Endocrine and metabolic considerations in critically ill patients 2

Nutritional support in critical illness and recovery

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This is the second paper in a Series of four papers about endocrine and metabolic considerations in critically ill patients

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An adequate nutritional status is crucial for optimum function of cells and organs, and for wound healing. Options for artificial nutrition have greatly expanded in the past few decades, but have concomitantly shown limitations and potential side-effects. Few rigorous randomised controlled trials (RCTs) have investigated enteral or parenteral nutritional support, and evidence-based clinical guidance is largely restricted to the first week of critical illness. In the early stages of critical illness, whether artificial feeding is better than no feeding intervention has been given little attention in existing RCTs. Expected beneficial effects of various forms of early feeding interventions on rates of morbidity or mortality have generally not been supported by results of recent high-quality RCTs. Thus, whether nutritional interventions early in an intensive care unit (ICU) stay improve outcomes remains unclear. Trials assessing feeding interventions that continue after the first week of critical illness and into the post-ICU and post-hospital settings are clearly needed. Although acute morbidity and mortality will remain important safety parameters in such trials, primary outcomes should perhaps, in view of the adjunctive nature of nutritional intervention in critical illness, be focused on physical function and assessed months or even years after patients are discharged from the ICU. This Series paper is based on results of high-quality RCTs and provides new perspectives on nutritional support during critical illness and recovery.

Introduction

Strategies for enteral nutrition (EN) and parenteral nutrition (PN) have developed over time in intensive care unit (ICU) and post-ICU settings. Concomitantly, the mortality rate in critical illness has steadily decreased in the past few decades, despite increasing age of patients and comorbidities that undoubtedly complicate rehabilitation in survivors. The focus of clinicians and investigators has shifted towards long-term functional outcomes in survivors of prolonged critical illness. Muscle weakness and wasting are likely to contribute to the physical and functional restrictions of patients and, therefore, nutritional interventions have received more attention than they did previously. Finally, the importance of trial quality has been increasingly appreciated. Adequate reporting of patient screening and selection, concealed treatment allocation, masking of outcome assessors, and provision of intention-to-treat analysis of preregistered clinically meaningful endpoints are conditions for a trial to be deemed of high quality.[1,2]

In this Series paper we focus on two clinical notions. First is the overestimation of the potential benefit provided by early feeding interventions in severe illness. Several high-quality RCTs[3–7] have drawn attention to the absence of clinical benefit and potential risks of such interventions in the ICU. Unfortunately, patients who are already severely malnourished and those receiving artificial nutrition before ICU admission are both underrepresented in most of these trials. Second is the underestimation of the incidence and importance of prolonged and unmonitored underfeeding during recovery, especially in the hospital after discharge from the ICU and in the patient's home after hospital discharge. Although RCT data are scarce, patient clinical outcomes and long-term physical function might be improved with intensified nutritional monitoring and support, and active mobilisation during recovery because patients are likely to be more susceptible to nutritional repletion during this time compared with during a severely catabolic state.

We discuss ICU nutrition during a broad time window and focus on pathophysiological perspectives. Additional attention is given to data published in 2014.[3,8–12] A concise overview of the results of recent high-quality RCTs assessing early nutritional interventions in critical illness has recently been published.[13]

In this Series paper, we largely focus on clinical outcome. Interventions tested in well designed RCTs without evidence of clinical benefit were considered ineffective until future trials provide new perspectives. This evidence-based approach results in, unavoidably, rather restrictive recommendations since even in adequately powered trials a beneficial effect might be overlooked. An approach to literature review that attributes more emphasis to observational associations, or pathophysiological deduction, could result in very different conclusions.[14] Finally, clinicians might also prefer not to change their clinical practice until consecutive RCTs consistently reproduce similar results in specific patient subsets. However, such approach could take several years to change clinical practice and might not be forthcoming for interventions for which initial RCT results indicate increased mortality, harm, or low cost-effectiveness.

Development of modern artificial nutritional support

Since 3500 BCE, artificial nutrition has been a last resource for patients unable to feed themselves.[15] Important progress in EN support was made during the

early 1900s, with technical developments—including electronic infusions pumps and small-bore nasogastric tubes—and improved safety of surgical techniques for gastrostomy and jejunostomy.[15] Additionally, commercially available complete EN formulations that provide all known essential macronutrients and micronutrients have been adapted from the purely elemental formulas provided to astronauts in early space flight.[16]

Continuous intravenous administration of nutrients was first described in about 1900. Up to 1000 kcal could be given daily by peripheral infusion of several litres of dextrose (5%) in critically ill patients after complicated abdominal surgery.[17] The first reports of successful total PN (TPN) were published in the late 1960s.[18] Early TPN was complicated by the absence of standardised and safe central venous access techniques for long-term use. Furthermore, the stability, sterility, and safety of the intravenous nutrient preparations were of concern. Finally, for the provision of adequate amounts of energy and aminoacids without volume overloading the patients, solutions with a high osmolality were required. By the early 1970s, reports showed the common prevalence of protein-calorie malnutrition in patients in hospital, stimulating the growth of multidisciplinary clinical services delivering EN and PN.[19]

Since then, complications associated with both EN and PN are better understood and safer practices for administration have been introduced.[14,20] For example, provision of excessive calories and hyperglycaemia were recognised to be common during PN administration in the ICU.[21,22] Complications associated with PN use, particularly in North America, inspired guidelines that suggested avoidance of PN for up to a week in patients who are non-malnourished and acutely ill.[23]

Rationale for artificial nutrition in critical illness

The rationale for administration of macronutrients (fat, protein, and carbohydrate, including essential aminoacids and fatty acids) and essential micronutrients (vitamins, trace elements, and minerals) to critically ill patients builds on several important clinical concepts: first, adequate nutritional status is essential for optimum function of cells and organs, and for wound healing; second, nutritional risk, as defined by available scoring systems on admission to ICU,[24–26] and accumulation of energy debt[27,28] during critical illness, are associated with adverse outcomes in several studies; and third, ICU-related muscle wasting seems to be a major factor in the morbidity of survivors of extended critical illness.[29]

Large observational studies[24] showed a strong association between compromised nutritional status on admission to ICU and increased mortality. For patients admitted to the ICU, no gold standard method exists to assess the nutritional status and nutritional risk that integrates variable objective and subjective parameters.[30] Whether simple clinical anthropometric measures, such as BMI[24,30] with or without recent nutrition-related history (eg, weight loss pattern from baseline and from ideal bodyweight),[25] are as informative as technical assessments of body composition parameters in identification of such risk is yet to be confirmed.[26] Whether feeding interventions improve clinical outcomes in patients with pre-existing severe malnutrition (BMI<17) and those requiring long-term artificial nutrition before ICU admission is also unknown. Most RCTs of nutrition did not specifically focus on such patients. Only the stratification of patients by predicted nutritional risk, present compromised nutritional status, or use of artificial nutrition before ICU admission can help to answer these questions.

Several studies suggest that nutritional support, particularly via the enteral route, does not reach targets for estimated energy needs, especially for patients early in critical illness, resulting in accumulating energy debt. This energy debt has been associated with morbidity and mortality in observational studies.[27,28] However, such analyses do not distinguish cause from consequence and whether patients are easier to feed when they are less ill or vice versa. Additionally, observational analyses of nutritional intake in the ICU are complicated by competing events (such as death in intensive care precluding analysis of time to discharge), time bias (improvements of average energy intake in patients who have a longer stay in an ICU),[31] and selection bias.[32] Of note, studies into protein or aminoacid needs of patients in the ICU and the clinical and metabolic effects of different protein or aminoacid doses are surprisingly scarce, as are studies of different regimens for vitamins and trace elements.[13,33]

Patients surviving acute critical illness often have functional restrictions for several years after ICU discharge.[29] This burden seems to be associated, in part, with skeletal muscle wasting and possibly ICU-acquired muscle weakness rather than with initial organ damage. ICU-acquired muscle weakness is strongly associated with increased mortality up to 1 year after ICU discharge.[34] However, even though weakness is intuitively linked to muscle catabolism and sarcopenia, microscopically, a reduced myofibre diameter does not predict ICU-acquired muscle weakness.[35]

Nutritional support in ICU settings is used to provide energy and essential micronutrients and macronutrients to support cell and organ function, both acutely and in the long term.[13,30] In this Series paper we discuss the effects of several early-feeding interventions from these perspectives (table).

Potential complications of EN and PN

Modern formulations for complete EN and PN consist of all known essential macronutrients and micronutrients.[23,30] EN is the first choice when oral feeding does not work because it is less expensive than PN and physiologically closer to voluntary feeding. Moreover, several additional beneficial effects have been attributed to EN (mostly in animal models), including protection of intestinal wall

	Improvements to acute outcome (survival and duration of ICU or hospital stay); prevention of energy deficit in the ICU	Attenuation of muscle wasting and improvement in patients' long-term functional ability	Patients expected to be at increased nutritional risk according to admission characteristics or underlying pathology
Early initiation of EN	Yes: improved survival with treatment initiated within 24 h of admission to ICU*[36]	Unknown: not assessed	Unknown: cannot be determined because of the very small number of patients assessed*[36]
Enhanced provision of EN	No: neutral in EDEN;[4] increased morbidity and mortality rates in three smaller RCTs†[9,37,38]	No: only assessed in EDEN;[4] no effect of trickle versus full feeding on physical function after 6 months or 12 months[39]	Unknown: low BMI categories: not assessed in the four RCTs;[9,37–39] mostly medical ICU and long ICU stay
Completion of failing EN with PN	No: neutral in supplemental PN trial[40] and early-PN study;[41] slightly increased morbidity with early PN to supplement early EN (EPaNIC);[5] mortality unaffected in all three RCTs.[5,40,41] Yes: reduced incidence of infections with normocaloric EN and PN compared with hypocaloric EN and PN[11]	Neutral: less subjective muscle wasting with early PN in Early-PN trial,[41] but no effect on physical function.[41] No: continuous macroscopic and microscopic muscle wasting despite early PN in EPaNIC;[35,42] similar ADL and 6-min walking distance at hospital discharge.[5] No: more ICU-acquired weakness with early PN to supplement early EN in EPaNIC[35]	Neutral: similar benefit of late PN in EPaNIC[5] preplanned subgroups with very high nutritional risk score (≥5; 863 patients) or at BMI extremes (<25 kg/m² or ≥40 kg/m²; 1989 patients)
Administration of PN when EN is contraindicated	No: more infectious complications and morbidity in EPaNIC[5] and in one mixed ICU and major surgery meta-analysis[43]	Neutral: not assessed in the EPaNIC[5] subgroup with EN contraindication; similar loss of lean body mass with normal PN versus hypocaloric PN in a small RCT[10] assessing patients requiring PN	Unknown: no specific data on patients with a low BMI in the EPaNIC[5] subgroup with a contraindication for EN, but severity of illness was very high and ICU stay long[5]

ADL=activities of daily life. EN=enteral nutrition. EPaNIC=Impact of Early Parenteral Nutrition completing enteral nutrition In Critical illness. ICU=intensive care unit. PN=parenteral nutrition. SPN=supplemental PN. RCT=randomised controlled trial. *Small number of participants and methodological limitations. †Ibrahim and colleagues[37] is a pseudo-randomised clinical trial.

Table: **Effectiveness of early nutritional interventions in the ICU**

barrier function and prevention of bacterial translocation.[44] Administration of EN also promotes splanchnic blood flow; however, this process might provoke a so-called steal phenomenon (blood flow being redirected or stolen from the unfed to the fed portion of the intestine) in low intestinal flow states, with the potential for non-occlusive bowel necrosis.[45] Adequately powered RCTs are needed for the assessment of the safety and effectiveness of different doses of EN given to patients who are haemodynamically compromised (eg, those requiring pressor drugs) because of the low incidence of non-occlusive bowel necrosis (0·1–0·3%).[46] Small observational studies[47] suggest that EN is feasible and safe in patients with unstable haemodynamics.

In an observational study[48] in 16 ICUs in Canada, up to 17% of patients admitted to this ward and placed on mechanical ventilation developed ventilator associated pneumonia, which is often associated with EN and aspiration of gastric content. The incidence of vomiting is greatly increased in patients receiving EN by comparison with those receiving PN, but EN does not result in more airway infections.[12] EN administration of more than 60% energy target is associated with increased incidence of diarrhoea;[49] however, this association has not been confirmed by data from RCTs. Although nasogastric feeding tubes might cause patient discomfort and gastro-oesophageal reflux, the use of surgical or percutaneous gastrostomy or jejunostomy has a risk of surgical site infection, leakage, peritonitis, and bleeding.[50]

The most common consequence of enteral feeding is failure to reach the energy and protein target due to interruptions for diagnostic and airway procedures or surgery, diarrhoea and vomiting, and delayed gastric emptying.[22,51] Moreover, how much of the administered EN is truly absorbed by the patient is difficult to assess.[52] If and when such underfeeding in the ICU compromises clinical outcomes is yet to be established.[32,53]

PN overcomes many of the barriers related to EN, but is less physiological because nutrients are infused directly into the circulation, bypassing the portal vein and liver.[30] Major complications associated with PN (which is typically delivered via a central venous catheter in the ICU) are infections, mechanical issues related to the presence of the catheter, and metabolic disturbances—including refeeding syndrome—related to the infused nutrients.[22,30] In the home setting, bloodstream infections occur significantly more often with peripherally-inserted central venous catheters (PICC) than with the use of tunnelled (eg, Hickman) catheters.[54] Bloodstream infections due to contamination of the PN infusion bag are rare, but might account for some of the infectious burden associated with PN;[55] the use of commercial all-in-one PN bags possibly reduces this risk.[56]

Data from small studies[57,58] suggest that infusion of intravenous fat emulsions, particularly those that are soybean oil-based, might compromise immune defences, particularly when rapidly administered. However, few rigorous trials[33] have compared clinical outcomes of newer lipid emulsions (eg, enriched in fish oil, olive oil, structured lipids, or combinations of these) with the standard soybean-oil based lipid emulsions. Several meta-analyses[59,60] have analysed existing data, and show possible improvement in survival and reduced morbidity with the newer lipid emulsion, but these are inconclusive because of statistical limitations. Findings from a double-blind RCT,[61] comparing clinical and metabolic outcomes in 100 adult patients of mixed sexes in the ICU who needed

PN for at least 7 days, showed no difference between conventional soybean oil-based PN and PN containing an 80% olive oil to 20% soybean oil lipid emulsion.

Many side-effects of PN might be mediated through hyperglycaemia, especially in RCTs done before landmark studies[62] reported on the efficacy of tighter blood glucose control in the ICU than was practiced before 2001. The effect of hyperglycaemia on immune function and organ failure is now well established in clinical trials and in animals.[63–65] However, the widespread implementation of glycaemic control in patients with different nutritional strategies and glucose measurement technology has been less self-evident, and in one study[66] glycaemic control even induced an unexplained increase in mortality. Perhaps the most common consequence of PN is energy intake exceeding the target, or overfeeding, particularly when drugs containing lipids or glucose as a source of hidden energy are co-administered.[30,67]

Interpretation of data from RCTs assessing nutrition in critical illness is complicated by uncertainty of how to define overfeeding and underfeeding. Energy intakes that are now considered to be excessive would have been judged as hypocaloric 20 years ago.[68] Several studies caution against the inability to calculate the estimated energy expenditure that is then used to predict measured energy expenditure (MEE), as determined by metabolic cart.[69] However, even if the use of MEE can avoid overfeeding in some cases, no solid data show that the use of MEE to guide nutritional support improves clinical outcomes.[40,67] Finally, the available metabolic carts might provide different MEE values and technical issues (eg, high inspired oxygen or air leaks) could preclude accurate measurement.[69,70]

Results from RCTs assessing early EN and PN in the ICU

Evidence-based feeding strategies in the ICU

An RCT of adequate power is the only reliable method to estimate and assess the effect on clinically meaningful and unbiased predefined endpoints of one feeding strategy versus another.[1,2] Unfortunately, almost all trials assessing nutritional interventions in the ICU are restricted to the first week of critical illness. Therefore, no reliable recommendations on feeding strategies after day 7 in the ICU can be made.

To feed or not to feed?

Strikingly, no RCT of adequate power has investigated whether artificial nutrition is better than various durations of minimal or no feeding in critical illness. An RCT comparing feeding versus no feeding early in critical illness would fill an important evidence gap. However, observations of people who go on hunger-strike have shown that more than 2 months of fasting is lethal, even in the absence of disease.[71] Although not evidence-based, in view of the myriad factors that can contribute to net micronutrient, energy, protein, and fat depletion in the ICU (eg, nutrient losses due to diarrhoea, fluid drains, or renal replacement therapies), death within 2 months is likely, either directly or indirectly, due to malnutrition or depletion of specific nutrients.

When to start EN if oral feeding is not an option?

If oral feeding is not feasible, clinicians need to consider when artificial nutrition should be started and via which route. Meta-analyses of some RCTs suggest that EN is better than PN[22] and that initiation of EN within 24 h of admission to ICU improves survival by comparison with late EN.[36] However, the total number of patients in these trials and other methodological restrictions caution against overinterpretation of findings.[72]

Benefit of avoidance of early underfeeding with EN in the ICU

Despite the strong association between underfeeding and compromised clinical outcome in several,[27,28] but not all,[8,31] observational studies, the clinical effect of full feeding to estimated energy goals has so far been disappointing. The EDEN RCT[4] (including 1000 patients) compared a 6 day regimen of low-dose trophic tube feeding (providing about 400 kcal/day) with full EN tube feeding (about 1300 kcal/day) in adults with acute lung injury. Low-dose tube feeding promotes gut mucosal integrity while avoiding the metabolic burden of early full EN. By contrast with other ICU studies, patients receiving full feeding easily reached the calculated energy target in 2 days.[4,8,51] Initial low-dose tube feeding provided energy, macronutrients, and micronutrients below requirements so patients in this group were given the full feeding regimen after 6 days.[4] Strikingly, the early restriction of nutrient intake did not affect short-term morbidity or mortality, and long-term functional outcome.[39]

Although early feeding to target energy goals provided no benefit in the EDEN trial,[4] clinical outcomes with such an approach were worse in small RCTs. For example, in a pseudo-randomised study[37] (150 patients), early full enteral feeding (about 500 kcal/day) initiated on the first day of admission to the ICU was compared with low-dose enteral feeding (about 130 kcal/day) and full feeding for 4 days was associated with increased airway infections and extended time on mechanical ventilation. Full feeding resumed after day 4 in both groups.[37] The absence of clinical benefit, but not the increased incidence of infections, with full feeding might be attributed to the low daily intake of calories achieved even in the full-feeding group.

In a trial with 240 critically ill patients, permissive underfeeding (60–70% of calculated target caloric intake) compared with target feeding (90–100% of intake target) was associated with improved hospital mortality and 180 day survival in a 2×2 factorial assessment of hypocaloric feeding and strict glycaemic control.[38] However, interpretation of these findings is complicated

by the small difference in energy intakes between the groups of about 200 kcal per day. In the INTACT trial,[9] involving 78 adult patients with acute lung injury, hospital mortality was increased with intensive delivery strategies for EN (via tube feeds and oral diet as tolerated) versus standard nutritional care. PN use was similar between groups and mean energy intakes were about 1800 kcal per day (intensive EN group) versus about 1200 kcal per day (standard care). The unexpected difference in mortality (40% with EN *vs* 16% with standard care, p=0·02) occurred despite a similar incidence of organ failure in both groups.[9]

In summary, four different RCTs[4,9,37,38] showed that early EN with increased calories did not improve clinical outcome, even if these trials were together underpowered to definitely refute potential benefit or confirm the harm noted (table). On one hand, the number of patients with a high nutritional risk, as defined by BMI, was low in all four RCTs. On the other hand, most patients had non-surgical diagnoses on admission and a prolonged ICU stay; they were thus expected to benefit from early enhanced feeding interventions. Effects of intensive EN (particularly in patients with underlying protein-energy malnutrition given EN later in the ICU course) on body composition, long-term functional outcomes, and quality of life are yet to be investigated.

These studies are consistent with the data from several cluster randomised studies,[73–75] which showed that successful implementation of feeding guidelines results in more patients being fed, earlier initiation of feeding, and, in some studies, achieving closer to energy and protein targets yet with little effect on clinical outcomes.

What to do when EN is insufficient?

If EN does not achieve the energy or protein target due to delayed gastric emptying, the use of prokinetic drugs or other methods to help with tube tip placement for post-pyloric feeding are options. Improvement of energy delivery with post-pyloric feeding by comparison with gastric feeding in patients in the ICU is complicated by delay in placing the small intestinal feeding tube, independent of gastro-intestinal transit. A meta-analysis[76] of 15 RCTs showed a slight (11%) increase in delivered energy and a 25% reduction in relative risk for pneumonia with small-intestinal compared with intragastric feeding, yet hard clinical outcome parameters were unaffected. Data from trials of feeding via the small intestine in patients with proven delayed gastric emptying are eagerly awaited.[50,76] Additionally, acceptance of higher gastric residual volumes or not measuring them, greatly enhanced enteral nutrient delivery in patients in the ICU.[77,78]

When to start PN?

If EN is insufficient despite the interventions mentioned, as is often the case in severe critical illness, initiation of PN could be considered.[5,8,51] However, RCTs[5,40,41] published between 2001 and 2013, which included more than 6000 patients with varying indications for PN, showed that early use of PN does not improve clinical outcomes in critically ill patients. The Australian Early-PN trial[41] with 1372 patients compared PN initiated within hours after ICU admission with pragmatic standard nutritional care. Although mechanical ventilation time was slightly shorter with early PN, and skeletal muscle and fat wasting was less pronounced, major clinical outcome parameters between the groups were unaffected.[41] Nevertheless, on the basis of the clinical results from this RCT,[41] a model-based simulation predicted a reduction in health-care related costs with early PN.[79]

In a randomised trial,[40] supplemental PN initiated on day 4 of admission to the ICU in 153 patients achieving less than 60% of energy target the previous day by EN resulted in a significant reduction in new ICU-acquired infections between days 9 and 28 of admission, compared with 152 patients who continued on EN alone. However, the effect of supplemental PN on infection was not different from the control group when all infections occurring after participants were randomly assigned were taken into account.[80,81] Functional outcomes were unaffected in the Early-PN trial[41] and were not assessed in Heidegger and colleagues[40] supplemental PN trial.

The Impact of Early Parenteral Nutrition completing enteral nutrition In Critical illness (EPaNIC) trial[5] involved 4640 patients who received either early or late PN. The energy target in the EPaNIC trial[5] was higher than in the Early-PN trial[41] and, as anticipated, EN failure was more pronounced than in the supplemental PN trial.[40] Together, a higher target and lower EN doses achieved resulted in a pronounced 7-day difference in energy and protein and aminoacid intake between both groups in the EPaNIC trial.[5] Patients in the early-PN group initially received dextrose (20%). If after 2 days of ICU admission EN was still insufficient, PN was initiated. Patients in the late-PN group received no PN before day 8 after admission to ICU, but were given glucose (5%) for adequate hydration. Until EN was sufficient, parenteral vitamins, trace elements, potassium, and phosphorus were administered in all patients to avoid refeeding syndrome. This method is a unique feature of this trial and might have contributed to decreased morbidity after refeeding on day 8.[82] Thus, differences between groups were probably due to macronutrient delivery.[5,33] Patients in the late-PN group recovered faster, left the ICU earlier, and developed fewer infectious complications than did patients in the early-PN group. Late PN also shortened duration of hospital stay without compromising functionality at hospital discharge.[5] Although bilirubin concentration peaked higher in patients in the late-PN group, use of early PN induced more biliary sludge (mixture of particulate solids precipitated from bile in the gallbladder) and hepatocellular damage.[83] Likewise, enhanced recovery and reduced number of infectious

complications in the late-PN group were accompanied by a large increase in C-reactive protein concentration, questioning the benefit of strategies aimed at attenuating inflammation early in critical illness.[5] Unsurprisingly, late PN was better in a health-economy analysis based on all individual patient invoices.[84] Preplanned subgroup analyses showed that the beneficial effect of late PN could be generalised to patients with extremely high nutritional risk (nutritional risk score ≥5; 863 patients) and 1989 patients in the very low (BMI <25 kg/m²) or very high (≥40 kg/m²) BMI ranges. Additionally, patients admitted after cardiac surgery, compared with other critically ill patients, reacted identically to the randomised intervention.[85] 517 patients with an absolute contraindication to EN were also included in EPaNIC,[5] and the benefit of withholding PN for 7 days was even more pronounced in these individuals. Of note, a meta-analysis[43] of 798 patients after major surgery or admitted to the ICU predicted standard care was better than PN, albeit excessive PN caloric delivery was routine at that time and possibly affected the results. In view of the entry inclusion or exclusion criteria, the results of EPaNIC[5] cannot be generalised to patients who are substantially malnourished (BMI <17) and re-admitted to the ICU before study entry, or patients who are receiving PN at home before admission to the ICU.

In summary, use of PN early in the ICU course does not seem to improve clinical outcomes and, in the EPaNIC trial,[5] even increased morbidity in a time and dose-dependent manner. Questions remain as to whether these results are due to the PN itself (which includes fat emulsion, aminoacids, and carbohydrate in addition to micronutrients) or the higher total energy intake. Indeed, in the EPaNIC[5] and TICACOS[67] trials, the patients receiving PN reached a higher energy intake than patients in the control group and had an increased morbidity. Findings from a small, but well designed, RCT suggested that total energy intake rather than feeding route could be responsible for septic complications.[10] In this study,[10] 50 patients requiring PN after major surgery were randomly assigned to receive nutrition at either 100% or 50% of their calculated energy target. Although the actual energy intake in both groups differed by only 150 kcal daily on average, an important reduction in septic complications and feeding related complications with permissive underfeeding was noted by unblinded outcome assessors.[10] The CALORIES trial,[12] which included 33 ICUs in England, provided crucial results. 2400 patients without contraindications to EN or PN were randomly assigned to receive exclusively one route of feeding for 5 days, beginning within 36 h after admission to the ICU.[12] This study[12] differs from the three previous RCTs[5,10,67] that investigated early PN because control treatment[12] relied on the very low levels of EN intake achieved in EPaNIC;[5] EN for participants was 30% below target energy goals in the supplemental PN trial;[40] and, administration of EN, PN, or no feeding to participants were decided by treating physicians in the Early PN trial.[41] In the CALORIES trial,[12] the control treatment was adequate EN. Clinical outcome was unaffected besides a significantly increased incidence of vomiting with EN and a trend towards increased incidence of raised liver enzyme concentrations with PN. No reduced mortality was noted with PN by contrast with predictions of a meta-analysis.[86] Taken together, these results suggest that the potential harm with early PN reported in the EPaNIC[5] and TICACOS[67] trials might relate to differences in overall macronutrient intake rather than route of nutrient administration.

A small but methodologically sound RCT that assessed normocaloric versus hypocaloric feeding in 100 critically ill patients who were expected to require artificial nutrition (EN, PN, or both) for at least 3 days supported early achievement of a patient's energy target.[11] Mean daily caloric intake of participants was about 20 kcal/kg in the normocaloric group and about 11 kcal/kg in the hypocaloric group. Participants in the normocaloric group received more PN and had more diarrhoea due to increased EN, but had significantly reduced incidence of total infectious complications, even though bloodstream infections and mortality were unaffected.

Why early enhanced feeding does not counter catabolism in the ICU

Early enhanced feeding in the ICU does not promote recovery, let alone improve patient survival. A reason for this failure might be that a low level of nutrients is unlikely to be the primary factor underlying the catabolic response in critical illness (figure).[30] Indeed, gluconeogenesis is not suppressed by exogenous energy administration.[90] As the ongoing mobilisation of endogenous nutrients (figure) is not measured by indirect calorimetry, MEE-guided feeding does not protect against overfeeding or underfeeding. In an EPaNIC sub-study,[42] femoral muscle volume decreased by 1% per day in the early-PN group during their first week in the ICU despite patients being given energy, protein, aminoacids, and insulin. Moreover, early PN apparently induced lipogenesis, an effect noted several decades ago with intensive nutritional support in pilot ICU body composition studies.[91] In 50 critically ill patients requiring PN, normocaloric and hypocaloric PN similarly did not attenuate loss of lean body mass.[10] In the EPaNIC trial,[35] after 1 week in the ICU the diameter of microscopic skeletal muscle myofibre was smaller than in healthy volunteers. Early PN was associated with increased incidence of muscle weakness compared with late PN, whereas expression of mRNAs encoding contractile myofibrillary proteins in muscle were decreased in the patients in the ICU independent of treatment allocation compared with expression in healthy controls.[35]

An estimated 65% of additional aminoacids administered to patients receiving early PN were excreted as urinary nitrogen, which suggests a metabolic resistance to protein anabolism early in critical illness.[92]

Although not experimentally proven, enhanced ureagenesis might contribute to an increased need for renal replacement therapy in patients receiving more aminoacids via PN, as noted in the EPaNIC[5] and Nephroprotective trials.[93] The Nephroprotective trial,[93] which included 474 critically ill patients, assessed parenteral aminoacid supplementation aimed at 2 g/kg per day compared with standard care.

A major driving force behind muscle wasting in the ICU is probably the catabolic hormonal environment, together with decreased protein synthesis from bed rest, thus provision of exogenous nutrients might be futile early during a patient's stay in the ICU (figure).[30] Unfortunately, growth hormone, despite its capacity to induce anabolism and positive nitrogen balances in critical illness,[94] increases ICU mortality rates.[95] However, this trial was done when tight glucose control was not practised and growth hormone-induced hyperglycaemia might have contributed to the adverse effects.[95] Early active mobilisation seems a promising method to promote recovery of physical function in patients in the ICU and might also help with anabolic responses to nutrient provision (figure).[88,96]

Potential benefit of nutrient restriction

As noted, some RCTs that achieve lower overall nutrient intake in the control arm also reported improved clinical outcomes compared with early feeding interventions that were designed to achieve energy goals.[5,9,10,38] Even if not all RCTs were adequately powered, these findings raise the question of how nutrient restriction could be beneficial apart from simply avoiding results of unrecognised overfeeding in a context of continuous endogenous nutrient mobilisation (figure).[97] In critically ill rabbits, parenteral nutrition provoked morphological deterioration in myofibres and hepatocytes[98] attributed to suppression of autophagy, a process of cellular degradation of damaged or dysfunctional components. Likewise, the beneficial effect of nutrient restriction on recovery of contractility after myocardial infarction in mice depends on adequate autophagy activation.[99]

In muscle biopsies obtained after 1 week in the EPaNIC trial,[35] early PN suppressed indexes of autophagy and inadequate autophagy activation was associated with ICU-acquired muscle weakness. Further study is needed to establish the clinical importance of insufficient

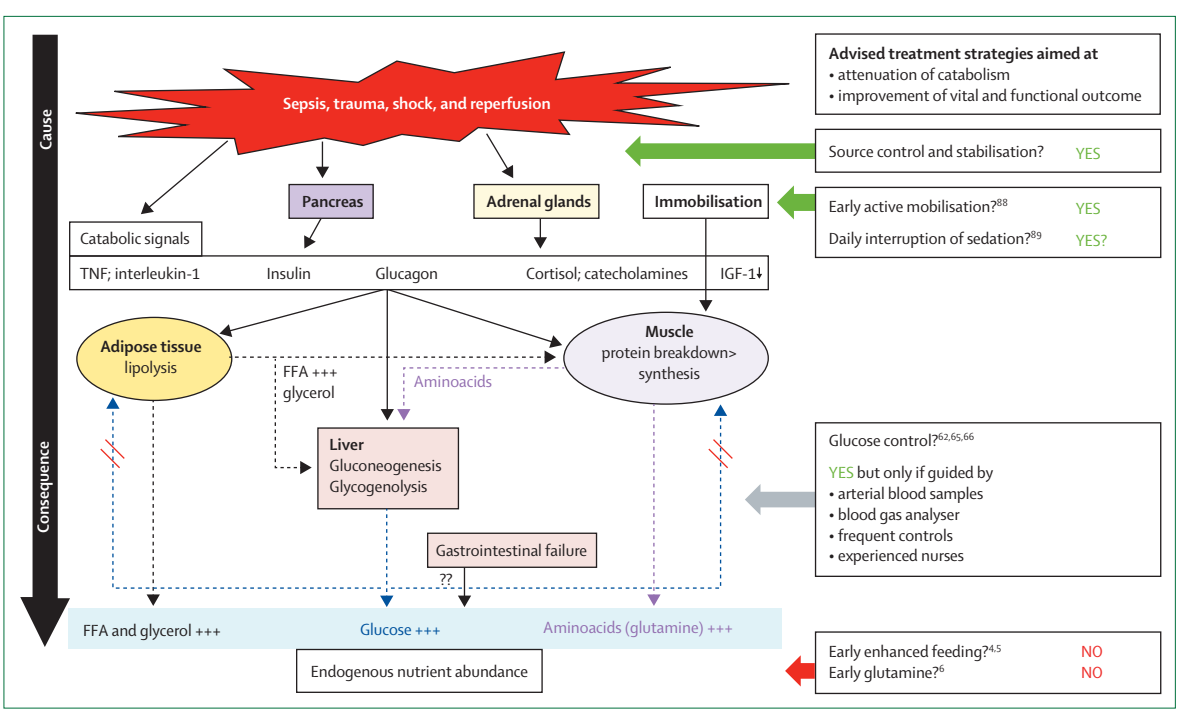

Figure: **Early critical illness: a state of nutrient abundance**
Sepsis, trauma, and shock and reperfusion induce a catabolic state. This state, together with immobilisation, provokes muscle protein breakdown that exceeds synthesis and, in adipose tissue, lipolysis that releases free fatty acids and glycerol into the blood circulation.[87] Together with peripheral insulin resistance and hepatic gluconeogenesis, fuelled by aminoacids and glycerol, this release results in an abundance of circulating endogenous nutrients. The effect of prompt treatment—directed at the underlying disease—on catabolism and clinical outcome is unlikely to be tested for ethical reasons. Early physical activity and mobilisation counteracts muscle-protein wasting and improves functional outcomes in patients.[88] Beneficial effects of daily interruption of sedation, a strategy favouring early spontaneous mobilisation, is not yet established.[89] Avoidance of hyperglycaemia reduces patient morbidity and improves survival.[62,65] However, if adequate glucose control and insulin titration is unavailable, undetected hypoglycaemia can also contribute to adverse clinical outcomes.[66] Catabolism is not mainly caused by anorexia (poor intake of nutrition), but by inflammation and inhibition of anabolic responses coupled with excessive nutrient losses.[33] Thus, unsuppressed catabolism might explain why increased administration of enteral nutrition, parenteral nutrition, or glutamine resulted in no benefit in the EDEN trial,[4] and even a signal of harm in EPaNIC[5] and REDOXs[6] trials, respectively. Purple text and lines show the flux of aminoacids. Blue text and lines show the flux of glucose. Black dotted lines show the flux of FFAs and glycerol. FFA=free fatty acids. IGF=insulin-like growth factor. \\=insulin resistance. ??=unknown interaction. +++=high concentrations.

autophagy in patients admitted to the ICU and to identify other mechanisms that might explain the failure of early feeding interventions.

Glutamine as a component of ICU nutritional therapy

Three issues inspired the study of administration of glutamine, particularly as a component of PN, in the ICU. First, glutamine needs might exceed endogenous synthetic capacity in some patients in the ICU. Substantial evidence suggests that endogenous glutamine production might be insufficient to meet increased glutamine requirements in some individuals during catabolic stress.[100] Indeed, low blood concentrations of glutamine have been associated with worse clinical ICU outcomes; thus, glutamine has been considered as a conditionally essential aminoacid.[101] Second, however, standard PN preparations do not contain this aminoacid because of its poor solubility and heat instability. Commercially available glutamine dipeptides are soluble and heat-stable so can therefore be readily admixed in PN formulations. Third, glutamine supplementation has salutary clinical and metabolic effects in both human and animal studies of critical illness; supplementation of PN with glutamine improves nitrogen balance in patients who are catabolic.[102] Both enteral and parenteral glutamine administration improves intestinal barrier function in animal models of catabolic stress.[103] These mechanisms and others could account for the reduced infectious morbidity and mortality with parenteral or enteral glutamine administration that was noted in some RCTs with critically ill patients.[100]

On the basis of previously mentioned positive results for RCTs of glutamine-supplemented PN, clinical practice guidelines (since 2009)[104] advocated parenteral glutamine use in critically ill patients receiving PN and enteral glutamine after trauma or burn injury. However, some high-quality RCTs[100] have tempered the optimism concerning glutamine. A pragmatic, multicentre, investigator-initiated RCT[105] assessed intravenous glutamine administration (0·28 g/kg per day) as a separate infusion during the entire ICU stay in 413 patients receiving PN or EN. Findings showed decreased ICU, but not 6 month, mortality in per-protocol analysis.[105] Similarly, the pragmatic SIGNET trial[7] (502 patients) did not show intention-to-treat benefits of glutamine administration in critically ill patients who required PN. The low dose (0·2–0·3 g/kg per day) and short duration (≤7 days if PN was stopped before day 7) of glutamine administration were identified as possible causes of glutamine failure in this study. A systematic review[106] of 26 studies (total of 2484 participants) of parenteral glutamine administered in critical illness (primarily as a component of PN) concluded that parenteral glutamine, given in conjunction with nutritional support, was associated with significantly decreased hospital mortality and length of stay, but did not decrease the number of hospital infections or overall mortality. A Cochrane review[107] of enteral and parenteral glutamine supplementation in critical illness or major surgery (53 RCTs, total of 4671 participants) reported some evidence for glutamine supplementation to reduce the rate of hospital infections and days on mechanical ventilation, low-quality evidence for reduced length of hospital stay, and little or no evidence of effect on mortality.

The REDOXS trial[108] is the largest RCT to include glutamine as an intervention; this study used a 2×2 factorial design study with 1223 patients from 40 ICUs in Canada, USA, and Europe. Combined parenteral and enteral administration of high-dose glutamine (0·35 g/kg per day intravenously plus 30 g/day enterally), with or without administration of a daily antioxidant mixture (500 μg selenium parenterally plus enteral administration of selenium [300 μg], zinc [20 mg], vitamin C [1500 mg], β-carotene [10 mg], and vitamin E [500 mg]) versus placebo was given to patients with shock and multiple organ failure. Unfortunately, this intervention was associated with an unexplained increase of in-hospital and 6 month mortality in participants who received glutamine supplementation, with or without supplemental antioxidants.[6] Inclusion of severely ill patients early in the course of shock and acute kidney or liver failure (which were exclusion criteria in most previous studies of glutamine supplementation in the ICU) might account for the substantial increase in mortality risk; furthermore, the enteral plus parenteral dose of glutamine was higher than previously given to patients in the ICU and higher then recommended in nutrition guidelines.[106,109] Initial glutamine concentrations were available in a very small number of patients, precluding interpretation of their effect on the noted outcomes.

Endogenous glutamine release from muscle is not attenuated by glutamine administration in critical illness.[110] Low blood concentrations of glutamine early in critical illness have been speculated to be an adaptive response in some patients. Although this assumption is not evidence-based, if true, correction with exogenous glutamine will be ineffective.[110,111] Relevant to this discussion is the Metaplus trial[3] of enteral nutrition supplemented with glutamine (30 g/1500 mL) plus antioxidants (vitamins C and E, selenium, and zinc) and omega-3 lipids in 300 patients who were stable but critically ill compared with a standard tube feed of high-protein. The supplemented formula did not reduce infectious complications or other hospital rates of morbidity or mortality; yet, unexpectedly, 6 month mortality increased in the prespecified septic subgroup.[3] Taken together, these recent data caution against reliance on the results of meta-analyses of several smaller studies unless confirmed by subsequent larger RCTs of high quality to define approaches to therapy.[112] On the basis of the mixed data so far, future

research should identify the potential role of glutamine-supplemented PN in specific subgroups of critically ill patients after resolution of shock and multiple organ failure.[13] While results of new RCTs are awaited, glutamine supplementation of PN and high-dose supplementation of EN should be avoided in multiple organ failure and shock.

Nutrition during recovery and after the ICU stay

Little information is available about the effect of nutritional support in the post-ICU hospital or home setting after a prolonged stay in the ICU.[33] Although the effect of early and enhanced EN or PN during acute critical illness is unclear so far,[13] these findings cannot be extrapolated to nutritional therapy after day 7 and outside the ICU to the hospital or home-rehab settings. Findings from a Cochrane analysis[113] of dietary advice or complete oral nutritional supplements in a mixed, but largely outpatient, population (3186 patients) at nutritional risk showed no difference in morbidity, mortality, or quality of life. However, the findings did show an increase in weight, muscle mass, and handgrip strength in some of the comparisons.[113] Oral nutritional supplements or tube feeding reduced the incidence of pressure ulcers in 1224 high-risk patients who were admitted to hospital.[114] Enhanced and early oral feeding is also a cornerstone (together with other interventions) of enhanced recovery after surgery strategies, which have shortened patients' stay in hospital.[115] Likewise, multimodal interventions (including nutritional intervention) substantially reduce disability, nursing home admissions, and mortality in patients recovering from hip fracture.[116] Present restricted data preclude identifying the relative contribution of nutritional interventions to the noted clinical benefit to enhanced recovery after surgery strategies, as these are co-administered with resistance training, medical counselling, smoking cessation, and other interventions. However, in sarcopenic outpatients the combination of exercise and oral protein supplements improved functional indexes more than did protein, exercise, or placebo alone.[117] In stable chronic obstructive pulmonary disease, growth hormone administration during rehabilitation improved muscle mass, but not function.[118] All these results together suggest that clinical outcome is more easily modified by nutritional support in patients who are not critically ill than in those who are critically ill and are thus less susceptible to nutrient repletion.

Most patients do not achieve adequate oral intake in the post-ICU hospital setting, which is associated with increased mortality.[119] Meals delivered to hospital patients provide complete nutrition, but are typically only partly consumed due to illness-associated anorexia, gastrointestinal symptoms, and meal interruptions for diagnostic tests or therapeutic procedures.[119,120] In this regard, multimodal and multidisciplinary institution-wide strategies for practice change have been proposed to improve the early identification of patients at risk of malnutrition, the continuous assessment of nutritional adequacy, and eventual action. These strategies now need to be validated in cluster randomised trials.[121]

Search strategy and selection criteria

We searched PubMed with the search term "randomized controlled trials" in combination with: first, "recovery AND nutrition AND ([critical illness] OR sepsis OR [major surgery])"; second, "rehabilitation AND nutrition AND (surgery OR trauma OR sepsis OR critical illness)"; and third, "critical Illness AND nutrition". This Series paper was based mainly (but not exclusively) on the results of these queries, prioritising high-quality studies from 2000–14. Randomised controlled trials were deemed to be of high quality if the patient screening and selection method was adequately reported (via a CONSORT diagram), intention-to-treat evaluation of predefined and publicly registered hard clinical endpoints was provided, and if interventions were allocated in a concealed manner. Double blinding is sometimes unfeasible in nutritional intervention studies; thus, blinding of outcome assessors was considered as reported. Older so-called milestone studies that have informed clinical practice were included, irrespective of the year of publication, to add meaningful perspective to this Series paper.

Conclusions

Prevention or attenuation of early energy and macronutrient deficiencies in critical illness has been a cornerstone in many ICU nutritional strategies. Results of recent RCTs challenged the effectiveness of such interventions and cautioned against possible harm. Whether the dose (full feeding *vs* moderate feeding), route of administration (EN *vs* PN), or a specific macronutrient (eg, higher dose glucose, protein, or glutamine) is responsible for these unexpected findings is unclear. These disappointing results should not be extrapolated beyond the acute phase of critical illness; once acute disease resolves the eventual metabolic burden of early nutritional interventions is probably outweighed by their anabolic benefits. Unfortunately, very little evidence-based guidance is available for feeding interventions after the first week in ICU. Therefore, future studies assessing interventions continuing beyond the most acute critical illness, and assessing outcome months and years after ICU discharge, would be very informative. For the time being, clinicians should consider refraining from high-dose nutritional interventions during the first week in ICU, particularly in patients who are severely ill and with high illness-severity scores, multiple organ failure, and haemodynamic instability. Thus, prudence with respect to administration of conventional doses of energy, glutamine and other aminoacids, carbohydrate, and fat might be important in the first week in ICU when the benefit to risk ratio is not well established, especially for PN. However, in patients

needing artificial nutritional therapy pre-ICU admission, few data are available. The use of micronutrients (eg, vitamins or trace elements) is even less evidence-based, but the consequences of occasional deficiencies (particularly on initiation of artificial nutrition) are well described. Yet the careful monitoring and prevention of prolonged underfeeding in and after ICU discharge merits even more attention in view of the sparse available data. Combined EN and PN, based on gastrointestinal function and comprehensive rehabilitation interventions in the general hospital ward, have barely been explored in ICU survivors and could contribute together to metabolic haemostasis.

Contributors

MPC wrote the first draft of this Series, TRZ edited the draft, and both authors reviewed and approved the final version of this manuscript.

Declaration of interests

We declare no competing interests.

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