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Review

Nutrition therapy in critically ill patients- a review of current evidence for clinicians

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SUMMARY

The provision of nutrition to critically ill patients is internationally accepted as standard of care in intensive care units (ICU). Nutrition has the potential to positively impact patient outcomes, is relatively inexpensive compared to other commonly used treatments, and is increasingly identified as a marker of quality ICU care. Furthermore, we are beginning to understand its true potential, with positive and deleterious consequences when it is delivered inappropriately. As with many areas of medicine the evidence is rapidly changing and often conflicting, making interpretation and application difficult for the individual clinician. This narrative review aims to provide an overview of the major evidence base on nutrition therapy in critically ill patients and provide practical suggestions.

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1. Nutrition risk in the ICU: can we measure it?

Malnutrition (referring to both under and overnutrition) in hospitalised patients is a common and concerning issue that is associated with poor clinical outcomes [1]. Reports of the prevalence of malnutrition in hospitalised patients vary depending on the geographical region, patient population studied, and the tool used in assessment [2]. It logically follows that critically ill patients may be malnourished (or at 'nutritional risk') as malnutrition is associated with disease states that involve acute inflammation (such as critical illness) [2]. However, the identification of those at risk or those already malnourished remains poorly defined in this population due to a lack of validated assessment tools [3]. Over the decades there have been several attempts to identify and develop new approaches to assess malnutrition in acute illness, but with no consensus achieved to date [3]. The common malnutrition screening tools and anthropometric measures which are available are inappropriate in critical illness, mostly due to the significant fluid shifts that occur, preventing accurate assessment of weight and other anthropometry assessments. Secondly, some screening tools require answers to questions which are impossible to obtain in patients who are ventilated or sedated and which are often unknown to relatives. This means that many of these available screening tools have not been validated or are unable to be validated in the ICU population. Other well-known body composition assessment techniques, such as bioelectrical impedance analysis, are also considered unreliable in critical illness due to altered hydration status [4]. Biochemical markers have long been considered a potential way to identify and measure nutrition status as it changes during hospitalisation, but are unreliable in critical illness due to biochemical variability as a result of the underlying disease. Such markers might include albumin or other proteins with a shorter half-life (such as transthyretin); however as these are also acute phase reactants they are frequently altered in critical illness, making their interpretation difficult [1,3].

To overcome some of these issues, new tools and concepts are being tested in the hope of finding an accurate, multifaceted, but easily applied assessment technique(s) at the bedside. The NUTRIC score has been developed as a potential scoring tool to identify nutrition risk in ICU patients [5]. It contains 6 variables which have been associated with nutrition risk and outcome in previous validity testing [5]. It remains to be determined how this tool performs on a large scale; however it is a potential step in the right direction in relation to assessment of nutrition risk in the ICU population [4].

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Commonly available practical tools gaining significant interest in the assessment of body composition for the purpose of nutrition risk or malnutrition identification are computed tomography, dual energy x-ray absorptiometry and bedside ultrasound. Ultrasound of the quadricept muscle, which is quick and readily available, has recently been shown to be reliable and may assist in identifying changes in muscle mass during hospitalisation [6]. Evidence for use and validity is being gathered on the other mentioned options. As the 'tailored nutrition approach' becomes more popular and people begin to understand that certain groups, like the malnourished or those at nutritional risk, may benefit from targeted and individualised nutrition, it is becoming even more important that we develop easy methods and tools which can be used daily at the bedside to identify these populations.

2. Energy and protein: how do we determine requirements and how much is the right amount?

2.1. Predictive equations

One of the biggest challenges in administration of nutrition therapy in critical illness is the prediction of each patient's true energy needs. This is commonly done using predictive equations based on age, gender, height, weight and severity of illness. There are many issues with these equations and their applicability to the individual patient, with accuracy varying significantly [7]. A common method is fixed prescription, with the estimate usually set between 25 and 35 kilocalories (kcal)/kg. However energy utilization in critically ill patients can vary between 20 and 35 kcal/kg/day, and it is unlikely that single predictions are accurate for all phases of an individual's critical illness [7]. Without measuring, a clinician does not know where on the spectrum the patient lies, rendering predictions imprecise [7]. Furthermore, the commonly used equations are generally not validated in those at higher risk of complications associated with poorly provided nutrition, such as malnourished, elderly and obese patients [8,9]. This means that if predictive estimation methods are used to guide nutrition practice the potential limitations must be acknowledged and prescriptions regularly reviewed with available clinical information.

2.2. Measuring energy expenditure in the critically ill

Indirect calorimetry (IC) is a more accurate method of assessing energy expenditure. To determine energy utilization using IC, a "metabolic cart" is attached to the patient's ventilator circuit to measure the utilization of oxygen and production of carbon dioxide and thereby derive a value for resting energy expenditure [10,11]. If adequate test stability can be achieved, IC measurements of only 15 min duration can successfully predict energy requirements with less than a 4% error in critically ill patients [12]. Given the issues with predictive equations, IC should be considered in ICU to allow for non-invasive, accurate and real-time determination of the metabolic response to injury in mechanically ventilated (MV) and critically ill individuals [11]. Clinical evidence to support this approach is currently in development. The TICACOS study was the first randomized controlled trial (RCT) to investigate the role of tight energy provision using IC versus a fixed prescription estimation method in critically ill patients. In a single centre design, the intervention group received a higher mean energy (2086 ± 460 vs. 1480 ± 356 kcal/day, $p = 0.01$) and protein intake (76 ± 16 vs. 53 ± 16 g/day, $p = 0.01$) [13]. Based on intention to treat analysis, there was a trend towards reduced hospital mortality (21/65 patients, 32.3% vs. 31/65 patients, 47.7%, $p = 0.058$) but length of MV and ICU stay increased in the intervention group [13]. These findings are currently being tested on a larger multicentre scale. This technology could eliminate the error associated with predictive equations and transform current nutrition practises by allowing precise adjustment of the nutrition regime [10,11,14,15]. However it must be noted that IC measurement needs to be repeated as the patient's clinical condition changes or its estimation will also become inaccurate. If IC is not available, in its absence it is suggested that 20–25 kcal/kg/day should be provided in the anabolic or initial stages of nutrition therapy, increasing to 25–30 kcal/kg/day in the recovery phase [16]. It must also be acknowledged that although we may estimate the amount of energy required, the desirable amount to actually target is unknown.

2.3. Which energy target?

Just as there is a challenge to know individual patients' energy needs, there is mixed evidence about the amount of energy to target in critical illness, causing much debate in the current literature. Two large retrospective analyses of observational data have found positive associations with clinical outcomes when energy provision is increased. The first, including 2772 mechanically ventilated patients, reported that provision of an additional 1000 kcal/day on top of an average delivery of 1034 kcal and 47 g of protein was associated with a reduction in 60 day mortality (Odds Ratio (OR) 0.76; 95% confidence interval (95% CI) 0.61–0.95, $p = 0.014$) and an increase in ventilator free days (VFD) (3.5 VFD, 95% CI 1.2–5.9, $p = 0.003$) [17]. When analysed by weight categories, these associations with mortality were observed in patients with a BMI < 25 kg/m^2 and >35 kg/m^2, with no associated benefit for patients with a BMI 25–35 kg/m^2 [17]. This association may be explained by the malnutrition that exists in these two extremes of BMI; further work needs to be conducted to explain these differences [17]. The second was an analysis performed on 2270 septic patients who received a mean energy intake of 1057 kcal/day and 49 g of protein [18]. Provision of an additional 1000 kcal per day to this group was also associated with improved 60-day mortality (OR 0.61; 95% CI 0.48–0.77, $p = 0.001$) and increased VFDs (2.81 days; 95% CI 0.53–5.08, $p = 0.02$) [18].

The alternative approach is 'hypocaloric' nutrition. On superficial evaluation the evidence surrounding this approach may appear contradictory. A recent RCT reported no difference in VFDs or 60-day mortality in patients with acute respiratory distress syndrome who received hypocaloric feeding for the first 6 days of ICU admission [19]. Of importance, this is a very specific patient group and hypocaloric feeding was only provided for a short period of time, the risk being that at some stage hypocaloric feeding will become starvation. Similarly, a recent post-hoc analysis on 1456 patients who were enrolled in an RCT investigating two levels of intensity of continuous renal replacement therapy reported no improved clinical outcome with increased daily energy intake in patients with acute kidney injury, despite a very low daily median energy intake of 10.9 ± 9 kcal/kg/day [20].

2.4. What about protein?

Synthesis of the evidence is complicated by the influence of protein intake in combination with energy intake. As with energy provision, we do not know the optimum amount of protein to target to elicit positive patient outcomes. Protein requirements in critical illness are increased, and even with appropriate provision, protein catabolism and the resultant negative nitrogen balance will never be prevented. The normal range of protein requirements for ICU patients is between 1.2 g/kg/day to 2.0 g/kg/day (2.0 g/kg is usually provided in significant burn injury, severe TBI and trauma) [1]. Providing above this amount has not shown any clinical benefit and does not overcome protein catabolism [1].

3. Enteral nutrition

Early provision of enteral nutrition (EN) via the gastrointestinal (GI) tract to critically ill patients has been established as standard and a marker of quality of care for critically ill patients. In 2009, a rigorous meta-analysis of RCTs demonstrated that compared to standard care, providing EN to critically ill patients within 24 h of admission resulted in a significant reduction in mortality (OR 0.34; 95% CI 0.14–0.85, p = 0.02) and pneumonia (OR = 0.31, 95% CI 0.12–0.78, p = 0.01) [21]. Early EN (within 24–48 h post admission to ICU) has subsequently been incorporated into most best practice guidelines for nutrition in ICU [16,22,23]. Provision of EN to critically ill patients is considered appropriate when the patient has a functioning GI tract and access via the gastric or jejunal route and/or the patient is unable or unwilling to meet nutrition needs orally. EN is contraindicated when there is an absence of intestinal function, a GI tract obstruction, a high output fistulae and/or the patient's condition is considered to be terminal [1]. Despite delivery of EN being common practice, there remains multiple challenges with its delivery.

3.1. EN delivery: the unachievable goal?

Ensuring EN delivery close to predicted energy requirements is a complex management problem. There are multiple barriers to adequate enteral delivery, including delayed placement of feeding tubes, interruptions for patient transports, poor adherence to or lack of unit feeding protocols, GI intolerance and fasting. Observational data on 2946 patients from the international nutrition survey (INS) reported that the average amount of energy provided via EN compared to prescribed is only 45.0% of energy and 45.5% of protein at the site level (site average range for energy provided was 4.1%–85.4% and for protein 3.5%–93.7%) [24]. Regarding fasting, a recent retrospective observational study reported that in trauma ICU patients who had a mean ICU stay of 18.7 days, EN was stopped for planned procedures for a mean duration of 30.8 h per patient, resulting in mean 7.2% energy and 7.7% protein deficits from fasting alone [25].

GI intolerance is common cause of inadequate delivery of EN. This intolerance is worsened by opiates, catecholamines and barbiturates [26]. Metoclopramide and erythromycin are two prokinetic drugs that can assist in the management of GI intolerance by improving gastric emptying. One double blind RCT of mixed medical ICU patients and one retrospective analysis of patients with traumatic brain injury demonstrated that combination prokinetic therapy is better than single therapy [27,28]. It is important to note that prokinetics should only be administered when delayed gastric emptying is observed and should not be prescribed prophylactically due to rapid development of tachyphylaxis. This effect was demonstrated in an RCT of 90 mixed medical ICU patients who were administered metoclopramide and erythromycin. When administered metoclopramide, 67% of patients tolerated EN at 24 h, reducing to 27% by day 3 and 16% on day 7 [29]. Tachyphylaxis with erythromycin was similar: 87% of patients tolerated EN at 24 h, 47% at day 3 and 31% on day 7 [29]. This study also supported the use of combination prokinetic therapy; in the 67 patients who failed monotherapy, combination therapy was attempted in 57 for a median duration of 4.8 days [29]. After 24 h of combination therapy, EN was successfully achieved in 92% of patients [29]. The prokinetic doses that have proved to be most effective on gastric emptying are 200 mg of intravenous erythromycin twice daily (in those without contraindications) and 10 mg of intravenous metoclopramide four times daily, and preferably delivered in combination [27]. Prolonged QT interval is a possible side effect of erythromycin.

To assist adequate delivery of EN, up to date nutrition protocols detailing the management and associated issues should be implemented. These protocols should incorporate fasting procedures and advocate for minimizing pre-operative fasting as much as possible and ensuring that EN is turned back on as soon as possible post operatively.

3.2. Improving EN delivery: what does the evidence suggest?

Much time and effort has gone into designing strategies that will overcome the barriers to achieving delivery of EN to meet nutrition goals, with mixed results. Evidence-based feeding algorithms are well accepted and improve nutrition outcomes, but clinical outcomes are varied [30–32]. A cluster RCT demonstrated that patients who were managed with an evidence-based, protocolised feeding strategy with rigorous implementation and education procedures received greater days of EN when compared to standard clinician directed feeding (6.7 v 5.4 per 10 patient-days; p = 0.042), had a shorter duration of hospital stay (25 v 35 days; p = 0.003) and had a strong trend towards improved survival (27% v 37% p = 0.058) [32]. A subsequent cluster RCT, published in 2008 and conducted in 27 ICUs in Australia and New Zealand, found that patients in the intervention centres commenced EN earlier (0.75 vs 1.37 mean days; mean difference = −0.62 (95% CI, −0.82 to −0.36; P = 0.001)) and achieved caloric goals more often (6.10 vs 5.02 mean days per 10 days of nutrition provision; mean difference = 1.07 (95% CI, 0.12 to 2.22; P = 0.03)) but there were no significant differences in hospital mortality or lengths of stay (LOS) at hospital or ICU between the two groups [30]. This strategy has been developed further by designing enhanced feeding protocols coupled with similar rigorous implementation and nursing education procedures [31]. In a RCT of 1059 MV critically ill adults from 18 centres with low baseline performance in nutrition delivery, use of this strategy compared to standard practice demonstrated improved protein and energy delivery. There was an improved absolute, adjusted, mean difference between groups in delivery of energy and protein (energy: 12% improvement (95% CI 5–20%; p = 0.004) and protein: 14% improvement (95%CI 5–23%; p = 0.005)) [33]. This study was not designed to determine the effect of this strategy on clinical outcomes such as LOS and mortality.

Another strategy is to deliver nutrients post-pylorically. Post-pyloric feeding also has the potential to reduce nosocomial infection by reducing gastric secretions and preventing aspiration. The largest RCT to date on this topic investigated if post-pyloric feeding reduced rates of VAP and improved nutrition delivery compared to gastric feeding; they found no difference in either outcome [34]. Despite this finding, best practice recommendations still state that post-pyloric feeding should be attempted before parenteral nutrition (PN) in the setting of EN intolerance; however it is unclear what is happening in practice [16,22]. It also remains to be determined if using enhanced nutrition delivery and education strategies would improve clinical and functional outcomes in the broader ICU community, including ICUs that already achieve good provision of nutrition.

3.3. Monitoring enteral nutrition: gastric residual volumes – useful or useless?

The degree of GI dysmotility in critical illness can be monitored by measurement of gastric residual volumes (GRV); however the utility of this method has been called into question by the results of recent research. In 2010 an unblinded RCT was conducted in 329 MV patients from 28 ICUs to determine if increasing the GRV limit to 500 ml (from the standard of 200 ml) improved delivery of EN and resulted in any differences to clinical outcomes. They

reported slightly higher rates of EN delivery in the intervention group (84% vs 88%, p = 0.0002) and higher rates of GI complications in the control group (63% vs 47%, p = 0.004); however when analysed more closely, the difference in complications was accounted for by an increased frequency of elevated GRVs (42% vs 26%, P = 0.003). There was no difference in other important clinical outcomes such as rates of VAP, duration of MV, or ICU LOS. Another multi-centre, open-label RCT found similar results: 452 adults who were MV for more than 2 days and received EN were randomised to receive no monitoring of GRV, and compared to a standard care group who had a GRV cut-off of 250 ml, measured 6 hourly [35]. There was no difference in rates of VAP between the two groups (16.7% in the study group vs 15.8% (difference 0.90; 90% CI, −4.8%–6.7%)). Importantly, the proportion of patients receiving 100% of their energy goal was higher in the intervention group (OR 1.77; 90% CI 1.25–2.51; P = 0.008) [35]. There were no differences in other important clinical outcomes and the authors concluded that not monitoring GRVs was not inferior to routine measuring. It is important to note that this study excluded patients who had abdominal surgery or GIT conditions, as well as those at risk of VAP and those who were not tolerating EN prior to screening. It must be considered that ceasing measurement of GRV may be appropriate in some populations but not in others. These findings do challenge the common belief that GRV is a reliable and useful clinical tool and support a lack of correlation between GRV and rates of gastric emptying and abdominal distension [36,37]. Furthermore, the measurement is very dependent on the clinician, patient position, feeding tube and syringe diameter [36,37]. As a result of these recent studies, many institutions now use a GRV cut-off of between 300 and 500 ml 4–6 hourly as a guide for EN tolerance.

4. The alternative to EN: parenteral nutrition

When EN cannot be provided it is common to provide parenteral nutrition (PN). Early data suggested that PN was associated with increased infectious complications and mortality in ICU patients; however more recent and emerging evidence from large clinical trials, which reflect modern day ICU care and use modern day PN solutions, have not confirmed those initial findings [38–42]. Despite this, best practice guidelines still differ in their recommendations for the commencement of PN in critically ill patients (ranging from 24 h to 7 days after admission to ICU) [22,23,43]. This is largely due to the quality of evidence informing these guidelines. Many studies on this topic were conducted in the 1980s when the consequences of overfeeding with PN, namely impaired immunity, increased CO_2 production and organ dysfunction, were not understood. Additionally, significant gains have been made regarding the quality of the lipid emulsions in modern day PN solutions, to ensure they are as safe and as well tolerated as possible. Furthermore, routine infection control, line care and blood glucose management were very different to contemporary practice. Although the evidence and best practice guidelines remain conflicting, it appears sensible to consider PN when EN cannot be delivered at all in patients who are:

- Malnourished (regardless of duration). PN should be commenced as early as possible if EN is contraindicated [1].
- In surgical patients who have impaired GI function (pre- or post-op) which would prevent oral or EN being commenced within 5–7 days [1].
- In critically ill patients whom EN or oral nutrition is contraindicated or not expected to commence within 3 days [43].

The use of PN in combination with EN is a relatively new concept and has been the focus of recent RCTs. A large, multicenter RCT was published in 2011 comparing early and late initiation of PN in 4640 patients who received EN [44]. PN commencement delayed until 8 days after ICU admission in those who remained in ICU resulted in fewer infections, less time on MV, an increased likelihood of patients being discharged from the ICU alive and a shorter median ICU and hospital LOS when compared to PN commenced within 48 h of ICU admission [44]. There are several concerns regarding the generalizability of this study. In particular, 60% of the study population were cardiac surgical patients who generally do not require PN; the study did not define a population in which EN delivery was likely or was currently inadequate; and intensive insulin therapy was provided in both groups (with a blood glucose aim of 4.4–6.1 mmol/l), which has been shown to increase patient mortality [45]. In addition the study used intravenous dextrose (20% or 5%) as a maintenance fluid for up to 8 days, which is not routine practice in many ICUs. Finally, the amount of energy provided (between 24 and 36 kcal/day per kg of ideal body weight depending on gender) may have been excessive given the relatively healthy study population. It is plausible that the results of this study are explained by overnutrition in the early PN group, causing these patients to have a longer duration of stay and poorer outcomes.

Seemingly contradictory results were found in a subsequent, smaller RCT from 2 sites in Switzerland that randomized 305 patients to standard care (EN only) or EN with supplemental PN (SPN) [46]. This trial only enrolled patients identified as likely to benefit most from achieving targeted energy needs, and the nutrition strategies were 'goal-directed' and individualized, meaning requirements were set on day 4 with IC. The SPN group received more energy than the EN group (103%, standard deviation (SD) ± 18%) vs 77% (SD ± 27%), had reduced nosocomial infections between days 9–28 (27% vs 38%, Hazard Ratio (HR) 0.65, 95% CI 0.43–0.97; p = 0.0338) and a reduced mean number of nosocomial infections per patient (HR −0·42, 95% CI −0·79 to −0·05; p = 0·0248) [46]. In our opinion (and as recommended by the European Society of Parenteral and Enteral Nutrition Guidelines on Parenteral Nutrition in Intensive Care), supplemental PN should be considered when EN is insufficient for more than 2 days to prevent energy and protein deficiency in critically ill patients [43].

5. Specific amino acids and micronutrients in critical illness

In addition to provision of energy and protein, considerable attention has been given to the potential benefits of supplementation of specific nutrients, of which glutamine has been the most controversial. Glutamine is an essential amino acid and is involved in many metabolic processes. Based on previous observational research that found associations between glutamine and reductions in morbidity, mortality, infectious complications, and improved glycaemic control, two of the three major best practice guidelines for management of nutrition in the critically ill currently recommend the use of glutamine-supplemented PN (to provide 0.2–0.4 g/kg/day of L-glutamine or 0.3–0.6 g/kg/day of ananyl-glutamine dipeptide) [23,43]. This now has to be carefully interpreted and considered in the face of more recent research. In 2013 the large and methodologically robust REDOX RCT investigated the role of glutamine supplementation and a range of micronutrients with 28 day mortality and other clinical outcomes in a 2-by-2 factorial design [47]. The trial showed an increase in mortality with high doses of glutamine provided enterally and parenterally in patients with more than two organ system failures [47]. This has led to the authors cautioning against the use of glutamine-

Table 1
Summary of commonly used nutrition practice guidelines for use in critical care.

Guideline	Features	Comment
Canadian clinical practice guidelines [16].	First published in 2003. Updated every 12–18 months Only use RCTs to derive recommendations. Develops recommendations from the RCTs based on consensus opinion from topic experts with standardised procedures.	The development method leads to high grade recommendations. Non-randomised studies are excluded from recommendations, potentially limiting pragmatic advice to aid clinical practice.
European Society of Parenteral and Enteral Nutrition (ESPEN) guidelines [10].	Various clinical topic guidelines available. Enteral ICU guidelines developed in 2006. Parenteral guidelines developed in 2009. Use observational and RCTs to derive guidelines. Develops recommendations based on consensus opinion from topic experts.	Guidelines are more encompassing and provide real advice to clinicians accounting for small but clinically useful research.
Society of Critical Care Medicine and the American Society of Parenteral and Enteral Nutrition (ASPEN) [44].	Developed in 2009. RCTs used to derive recommendations using a grade of evidence system.	These recommendations are controversial as they conflict in some areas with the European and Canadian guidelines Methods in which they were formulated have been questioned and may not be as objective as the available alternatives.

supplemented PN in patients with multi-organ failure [47]. Whilst the results of this trial are important to the intensive care community, the interpretation is complicated by several factors: the patients were not glutamine deficient (as was demonstrated in smaller pilot work conducted by the same investigators prior to the definitive trial) [24], the amount of glutamine delivered to the patients was significantly higher than that provided in currently available commercial PN solutions, and the study patients were generally under-fed, receiving only a mean (SD) of 909 (±554) energy and 44 (±28.5) g of protein. This was 49.9% (±29%) and 45.4% (±28%) of their overall energy and protein goals, respectively, meaning that the patients received minimal balanced nutrition and a large load of protein (in the form of glutamine). This cannot be considered a physiological way to provide nutrition. These considerations make the interpretation of the results and the role for glutamine in critically ill patients confusing to the clinician, particularly as there is some evidence that still demonstrates benefit in trauma, burns and other ICU patients without multi-organ failure [48].

In the same RCT, the authors also tested a combination of antioxidant micronutrients. The patients were randomized (in addition to glutamine or placebo) to receive combined high dose selenium (500 μg intravenously and 300 μg enterally) and via the enteral route only, zinc (20 mg), beta carotene (10 mg), Vitamin E (500 mg) and Vitamin C (1500 mg), versus placebo (also received both enterally and parenterally). The authors found no difference in mortality between the antioxidant and placebo groups, with mortality in the antioxidant group of 30.8% vs 28.8% in the group who did not receive antioxidants (adjusted OR, 1.09; 95% CI, 0.86 to 1.40; $p = 0.48$) [47]. Regardless of this finding, the recently updated Canadian Clinical Practice Guidelines (which includes the REDOX results) still recommend that supplemental antioxidant micronutrients be considered in critically ill adults; however they do acknowledge that the optimal composition and dose is not established [49]. Their meta-analysed results included 7 level 1 studies and 17 level 2 studies and suggested a potential mortality benefit (regardless of delivery route) of OR 0.86 (95%CI 0.75–0.99, $p = 0.03$). It must be noted that there are specific sub-populations where supplementary micronutrients certainly have a role and their benefit has been proven, such as the burns population [50]. This again supports the potential role that individualized nutrition may have in the critically ill population and may explain why research on heterogeneous populations has failed to provide a definitive answer to date.

6. Guidelines to assist management of nutrition in ICU

There are three widely disseminated guidelines that assist clinicians to manage nutrition in ICU, summarised in Table 1 [16,23,51]. Whilst these guidelines are imperative to the effective delivery of nutrition therapy, they must be considered within a clinician's individual ICU. In deciding which practice guideline to use, clinicians may choose to take elements from several to address their population needs.

7. The future of nutrition for the critically ill

It has become standard practice to provide nutrition to critically ill patients although it is unclear how much nutrition patients actually need to achieve optimum clinical and functional outcomes. Regardless, in the absence of definitive trials, current practice should be to make use of the evidence we do have and optimise the provision of nutrition as much as possible. Estimation of nutrition needs remains difficult and prolonged periods of hypocaloric nutrition should be cautioned until definitive answers are achieved. In our view, clinicians should pay particular attention to the metabolic stages of illness and regularly assess and re-estimate requirements whilst minimising the risk of overfeeding as much as possible. Where available and well understood, indirect calorimetry may be a useful technological aid. Clinicians should remain proactive in promoting delivery of EN to consensus targets by limiting fasting, interruptions and intolerance. The use of PN as an alternative or supplement to EN is becoming more accepted, whilst the use of glutamine remains controversial.

Large-scale research on nutrition for the critically ill is now starting to focus on the impact of nutrition on a patient's whole hospital journey, from ICU to the ward, and their post-hospital outcomes, including quality of life [44,52–54]. Further work should also focus on determining who will benefit most from which delivery mechanism, and at what point to intervene. This may require a tailored, individualised approach to nutrition rather than one-size-fits-all.

Conflict of interest

None.

References

[1] Sobotka L, editor. Basics in clinical nutrition. 4th ed. Czech Republic: Publishing House Galen; 2011.
[2] Jensen GL, Mirtallo J, Compher C, Dhaliwal R, Forbes A, Grijalba RF, et al. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee. JPEN J Parenter Enteral Nutr 2010;34(2):156–9.
[3] Jensen GL, Wheeler D. A new approach to defining and diagnosing malnutrition in adult critical illness. Curr Opin Crit Care 2012;18(2):206–11.
[4] Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Manuel Gomez J, et al. Bioelectrical impedance analysis-part II: utilization in clinical practice. Clin Nutr 2004;23(6):1430–53.
[5] Heyland DK, Dhaliwal R, Jiang X, Day AG. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. Crit Care 2011;15(6):R268.
[6] Tillquist M, Kutsogiannis DJ, Wischmeyer PE, Kummerlen C, Leung R, Stollery D, et al. Bedside ultrasound is a practical and reliable measurement tool for assessing quadriceps muscle layer thickness. JPEN J Parenter Enteral Nutr 2014;38(7):886–90.
[7] Walker RN, Heuberger RA. Predictive equations for energy needs for the critically ill. Respir Care 2009;54(4):509–21.
[8] Frankenfield DC. Obesity. World Rev Nutr Diet 2013;105:144–53.
[9] McClave SA, Kushner R, Van Way 3rd CW, Cave M, DeLegge M, Dibaise J, et al. Nutrition therapy of the severely obese, critically ill patient: summation of conclusions and recommendations. JPEN J Parenter Enter Nutr 2011;35(5 Suppl):88S–96S.
[10] Battezzati A, Vigano R. Indirect calorimetry and nutritional problems in clinical practice. Acta Diabetol 2001;38(1):1–5.
[11] da Rocha EE, Alves VG, da Fonseca RB. Indirect calorimetry: methodology, instruments and clinical application. Curr Opin Clin Nutr Metab Care 2006;9(3):247–56.
[12] McClave SA, Spain DA, Skolnick JL, Lowen CC, Kieber MJ, Wickerham PS, et al. Achievement of steady state optimizes results when performing indirect calorimetry. JPEN J Parenter Enter Nutr 2003;27(1):16–20.
[13] Singer P, Anbar R, Cohen J, Shapiro H, Shalita-Chesner M, Lev S, et al. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. Intensive Care Med 2011;37(4):601–9.
[14] Berger MM, Chiolero RL. Hypocaloric feeding: pros and cons. Curr Opin Crit Care 2007;13(2):180–6.
[15] Dempsey DT, Guenter P, Mullen JL, Fairman R, Crosby LO, Spielman G, et al. Energy expenditure in acute trauma to the head with and without barbiturate therapy. Surg Gynecol Obstet 1985;160(2):128–34.
[16] Kreymann KG, Berger MM, Deutz NE, Hiesmayr M, Jolliet P, Kazandjiev G, et al. ESPEN guidelines on enteral nutrition: intensive care. Clin Nutr 2006;25(2):210–23.
[17] Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R, et al. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. Intensive Care Med 2009;35(10):1728–37.
[18] Elke G, Wang M, Weiler N, Day AG, Heyland DK. Close to recommended caloric and protein intake by enteral nutrition is associated with better clinical outcome of critically ill septic patients: secondary analysis of a large international nutrition database. Crit Care 2014;18(1):R29.
[19] Rice TW, Mogan S, Hays MA, Bernard GR, Jensen GL, Wheeler AP. Randomized trial of initial trophic versus full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure. Crit Care Med 2011;39(5):967–74.
[20] Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lee J, et al. Calorie intake and patient outcomes in severe acute kidney injury: findings from the randomized evaluation of normal vs. augmented level of replacement therapy (RENAL) study trial. Crit Care 2014;18(2):R45.
[21] Doig GS, Heighes PT, Simpson F, Sweetman EA, Davies AR. Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials. Intensive Care Med 2009;35(12):2018–27.
[22] Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. JPEN J Parenter Enter Nutr 2003;27(5):355–73.
[23] Martindale RG, McClave SA, Vanek VW, McCarthy M, Roberts P, Taylor B, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: society of critical care medicine and american society for parenteral and enteral nutrition: executive summary. Crit Care Med 2009;37(5):1757–61.
[24] Cahill NE, Dhaliwal R, Day AG, Jiang X, Heyland DK. Nutrition therapy in the critical care setting: what is "best achievable" practice? an international multicenter observational study. Crit Care Med 2010;38(2):395–401.
[25] Passier RH, Davies AR, Ridley E, McClure J, Murphy D, Scheinkestel CD. Peri-procedural cessation of nutrition in the intensive care unit: opportunities for improvement. Intensive Care Med 2013;39(7):1221–6.
[26] Mentec H, Dupont H, Bocchetti M, Cani P, Ponche F, Bleichner G. Upper digestive intolerance during enteral nutrition in critically ill patients: frequency, risk factors, and complications. Crit Care Med 2001;29(10):1955–61.
[27] Nguyen NQ, Chapman M, Fraser RJ, Bryant LK, Burgstad C, Holloway RH. Prokinetic therapy for feed intolerance in critical illness: one drug or two? Crit Care Med 2007;35(11):2561–7.
[28] Dickerson RN, Mitchell JN, Morgan LM, Maish 3rd GO, Croce MA, Minard G, et al. Disparate response to metoclopramide therapy for gastric feeding intolerance in trauma patients with and without traumatic brain injury. JPEN J Parenter Enter Nutr 2009;33(6):646–55.
[29] Nguyen NQ, Chapman MJ, Fraser RJ, Bryant LK, Holloway RH. Erythromycin is more effective than metoclopramide in the treatment of feed intolerance in critical illness. Crit Care Med 2007;35(2):483–9.
[30] Doig GS, Simpson F, Finfer S, Delaney A, Davies AR, Mitchell I, et al. Effect of evidence-based feeding guidelines on mortality of critically ill adults: a cluster randomized controlled trial. JAMA 2008;300(23):2731–41.
[31] Heyland DK, Murch L, Cahill N, McCall M, Muscedere J, Stelfox HT, et al. Enhanced protein-energy provision via the enteral route feeding protocol in critically ill patients: results of a cluster randomized trial. Crit Care Med 2013;41(12):2743–53.
[32] Martin CM, Doig GS, Heyland DK, Morrison T, Sibbald WJ. Multicentre, cluster-randomized clinical trial of algorithms for critical-care enteral and parenteral therapy (ACCEPT). CMAJ 2004;170(2):197–204.
[33] Sinuff T, Muscedere J, Cook DJ, Dodek PM, Anderson W, Keenan SP, et al. Implementation of clinical practice guidelines for ventilator-associated pneumonia: a multicenter prospective study. Crit Care Med 2013;41(1):15–23.
[34] Davies AR, Morrison SS, Bailey MJ, Bellomo R, Cooper DJ, Doig GS, et al. A multicenter, randomized controlled trial comparing early nasojejunal with nasogastric nutrition in critical illness. Crit Care Med 2012;40(8):2342–8.
[35] Reignier J, Mercier E, Le Gouge A, Boulain T, Desachy A, Bellec F, et al. Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding: a randomized controlled trial. JAMA 2013;309(3):249–56.
[36] Zaloga GP. The myth of the gastric residual volume. Crit Care Med 2005;33(2):449–50.
[37] Moreira TV, McQuiggan M. Methods for the assessment of gastric emptying in critically ill, enterally fed adults. Nutr Clin Pract 2009;24(2):261–73.
[38] Gramlich L, Kichian K, Pinilla J, Rodych NJ, Dhaliwal R, Heyland DK. Does enteral nutrition compared to parenteral nutrition result in better outcomes in critically ill adult patients? A systematic review of the literature. Nutrition 2004;20(10):843–8.
[39] Il'yasova D, Hertz-Picciotto I, Peters U, Berlin JA, Poole C. Choice of exposure scores for categorical regression in meta-analysis: a case study of a common problem. Cancer Causes Control 2005;16(4):383–8.
[40] Simpson F, Doig GS. Parenteral vs. enteral nutrition in the critically ill patient: a meta-analysis of trials using the intention to treat principle. Intensive Care Med 2005;31(1):12–23.
[41] Doig GS, Simpson F, Sweetman EA, Finfer SR, Cooper DJ, Heighes PT, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. JAMA 2013;309(20):2130–8.
[42] Harvey SE, Parrott F, Harrison DA, Bear DE, Segaran E, Beale R, et al. Trial of the route of early nutritional support in critically ill adults. N Engl J Med 2014;371(18):1673–84.
[43] Singer P, Berger MM, Van den Berghe G, Biolo G, Calder P, Forbes A, et al. ESPEN guidelines on parenteral nutrition: intensive care. Clin Nutr 2009;28(4):387–400.
[44] Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med 2011;365(6):506–17.
[45] Investigators N-SS, Finfer S, Chittock DR, Su SY, Blair D, Foster D, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360(13):1283–97.
[46] Heidegger CP, Berger MM, Graf S, Zingg W, Darmon P, Costanza MC, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet 2013;381(9864):385–93.
[47] Heyland D, Muscedere J, Wischmeyer PE, Cook D, Jones G, Albert M, et al. A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med 2013;368(16):1489–97.
[48] Wernerman J. Glutamine supplementation to critically ill patients? Crit Care 2014;18(2):214.
[49] Manzanares W, Dhaliwal R, Jiang X, Murch L, Heyland DK. Antioxidant micronutrients in the critically ill: a systematic review and meta-analysis. Crit Care 2012;16(2):R66.
[50] Rousseau AF, Losser MR, Ichai C, Berger MM. ESPEN endorsed recommendations: nutritional therapy in major burns. Clin Nutr 2013;32(4):497–502.
[51] Heyland DK, Dhaliwal R, Day A, Jain M, Drover J. Validation of the Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients: results of a prospective observational study. Crit Care Med 2004;32(11):2260–6.

[52] Needham DM, Dinglas VD, Bienvenu OJ, Colantuoni E, Wozniak AW, Rice TW, et al. One year outcomes in patients with acute lung injury randomised to initial trophic or full enteral feeding: prospective follow-up of EDEN randomised trial. BMJ 2013;346:f1532.
[53] Casaer MP, Langouche L, Coudyzer W, Vanbeckevoort D, De Dobbelaer B, Guiza FG, et al. Impact of early parenteral nutrition on muscle and adipose tissue compartments during critical illness. Crit Care Med 2013;41(10):2298–309.
[54] Hermans G, Casaer MP, Clerckx B, Guiza F, Vanhullebusch T, Derde S, et al. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. Lancet Respir Med 2013;1(8):621–9.