICU patient population due to feed interruptions and gastro-intestinal intolerance. This has led to significant interest in investigating different modalities for the delivery of enteral nutrition. A recent systematic review and meta-analysis found safety, tolerance and effectiveness of intermittent enteral nutrition to be comparable to that of continuous enteral nutrition in the ICU. Studies with larger sample sizes will be required to better define the most appropriate methods for the delivery of enteral nutrition [29].

Given the significant degree of heterogeneity and low quality of evidence in the literature, a lack of clinical biomarkers and infrequent use of indirect calorimetry, patients' energy needs should be assessed individually. This assessment should consider the following: the stage of critical illness; metabolic tolerance; nutritional status; comorbidities [9]; and body composition. When planning nutrition regimens, the contribution of other exogenous non-nutritional energy sources, namely propofol and citrate, require careful consideration [5, 9].

Energy dosing

There are significant challenges in accurately estimating energy requirements and hence the optimal dosing of nutrition. Indirect calorimetry is regarded as the gold standard for monitoring energy expenditure and tailoring energy targets in critically ill patients [5, 25]. It provides a method of personalising energy prescriptions across the different phases of critical illness [30], thus minimising the risks of either under- or overfeeding. Two recently published systematic reviews and meta-analyses showed a reduction in short-term mortality when indirect calorimetry was used to guide energy provision in critically ill patients [31, 32]. The new generation Q-NRG+™ indirect calorimeter (Cosmed Metabolic Company, Rome, Italy), validated in vitro against mass spectrometry [33], overcomes previous limitations of the technique. With recent advancements and innovations, it is predicted that the use of indirect calorimetry will increase, both clinically in the ICU and as a research tool [34, 35]. The increasing focus on functional and patient-centred quality of life outcomes [36] favours the use of methods which provide tailored energy targets.

In the absence of indirect calorimetry, predictive equations are recommended to estimate patients' energy needs. The inaccuracy of these equations is universally accepted, with variations of up to 75% [5, 25]. Therefore, both the European and American Societies for Parenteral and Enteral Nutrition recommend a simplistic approach using weight-based equations to calculate energy targets. In the early stages of critical illness, endogenous glucose production is strongly activated and is thought to provide a significant proportion of patients' energy requirements. As a result of this it has been recommended that rapid attainment of energy targets early in the ICU admission be avoided [5]. The European Society of Parenteral and Enteral Nutrition recommends hypocaloric feeding (approximately 70% of estimated requirement in the first 7 days of ICU admission) using a weight-based equation of 20–25 $kcal.kg^{-1}.d^{-1}$. Due to a lack of high-quality data, the updated American Society guidelines suggest energy targets of 12–25 $kcal.kg^{-1}.d^{-1}$ (the range of mean energy intakes examined) in the first 7–10 days of a patient's ICU stay [15]. There is an emphasis on expecting clinicians to use their clinical judgement when calculating energy targets [15]. These differ from the previous recommendations of 25–30 $kcal.kg^{-1}.d^{-1}$ [25].

Protein delivery and dosing

Protein delivery and the effects of this on clinical and functional outcomes continues to be an area of significant research interest [37]. Unfortunately, there is a paucity of high-quality randomised controlled trials to guide protein dosing and consequent patient outcomes. Studies are frequently underpowered and not comparable in terms of patient selection, energy and protein delivery and timing of nutrient delivery. Poor study design and heterogeneity has impacted on meta-analyses and guideline development; international guidelines for protein provision are therefore predominately based on observational studies and expert opinion.

The European Society of Parenteral and Enteral Nutrition recommends aiming for protein delivery of 1.3 $g.kg^{-1}.d^{-1}$ whereas the American Society for Parenteral and Enteral Nutrition/Society for Critical Care Medicine guidelines suggest a larger range of 1.2–2.0 $g.kg^{-1}.d^{-1}$, with higher targets for patients with burns, obesity or following polytrauma [5, 15]. A recent meta-analysis reported no significant differences in overall mortality (RR [95%CI] 0.91 [−0.75–1.10], p = 0.34) or other clinical, muscle and functional outcomes when comparing mean (SD) protein delivery of 1.31 (0.48) with 0.90 (0.30) $g.kg^{-1}$ [38]. This level of protein delivery represents a `standard´ ICU recommended amount vs. the recommended daily allowance for a general population, rather than a true `high vs. low´ group. High-protein provision has been associated with increased survival in observational studies [39, 40].

The effect of higher protein dosing in critically ill patients trial (EFFORT) is a large multicentre randomised controlled trial looking at the effects of high protein dose (≥2.2 $g.kg^{-1}.d^{-1}$) vs. low protein dose (≤1.2 $g.kg^{-1}.d^{-1}$), via the enteral or parenteral route, with the primary outcome measure of 60-day mortality. Secondary outcome measures include hospital and ICU length of stay, hospital mortality and days of mechanical ventilation [41]. A sub-study of the EFFORT trial will assess functional and health-related quality of life outcome measures (NCT04931940).

The multicentre randomised controlled trial – protein provision in critical illness (PRECISe) is currently underway (NCT04633421) and randomly allocates patients to a standard protein (1.2 $g.kg^{-1}.d^{-1}$) or a high protein (2.0 $g.kg^{-1}.d^{-1}$) diet. Outcome data are collected at day 0, 30, 90 and 180 days after ICU admission using questionnaires and physical tests. The TARGET Protein trial endorsed by the Australian and New Zealand Intensive Care Society is a randomised, cross-sectional double crossover, registry-embedded, pragmatic clinical trial (www.anzics.com.au/target-protein-2022). Its aim is to evaluate the effect of isocaloric higher protein delivery on outcomes of critically ill patients when compared with usual care. Results from these trials may provide further insights into the effects of high- vs. low-protein diet provision in critically ill patients, in short term and longer-term patient outcomes.

Strategies to reduce muscle wasting

Potential strategies to reduce muscle wasting or improve muscle strength include nutritional strategies, and/or exercise, or drug treatments. No current nutritional strategy has been shown to be effective in reducing muscle wasting; possible strategies are discussed below.

The role of protein dosing has been mentioned. There is also significant interest in which types of amino acids are provided as part of this strategy. Leucine or hydroxymethylbutyrate supplementation have been investigated [42] as potential strategies to reduce muscle wasting. Hydroxymethylbutyrate has been shown to increase muscle strength and size in patient populations other than those in the ICU. The effect size, however, was small and of doubtful clinical significance [43]. A recent randomised controlled trial using hydroxymethylbutyrate supplementation over a period of 30 days in ICU patients found no differences in muscle wasting over a 10-day period, although net protein breakdown was reduced [44].

Intermittent vs. continuous feeding has also been investigated. Intermittent feeding was felt to be beneficial in allowing cells to undergo necessary autophagy [45]. A recent systematic review and meta-analysis showed that there were no differences in muscle-related outcome measures [29], although protein targets were not adequately met in included randomised controlled trials. Ketogenic nutrition is another area of interest. Ketones enhance metabolic efficiency, and could thus potentially help to reduce muscle wasting; randomised controlled trials are required to investigate this hypothesis further [45].

The role of exercise while critically ill, when combined with nutrition, remains uncertain. Early exercise with amino acid supplementation has so far not demonstrated any benefit in terms of muscle strength, although some studies have demonstrated surrogate outcomes such as retention of myofibre size [46]. Even if myofibre size is retained, data are still lacking to demonstrate that this translates into improvements in muscle function, strength and outcomes [46]. The current sub-study of the trial registry-based trial by Heyland et al., with early in-bed cycling and intravenous amino acid supplementation [41], may shed more light on this area. There appears to be no current role for passive exercise in the form of neuromuscular electrical stimulation. No effects on muscle strength and function have been shown [47].

Finally, various candidate drugs have been tested for roles in either reducing muscle catabolism or promoting anabolism. Propranolol (a beta-blocker) and oxandrolone (a testosterone analogue) have shown promise in reducing catabolism in burns patients [48, 49]; these effects, however, are yet to be tested in populations of other critically ill patients [50].

Optimising nutrition delivery

Nutrition targets are rarely achieved in practice due to fasting for procedures/tests, feed intolerance, lack of dietetic presence and gaps in education and knowledge. A number of strategies exist to improve the provision of nutrition to patients in the ICU (Box 1).

Nutrition in the recovery phase of critical illness

Post-intensive care syndrome is a collective term used to describe a host of issues ICU survivors may experience [56]. These pronounced functional, cognitive and psychological symptoms impact patients' recovery from critical illness. Optimising nutritional status may translate into improved functional, cognitive, and mental health and therefore plays an important role in ICU recovery and rehabilitation. Despite this, little is known about the recovery phase of critical illness and there is a gap in the research relating to nutritional interventions for ICU survivors [4, 36].

It is increasingly evident that there is a reduction in oral intake during the recovery phase of critical illness. A study of 50 patients from a mixed medical/surgical ICU showed that energy and protein intakes were < 55% and 37% of their

Box 1 Strategies to improve the provision of nutrition to patients in the ICU

1. The presence of an ICU-trained dietitian to advocate, advise and troubleshoot nutrition issues and provide individual assessments of energy and protein targets [51, 52].
2. A local enteral feeding protocol to guide the initial provision of nutrition [9, 25, 26].
3. Adherence to fasting guidelines and ensuring that site specific guidelines reflect best practice [53, 54].
4. The use of volume-based feeding practices to reduce nutritional deficits from periods of fasting/interruptions of feed [25, 55].
5. Clear guidance for the management of feed intolerance. The European Society of Parenteral and Enteral Nutrition recommends using a gastric residual volume cut-off of >500 m.6 h^{-1} as the indication for intervention (prokinetics, reduced or delayed enteral nutrition) [5]. The American Society for Parenteral and Enteral Nutrition recommends the removal and measurement of gastric residual volumes as a routine of care to monitor ICU patients, as opposed to using other clinical signs: vomiting; abdominal distention; complaints of discomfort; high nasogastric output; diarrhoea; reduced passage of flatus and stool; or abnormal abdominal radiographs to assess for poor feed tolerance [25].
6. Early access to post-pyloric feeding when feed tolerance is poor to reduce the risks of aspiration and increase nutrition delivery [5, 26].
7. A strong multidisciplinary team framework with regular education regarding the importance of nutrition in the critically ill.

respective targets during the first 7 days following tracheal extubation [57]. Similar results were found during the early phase of ward-based recovery, with more prominent nutritional deficits seen in patients relying on oral diet alone. Intakes ranged from between 55% and 75% of energy and 27% and 74% of relevant protein targets [58–60]. By way of comparison, patients who continued to be enterally fed post ICU, with or without oral intake, achieved significantly higher nutritional intakes, receiving 62–104% of energy and 59–100% of protein targets [58–60].

Several factors contribute to reductions in oral intake. These include: poor appetite [61]; taste and smell changes; early satiety; nausea and vomiting; swallowing issues; gastro-intestinal disturbances; pain; muscle loss [6]; and weakness and fatigue [62]. Poor appetite is the most commonly reported symptom influencing dietary intake and can last for up to 3 months after ICU discharge [63]. Psychosocial factors such as low mood, anxiety, sleep disturbances, delirium [64] and social isolation [62] can also negatively impact nutrition intake.

Challenges to consuming adequate nutrition post ICU come at a time when a patient's metabolic demands are often at their highest. Energy and protein targets of > 35 $kcal.kg^{-1}.d^{-1}$ and 1.5–2.5 $g.kg^{-1}.d^{-1}$ [4] have been suggested in the absence of robust evidence. With increased use of indirect calorimetry, the targets in this patient group may be better understood in the future. Despite this, individualised nutrition therapy post ICU is required and should be a core component of the rehabilitation process. For muscle to gain mass and quality (and therefore increase function), a combination of protein and exercise is required.

Strategies to improve nutritional intake in ICU survivors

To date, there has been remarkably little research that has looked at nutritional interventions in the recovery phase of critical illness. Strategies shown to facilitate improvements in nutrition adequacy include continuation of enteral feeding after discharge from ICU. Early removal of enteral access is one of the biggest factors associated with suboptimal oral intake post ICU [65], and supplemental enteral feeding after discharge from ICU has been shown to improve calorie and protein delivery [66]. Despite popular belief, continuing enteral nutrition once a patient has started on oral diet has not been showed to negatively impact on appetite [67]. Improvements in transitions of care from ICU to the ward are essential. Due to the complexity of this patient population, the nutritional management plan on discharge from ICU requires clear documentation. This should include any factors affecting nutrition, a summary of the nutrition provision in ICU, the current nutrition plan, and ongoing recommendations.

At the point of hospital discharge there is a need for a co-ordinated discharge plan. This includes the provision of tailored nutritional information. Common ongoing nutrition-related symptoms including poor appetite, taste changes and muscle loss. These can take months or even years to resolve [2, 28]. Nutritional education to patients and/or relatives and care givers is therefore important. This should include advice on managing nutrition related symptoms, ensuring appropriate calorie intake, and emphasising the importance of protein and exercise. Patients should be referred to community services as required. A multidisciplinary approach to rehabilitation is most effective. As nutrition plays an important role in recovery from critical illness, dietitians should link in with rehabilitation pathways and establish referral criteria. Multidisciplinary ICU follow up services are becoming more common; where nutritional status can be monitored, and further intervention instituted to optimise recovery.

Future directions

Research into the role played by nutrition in critically ill patients is rapidly advancing. With an enhanced focus on ICU survivorship, answering questions as to how to optimally feed a critically ill patient is of particular interest. Increased use of indirect calorimetry both clinically and as a research tool will assist clinicians in estimating a patient's energy needs, particularly in patient groups where the quality of evidence is poor. Similarly, future randomised controlled trials looking at protein dosage in association with short- and long-term clinical, functional and physical patient-centred outcomes will guide clinical practice. With the importance of the recovery phase of critical illness becoming increasingly clear, more focus should fall on continuing individualised nutritional care beyond the ICU by incorporating realistic nutritional, physical and functional outcome measures.

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