REVIEW PAPER OUTLINE

NUTRITION SUPPORT IN CRITICAL ILLNESS AND RECOVERY

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Abstract (Word count 213)

Adequate nutritional status is critical for optimal cell and organ function and wound healing. Options for artificial nutrition therapy have expanded enormously over the last several decades but concomitantly revealed limitations and potential side effects. Relatively few rigorous randomized controlled trials (RCTs) have been conducted using enteral nutrition (EN) and/or parenteral nutrition (PN) support, and evidence-based clinical guidance is largely restricted to the first week of critical illness. Whether artificial feeding is better than no feeding early in critical illness has been little addressed in existing RCTs. The expected beneficial effects on morbidity or mortality with various paradigms of early feeding interventions have generally not been supported by results of recent high quality RCTs. Thus, whether nutritional interventions early in an intensive care unit (ICU) course improve outcome remains unclear. Trials evaluating feeding interventions continuing beyond the first week of critical illness and into the post-ICU and post-hospital setting are clearly needed. While acute morbidity and mortality will remain important safety parameters in such trials, given the adjunctive nature of nutrient intervention in critical illness, primary outcomes should perhaps be focused on physical function, evaluated months to even years after ICU discharge. This review is based on results of high-quality RCTs and provides new perspectives on nutrition support during critical illness and recovery.

Search strategy

We searched Pubmed with the filter "Randomized Controlled Trials" and

with the search terms

1 "recovery AND nutrition AND ((critical illness) OR sepsis OR (Major Surgery))"

2 "rehabilitation AND nutrition AND (surgery OR trauma OR sepsis OR critical illness)"

3 "Critical Illness AND nutrition"

The review was based –though not exclusively- on the results of these queries, prioritizing recent "high quality studies". RCTs were considered "high quality" if the patient screening and selection was adequately reported (via a CONSORT diagram), intention to treat evaluation of predefined and publicly registered hard clinical endpoints was provided and interventions were allocated in a concealed manner. Double blinding is sometimes unfeasible in nutrition intervention studies; thus, blinding of outcome assessors was considered as reported. Older "milestone" studies were included, irrespective of the year of publication, to add meaningful perspective to the review from studies that have informed clinical practice.

In this article we will overview:

The development of modern artificial nutrition support

Administration of nutrition support in the ICU

- **Rationale for artificial nutrition in critical illness**
- **Potential complications of EN and PN**
- **Results of recent trials evaluating early EN and PN in ICU**

Understanding the failure of early enhanced feeding to counter catabolism in ICU

Understanding the possible benefit of nutrient restriction

Glutamine as a component of ICU nutrition therapy

Nutrition during recovery after ICU discharge

General conclusion

Introduction

Strategies for enteral nutrition (EN) and parenteral nutrition (PN) have evolved in both intensive care unit (ICU) and post-ICU settings. Concomitantly, the mortality rate in critical illness has steadily declined over the last several decades, despite increasing age and comorbidities that undoubtedly complicate rehabilitation in ICU-survivors. The focus of clinicians and investigators has shifted towards longer-term functional outcomes of survivors of prolonged critical illness. As muscle weakness and wasting, likely contribute to the physical and functional limitations experienced by these patients, nutritional interventions have received more attention. Finally the importance of methodological trial quality has been increasingly appreciated. Adequate reporting of patient screening and selection, concealed treatment allocation, blinding of outcome assessors and provision of intention to treat analysis of preregistered clinically meaningful endpoints are conditions for a trial to be considered "high quality".(1;2)

In this review article, we will particularly focus on two clinical paradigms:

1. The overestimation of the potential benefit provoked by early feeding interventions in severe illness. Today, several recent high quality RCTs have drawn attention to the absence of clinical benefit and potential risks of such interventions in in the ICU. Unfortunately, patients with pre-existing severe malnutrition and receiving artificial nutrition prior to ICU admission are underrepresented in most of these RCTs.

2. The underestimation of the incidence and importance of prolonged and undetected underfeeding during recovery, particularly after ICU-discharge and in the post-hospital home setting. Although RCT data remain limited, intensified nutritional monitoring and support, coupled with active mobilization, during recovery, when patients are likely to be avid for nutritional repletion compared to during the severely catabolic state, may improve clinical outcome and long-term physical function.

A concise overview of the results of recent high quality RCTs evaluating early nutritional interventions in critical illness has been recently published.(3) In this paper, we will discuss ICU nutrition over a broader time window and with focus on pathophysiologic perspectives. Special attention will be given to data published very recently.(4-9)

The focus of the review will be largely on clinical outcome. Interventions that have been tested in well-designed RCTs without evidence of clinical benefit were considered "ineffective" until future trials provide new

perspectives. This evidence-based approach results unavoidably in rather restrictive recommendations, while, even in adequately powered trials, the risk of overlooking a beneficial effect exists. An approach attributing more weight to observational associations, or pathophysiological deduction may result in very different conclusions.(10) Finally, clinicians may also prefer not to change their clinical practice until consecutive RCTs consistently reproduce similar results in specific patient subsets. This, however, may take several years and may not be forthcoming for interventions for which initial RCT results indicate increased mortality, harm or low cost-effectiveness.

The development of modern artificial nutrition support

Artificial nutrition as last resource in patients unable to feed themselves has been described since ancient times as reviewed elsewhere.(11) Important progress in EN support was made during the last century with technical developments, including electronic infusions pumps, small-bore nasogastric tubes and safer surgical techniques for gastrostomy and jejunostomy.(11) Also commercially available complete EN formulations, that provide all known essential macro- and micronutrients, have evolved from the purely elemental formulas provided to astronauts in early space flight.(12)

Continuous intravenous administration of nutrients was first described around 1900. Up to 1000 kcal could be administered daily by peripheral infusion of several liters of dextrose 5% in critically ill patients after complicated abdominal surgery.(13) The first reports of successful total parenteral nutrition (TPN) were published in the late 1960's.(14) Early TPN was complicated by lack of standardized and safe central venous access techniques for prolonged use. Also the stability, sterility and safety of the intravenous nutrient preparations was a concern. Finally provision of adequate amounts of energy and amino acids without volume overloading the patient required solutions with a high osmolality. By the early 1970's, reports on the common prevalence of protein-calorie malnutrition in hospital patients were published, stimulating the growth of multidisciplinary clinical services delivering EN and PN.(15)

Over time, complications associated with both EN and PN became better understood and safer practices for administration were introduced.(10;16) For example, it was recognized that provision of excessive amounts of calories and hyperglycemia were common during PN-administration in ICU.(17;18) Particularly in North

America, complications associated with PN use inspired guidelines suggesting avoiding PN for up to a week in non-malnourished acutely ill patients.(19)

Artificial nutrition in the ICU

Rationale for artificial nutrition in critical illness

The rationale for administration of macronutrients (fat, protein, carbohydrate, including essential amino acids and fatty acids) and essential micronutrients (vitamins, trace elements and minerals) to critically ill patients builds on several important clinical concepts: 1) adequate nutritional status is essential for optimal cell and organ function and wound healing; 2) nutritional risk as defined by available scoring systems upon ICU admission and accumulation of energy debt during critical illness is associated with adverse outcomes in several studies; and 3) ICU-related muscle wasting appears a major factor in the morbidity of survivors of prolonged critical illness.(20)

Large observational studies established a strong relationship between compromised nutritional status upon ICU admission and increased mortality.(21) In ICU patients, there is currently no gold standard method to assess nutritional status and nutritional risk integrating variable objective and subjective parameters.(21) Whether simple clinical anthropometric measures, such as body mass index (BMI; kg/m^2)(22) with or without recent nutrition-related history (e.g. weight loss pattern from baseline and from ideal body weight (IBW))(23) are as informative as technical evaluations of body composition parameters in identifying such risk remains to be confirmed.(24) Moreover, it is currently unknown if feeding interventions improve clinical outcomes in patients with preexisting severe malnutrition (BMI<17) and those requiring long-term artificial nutrition prior to ICU admission. Recent nutrition RCTs didn't specifically focus on such patients. Only stratifying patients by predicted nutritional risk, current compromised nutritional status or pre-ICU artificial nutrition utilization can answer these questions.

Several studies indicate that nutrition support, particularly via the enteral route, fails to reach targets for estimated energy requirements, particularly early in critical illness, resulting in accumulating energy debt. This has been associated with morbidity and mortality in observational studies.(25;26) Such analyses, however do not distinguish cause from consequence; whether patients are easier to feed when they are less ill or vice versa. In addition, observational analyses of nutritional intake in the ICU are complicated by competing events (such as death in ICU precluding analysis of time to ICU-discharge), time bias (average energy intake improving in patients who have a longer ICU stay)(27) and selection bias.(28) Of note, studies on protein/amino acid

requirements in the ICU and the clinical and metabolic impact of different protein/amino acid doses remain surprisingly limited, as do studies on different regimens of vitamins and trace elements.(3;29)

Patients surviving acute critical illness often experience functional restrictions for several years after ICU discharge.(20) This post-ICU-burden appears to be related, in part, to skeletal muscle wasting and possibly ICU-acquired-muscle-weakness (ICU-AW) rather than to initial organ damage. ICU-AW is strongly associated with increased mortality up to one year after ICU discharge.(30) However, even though weakness is intuitively linked to muscle catabolism and sarcopenia, microscopically, a reduced myofiber diameter does not predict ICU-AW.(31)

In summary, the aim of nutrition support in ICU settings is to provide energy and essential micro- and macronutrients in support of cell and organ function, both acutely and longer-term.(3;21) We will discuss the impact of several early feeding interventions from these perspectives. (Table 1)

Table 1

Effectiveness of early nutrition interventions in the ICU setting: Results of some recent randomized controlled trials

Therapeutic Target / **Nutrition Intervention**	**Improving acute outcome (survival and length of stay)-- prevention of energy deficit in ICU**	**Attenuating muscle wasting and improving long term function**	**Protecting patients expected to be at increased nutritional risk according to admission characteristics or underlying pathology**
Early initiation of EN	Yes: improved survival when initiated within 24 hours(32) *	Not assessed	Impossible to determine: given the very small number of patients evaluated (32)
Enhanced provision of EN	No: -Neutral in EDEN(33) -Increased morbidity and/or mortality in 3 smaller RCTs(5;34;35)**	No: Only in EDEN: no effect of trickle versus full feeding on physical function after 6 & 12 months.(36)	Low BMI categories: - not evaluated in the 4 RCTs - mostly medical ICU and long-ICU stay
Completing failing EN with PN	*No:* *- Neutral in SPN trial (37) and Early-PN study(38)* *- Modestly increased morbidity with early PN to supplement early EN (EPaNIC)(39)* *- Mortality unaffected in all 3 RCTs* *-Reduced incidence of infections with normocaloric EN+PN as compared to hypocaloric EN+PN?(7)*	Neutral: Less subjective muscle wasting with Early-PN in Early-PN trial but no effect on physical function(38) No: -Ongoing macroscopic and microscopic muscle wasting despite Early PN in EPaNIC(31;40) - Similar ADL and 6-MWD at hospital discharge(39) - More ICU-acquired weakness with early PN to supplement early EN	Similar benefit of Late PN in EPaNIC(39) preplanned subgroups: -with very high NRS (≥ 5, N = 863) -with extreme BMI (<25 or ≥ 40, N = 1989)

		in EPaNIC(31)	
Administration of PN when EN is contra indicated	No: more infectious complications and morbidity in EPaNIC and in one mixed ICU and major surgery meta-analysis (39;41)	Not assessed in the EPaNIC(39) sub-group with EN contra indication *Similar loss of lean body mass with normo- versus hypocaloric PN in a small RCT evaluating patients requiring PN (6)*	No specific data on patients with a low BMI in the EPaNIC subgroup with a contra-indication for EN but severity of illness was very high and ICU stay long(39)

* small number and methodological limitations ** Ref 32 is a pseudo-randomized clinical trial
ADL = Activities of daily live, 6-MWD six minutes walking distance, NRS =Nutritional Risk Score, BMI = Body Mass Index

Potential complications of EN and PN

Modern complete EN and PN formulations contain all known essential macro- and micronutrients.(19;21) EN is intuitively the first choice when oral feeding fails. 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), among them the protection of intestinal wall barrier function and prevention of bacterial translocation.(42) Administration of EN also promotes splanchnic blood flow; this however, may provoke a "steal" phenomenon in low intestinal flow states, with the potential for non-occlusive bowel necrosis(NOBN).(43) Evaluation of the safety and impact of different amounts of EN administered to hemodynamically compromised patients (e.g. those requiring pressor agents) will require adequately powered RCTs, given the low incidence of NOBN (1-3/1000).(44) Small observational studies suggest that EN in the hemodynamically unstable patient is feasible and safe.(45)

Ventilator associated pneumonia occurs in up to 17 % of patients in ICU and is often associated with EN and aspiration of gastric content.(46) The incidence of vomiting is indeed highly increased in patients receiving EN as compared to PN but doesn't result in more airway infections.(9) EN administration higher than 60% is associated with increased incidence of diarrhea.(47) However, the latter relationship has not been confirmed in RCTs. While nasogastric feeding tubes might induce patient discomfort and gastro-esophageal reflux, surgical or percutaneous gastrostomy or jejunostomy has a risk of surgical site infection, leakage, peritonitis and bleeding.(48)

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, diarrhea and vomiting and delayed gastric emptying.(18;49) Moreover, it is difficult to assess how much of the administered EN is truly absorbed by the patient.(50) If and when such underfeeding in ICU compromises clinical outcome remains to be established.(28;51)

PN overcomes many of the barriers related to EN, but is less physiologic as nutrients are infused directly into the circulation, bypassing the portal vein and liver.(21) The major complications associated with PN (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.(18;21) In the home-PN setting, the occurrence of bloodstream infections is significantly higher when peripherally-inserted central venous catheters (PICC) are used compared to tunneled (e.g. Hickman) catheters.(52) Blood stream infections due to rare contamination of the PN infusion bag may also explain some of the infectious burden with PN(53) but the use of commercial all-in-one PN bags possibly reduces this risk. (54)

Earlier data from small studies suggested that infusion of intravenous fat emulsions, particularly those that are soybean oil-based may compromise immune defenses, particularly when administered rapidly.(55;56) However, few rigorous trials comparing clinical outcomes with newer lipid emulsions (e.g. enriched in fish oil, olive oil, structured lipids or their combinations) compared to the standard soybean-oil based lipid emulsions have been performed to date, although several meta-analyses have recently been published on existing data.(29;57;58) A recent double-blind RCT comparing clinical and metabolic outcomes in 100 adult mixed ICU patients deemed to require PN for at least 7 days found no difference with conventional soybean oil-based PN as compared to PN containing an 80% olive oil/20% soybean oil lipid emulsion.(59)

Many side effects of PN might be mediated through hyperglycemia, particularly in RCTs performed before the publication of recent landmark papers on the efficacy of tighter blood glucose control in the ICU than was practiced for several decades.(18;60) The effect of hyperglycemia on immune function and organ failure is now well established in human and animal experiments.(61-63) The widespread implementation of glycemic control in patients with different nutrition strategies and glucose measurement technology, however, has been less self-evident and in one study even induced an unexplained increase of mortality.(64) Perhaps the most common consequence of PN is energy intake exceeding the target, or "overfeeding", particularly when medication containing lipid or glucose as a source of "hidden" energy are co-administered.(21;65)

The interpretation of all RCTs' evaluating nutrition in critical illness is complicated by uncertainty how to define over- and underfeeding. Energy intakes considered excessive today would have been judged hypocaloric twenty years ago.(66) Several studies caution against the inability of calculated estimated energy expenditure to predict measured energy expenditure(MEE), as determined by metabolic cart.(67) However, even if MEE may avoid overfeeding in some cases, there is no solid data demonstrating that using MEE to guide nutrition support

improves clinical outcome. (37;65) Finally, the available metabolic carts may provide different MEE values and technical issues (e.g. high inspired oxygen, air leaks) may preclude accurate measurement.(67;68)

Results from RCTs evaluating early EN and PN in ICU

The only reliable method to estimate the effect of one versus another feeding strategy is a RCT of adequate power to assess the effect on clinically meaningful and unbiased *pre-hoc* endpoints.(1;2) Unfortunately, almost all RCTs evaluating nutritional interventions in ICU are restricted to the first week of critical illness. Hereby no reliable recommendations on feeding strategies beyond day 7 in ICU can be made at this time.

To feed or not to feed?

Strikingly, an adequate RCT answering the question whether artificial nutrition is superior to various durations of minimal or no feeding in critical illness has not been performed. An RCT comparing feeding versus no feeding early in critical illness would fill an important gap in the evidence. Observations in hunger-strikers however revealed that more than two months of fasting is lethal, even in the absence of disease.(69) Although not evidence based, given the myriad of factors that may contribute to net micronutrient, energy, protein and fat depletion in the ICU (e.g. lack of food intake, nutrient losses via diarrhea, drains, renal replacement therapies, etc.), it is likely that death directly or indirectly due to malnutrition/depletion of specific nutrients could occur sooner.

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

Thus, the first question is *when* artificial nutrition should be started and a second question is via which route. Meta-analyses of relatively old RCTs suggest that EN is superior to PN(18) and that initiation of EN within 24 hours improves survival as compared to late EN.(32) The total number of patients included in these trials and other methodological limitations, however, caution against over-interpretation.(70)

Benefit of avoiding early underfeeding with EN in ICU?

Despite the strong association between underfeeding and compromised clinical outcome in several(25;26) but not all (4;27) of the observational studies, the clinical impact of full feeding to estimated energy goals has been disappointing to date. The EDEN RCT (N=1000) compared a 6-day regimen of low-dose "trophic" tube feeding (providing approximately 400/kcal/day) versus feeding at ~1300 kcal/day in adults with acute lung injury.(33) The rationale for low-dose tube feeding is promoting gut mucosal integrity while avoiding the metabolic burden of early full EN. In contrast to other ICU studies, patients in the EDEN full feeding arm reached the calculated

energy target easily within two days.(4;33;49) The initial low-dose tube feeding thus provided energy, macronutrients and micronutrients below requirements and was followed after 6 days by the full feeding regimen.(33) Strikingly, the early restriction of nutrient intake did not affect morbidity or mortality nor long-term functional outcome.(36)

While early feeding to target energy goals provoked no benefit in EDEN, clinical outcomes with such an approach were worse in small RCTs. In a pseudo-randomized study (N=150), early full enteral feeding (~500 kcal/day) begun on the first ICU day, as compared to low-dose enteral feeding for 4 days ~130 kcal/day) was associated with increased airway infections and prolonged mechanical ventilation time.(34) The absence of benefit (but not the increased incidence of infections) with "full" feeding might be explained by the low daily intake achieved even in the "full" feeding arm.

In a trial with 240 subjects, "permissive underfeeding" (~1100 kcal/day) was associated with improved hospital and 180-day survival in a 2 by 2 factorial evaluation of hypocaloric feeding and strict glycemic control.(35) Interpretation is complicated by the small difference in energy intakes between the groups(±200 kcal/day). In the recent INTACT trial in 78 adult patients with acute lung injury, increased hospital mortality with intensive delivery strategies for EN (via tube feeds and oral diet as tolerated) versus standard nutritional care occurred. PN use was similar between groups and mean energy intakes were ~1800 versus ~1200 kcal/d .(5) The unexpected mortality difference (40% versus 16% p=0.02) was not explained by differences in organ function.(5)

In summary, in four different RCTs early increased EN did not improve clinical outcome, even if they were together underpowered to definitely refute potential benefit or confirm the observed harm.(Table 1). The number of patients with a high nutritional risk as defined by BMI was low in all four studies. On the other hand, most patients had non-surgical admission diagnoses and a prolonged ICU stay and were thus expected to benefit from early enhanced feeding interventions. The impact of intensive EN, particularly in patients with underlying protein-energy malnutrition and given later in the ICU course, on body composition, long term functional outcomes and quality of live remains to be investigated.

These studies outlined above are consistent with the data from several cluster randomized studies, which show that successful implementation of feeding guidelines results in more patients being fed, feeding initiated earlier and, in some studies closer to energy and protein target, yet with little effect on clinical outcomes.(71-73)

What to do when EN remains insufficient?

If enteral nutrition does not achieve the energy and or protein target due to delayed gastric emptying, use of prokinetic agents or other methods to facilitate post-pyloric feeding tube tip placement are options. Improving energy delivery through post-pyloric feeding as compared to gastric feeding in unselected ICU patients is complicated among others by the delay until the small intestinal feeding tube is in place. Recent meta- analysis of 15 RCTs' revealed a modest (11%) increase in delivered energy and 25% reduction in relative risk for pneumonia, yet clinical hard outcome parameters were unaffected. Trials of small intestinal feeding in patients with proven delayed gastric emptying are eagerly awaited.(48;74) Also accepting higher gastric residual volumes or simply not measuring them, significantly enhanced enteral nutrient delivery in ICU patients.(75;76)

When to start PN?

If despite the above interventions EN remains insufficient as is often the case in severe critical illness, initiation of PN could be considered.(4;39;49) However recent RCTs, including more than 6000 patients with varying indication for PN, each showed that early use of PN does not improve clinical outcomes in critically ill patients. The Australian Early-PN trial in 1372 patients compared PN initiated within hours after ICU admission versus pragmatic standard nutritional care. Although mechanical ventilation time was slightly shorter with early-PN and skeletal muscle and fat wasting less pronounced, major clinical outcome parameters between the groups were unaffected.(38) Nevertheless, based on the RCTs' clinical results, a model-based simulation predicted a reduction of health care related costs with Early-PN.(77)

Supplemental PN (SPN) initiated on ICU day 4 in 153 patients achieving less than 60% of energy target the previous day by EN, resulted in a significant reduction in new hospital infections between days 9 and 28 of admission compared to 152 patients continued on EN alone.(37) However, the impact of supplemental PN on infection was not different from control subjects when all infections occurring after randomization were taken into account.(78;79) Functional outcomes were unaffected in the Early-PN trial and not assessed in the SPN trial.(37;38)

In the EPaNIC trial (n=4640), the energy target was higher than in the Early-PN trial and EN failure (as anticipated) was more pronounced than in the SPN trial.(39) This resulted in a pronounced 7-day difference in energy and protein/amino acid intake between both groups. Patients in the Early-PN arm received initially dextrose 20%. If after 2 days EN remained insufficient, PN was initiated. The Late-PN patients received no PN before day 8 but glucose 5% for adequate hydration. In all subjects, parenteral vitamins, trace elements, potassium and phosphorus were administered until EN was sufficient, in order to avoid refeeding syndrome. This is a unique feature of this trial and may have contributed to decreased morbidity upon refeeding on day 8.(80)

Thus, differences between groups were likely due to macronutrient delivery.(29;39) Late-PN patients recovered faster, left ICU earlier and developed less infectious complications. Late-PN also shortened hospital stay without compromising functionality at hospital discharge.(39) Although bilirubin peaked higher in the Late-PN patients, Early-PN induced more sludge and hepatocellular damage.(81) Likewise, enhanced recovery and reduced infectious complications in the Late-PN arm were accompanied by higher rise in C-reactive protein, questioning strategies aimed at attenuating inflammation early in critical illness.(39) Not surprisingly, as withholding an expensive intervention prevented complications, Late-PN was superior in a health economy analysis based on all individual patient invoices.(82) Preplanned subgroup analyses revealed that the beneficial effect of late-PN could be generalized to patients with extremely high nutritional risk (NRS $\geq$ 5, N=863) and patients in the very low (<25 kg/m²) or very high BMI ($\geq$ 40 kg:m²) range (N=1989). Also patients admitted after cardiac surgery as compared to other critically ill patients reacted identically to the randomized intervention.(83) Patients with an absolute contra-indication to EN were also included in EPaNIC (n=517) and the benefit of withholding PN for 7 days was even more pronounced in these individuals.(39) Of note, a meta-analysis in 798 patients after major surgery or in the ICU published in 2001, predicted superiority of standard care over PN, albeit excessive PN caloric delivery was routine at that time and possibly influenced the results.(41) Given the entry inclusion/exclusion criteria, the results of EPaNIC cannot be generalized to significantly malnourished patients (BMI<17), those who were readmitted to the ICU prior to study entry, or patients receiving home-PN prior to ICU admission.(39)

Summarizing the above trials, use of PN early in the ICU course does not appear to improve clinical outcomes and, in the EPaNIC trial, increased morbidity in a time and dose-dependent manner. Questions remain as to whether these results are due to the PN per se (which includes fat emulsion, amino acids, and carbohydrate in addition to micronutrients) or the higher total energy intake. Indeed, in the EPaNIC and TICACOS trials, the patients receiving PN reached a higher energy intake than control patients and experienced more morbidity.(39;65) A recent small, but well-designed, RCT suggests that total energy intake rather than feeding route may be responsible for septic complications.(6) In this study, 50 patients requiring PN after major surgery were randomized to receive either 100% or 50% of calculated energy target. Although the actual energy intake in both groups differed only by 150 kcal daily on average, an important reduction in septic complications and feeding related complications with permissive underfeeding was observed by un-blinded outcome assessors.(6) The recently published CALORIES trial, performed in 33 English ICUs provides crucial results. A total of 2400 patients without contra-indications to EN or PN were randomized to receive exclusively one route of feeding for

5 days beginning within 36 hours after admission to the ICU.(9) The study differs from the 3 previous RCTs on early PN: 1) Randomization to late PN in EPaNIC meant relying on the very low levels of EN intake achieved(39); 2) in SPN, subjects remaining 30% below target energy goals for 4 days were randomized (37); while in the Early PN trial, physician discretion dictated EN, PN or no feeding (38). In CALORIES "no PN" meant "adequate EN".(9) Clinical outcome was unaffected besides a significantly increased incidence of vomiting with EN and a trend towards increased incidence of elevated liver enzymes with PN. There was no reduced mortality with PN in contrast to what was predicted by earlier meta-analysis.(84) Taken together, these results suggest that the potential harm with early PN observed in EPaNIC and TICACOS trials may relate to differences in overall macronutrient intake rather than route of nutrient administration.

One recent small, but methodologically sound, RCT evaluating "normocaloric" versus hypocaloric feeding in 100 critically ill patients expected to require artificial nutrition (EN, PN or both) for at least 3 days pleads in favor of achieving energy target early.(7) The mean daily caloric intake was ~20 kcal/kg in the normocaloric group and ~11 kcal/kg in the hypocaloric group. Subjects in the normocaloric group received more PN and developed more diarrhea due to increased EN but exhibited significantly reduced incidence of total infectious complications even though blood stream infections and mortality were unaffected.

Understanding the failure of early enhanced feeding to counter catabolism in ICU (figure 1)

Legend with figure 1: Early Critical Illness: a state of nutrient abundance

Sepsis, shock/reperfusion and trauma induce a catabolic state. Together with immobilization, this provokes muscle protein breakdown that exceeds synthesis and, in adipose tissue, lipolysis releasing free fatty acids and glycerol into the circulation.(85) Together with hepatic gluconeogenesis, fueled by certain amino acids and glycerol, and peripheral insulin resistance, this results in an abundance of circulating endogenous nutrients.

The effect of prompt therapy -directed at the underlying disease- on catabolism and on clinical outcome is unlikely to be tested for ethical reasons.

Early physical activity and mobilization counteracts muscle protein wasting and improves functional outcome.(86) The beneficial effect of daily interruption of sedation, a strategy favoring early spontaneous mobilization is not yet definitely established.(87)

Avoiding hyperglycemia reduces morbidity and improves survival.(60;63) However, if adequate glucose control and insulin titration is unavailable, undetected hypoglycemia may contribute to adverse clinical outcomes.(64)

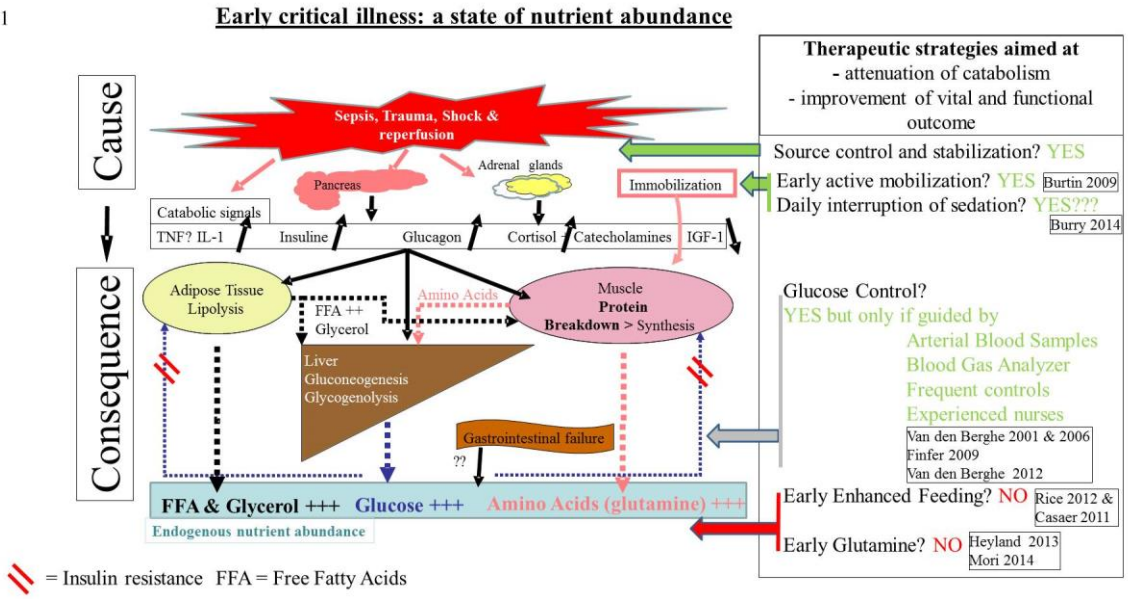
Catabolism is primarily not caused by anorexia (lack of intake) but by inflammation and inhibition of anabolic responses, coupled with excessive nutrient losses.(29) Thus provision of exogenous macronutrients is likely an incomplete therapy. This might explain why aiming at increased administration of EN, PN or glutamine resulted in no benefit in the EDEN trial and even a signal of harm in EPaNIC and REDOXs trials respectively.(33;39;88) As discussed above, early enhanced feeding in the ICU fails to promote recovery, let alone improve survival. One reason for this failure might be that lack of nutrients is unlikely to be the primary factor underlying the catabolic response in critical illness.(Figure 1)(21) Indeed gluconeogenesis is not suppressed by exogenous energy administration.(89) As the ongoing mobilization of endogenous nutrients (figure 1) is not measured by indirect calorimetry, MEE-guided feeding doesn't protect against over- or underfeeding. In an EPaNIC sub-study, femoral muscle volume decreased by 1% per day over the first ICU-week in the Early-PN group despite delivery of energy, protein/amino acids and insulin.(40) Moreover, Early-PN apparently induced lipogenesis, an effect noted several decades ago with intensive nutrition support in pilot ICU body composition studies.(90) In 50 critically ill patients requiring PN, normocaloric as compared to hypocaloric PN likewise did not attenuate loss of lean body mass.(6) In EPaNIC, microscopic skeletal muscle myofiber diameter was reduced after one week in ICU, as compared to healthy volunteers.(31) Early-PN was associated with increased incidence of muscle weakness compared to Late-PN, while mRNAs encoding contractile myofibrillary proteins in muscle were decreased in the ICU patients-independent of treatment allocation- compared to expression in healthy controls.(31)

The appearance of approximately 65% of additional amino acid administered in the Early-PN patients as urinary nitrogen suggest a metabolic resistance to protein anabolism early in critical illness.(91) Although not experimentally proven, enhanced ureagenesis may contribute to increased need for renal replacement therapy in patients receiving more amino acids via PN as observed in the EPaNIC trial and in the Nephroprotective trial.(39;92) The latter trial evaluated parenteral amino acid supplementation aimed at 2 gram/kg/day compared to standard care in 474 critically ill patients. *(protocol_at_www.Evidencebased.net/NephroProtect)*

A major driving force behind muscle wasting in the ICU is likely the catabolic hormonal environment, coupled with decreased protein synthesis due to bed rest, thus provision of exogenous nutrients might be futile early in ICU.(figure 1)(21) Unfortunately growth hormone, despite its capacity to induce anabolism and positive nitrogen balances in critical illness(93), was shown to increase ICU-mortality, although this trial was conducted in an era when tight glucose control was not practiced and growth hormone-induced hyperglycemia may have contributed to the adverse effects.(94) Early active mobilization appears to be a promising method to promote recovery of

physical function in ICU-patients and may also facilitate anabolic responses to nutrient provision.(86;95)(Figure 1)

Figure 1



Understanding the potential benefit of nutrient restriction.

As noted, some RCTs that achieve lower overall nutrient intake in the control arm report improved clinical outcomes compared to early feeding designed to achieve energy goals.(5;6;35;39) Acknowledging that not all were adequately powered, this raises the provocative question of how nutrient restriction could be beneficial apart from simply avoiding unrecognized overfeeding consequences in a context of ongoing endogenous nutrient mobilization.(96)(figure 1) In severely burned rabbits, parenteral nutrition provoked morphological deterioration in myofibers and hepatocytes(97) explained by 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.(98)

In muscle biopsies obtained after one week in EPaNIC, Early-PN suppressed indexes of autophagy and inadequate autophagy activation was associated with ICU-AW.(31) Further study is required to determine the clinical importance of insufficient autophagy in ICU patients and to identify other mechanisms that may explain failure of early feeding interventions.

Glutamine as a component of ICU nutrition therapy

3 paradigms inspired the study of administration of glutamine, particularly as a component of PN, in the ICU:

1° Absence in conventional PN: Standard PN preparations do not contain the L-amino acid, for reasons of chemical stability. Nevertheless commercially available glutamine dipeptides are soluble and heat-stable.

2° Glutamine needs may exceed endogenous synthetic capacity in some ICU patients: Substantial evidence from animal and human models suggests that endogenous glutamine production might be insufficient to meet increased glutamine requirements in some individuals during catabolic stress. Low glutamine levels in blood have been associated with worse clinical ICU outcomes; thus, glutamine has been considered a "conditionally essential" amino acid.(99)

3° Salutary effects in human and animal studies: Supplementation of PN with glutamine improves nitrogen balance in catabolic patients. (100) Both enteral and parenteral glutamine administration improves intestinal barrier function in animal models of catabolic stress.(101) These and other mechanisms may explain reduced infectious morbidity and mortality with parenteral or enteral glutamine administration seen in some RCTs performed in critically ill patients.(102) Based on the earlier salutary results for RCTs of glutamine-supplemented PN, clinical practice guidelines (from 2009) advocate parenteral glutamine use in critically ill patients receiving PN and enteral glutamine after trauma or burn injury.(103) However, recent high quality RCTs have tempered the optimism concerning glutamine.(102) A pragmatic multicenter, investigator initiated RCT evaluating intravenous glutamine administration 0.28 g/kg/d as a separate infusion during the entire ICU stay in 413 patients receiving PN or EN showed decreased ICU, but not 6-month mortality, in per-protocol analysis.(104) Likewise the pragmatic SIGNET trial (N=502) failed to show intent-to-treat benefits of glutamine administration in critically ill patients requiring PN.(105) The low dose (0.2–0.3 g/kg/day) and short duration of glutamine administration were identified as possible causes of glutamine failure in this study. A recent systematic review of 26 studies (n=2,484) of parenteral glutamine administered in critical illness (primarily as a component of PN) concluded that parenteral glutamine, given in conjunction with nutrition support, is associated with significantly decreased hospital mortality and length of stay, but did not decrease hospital infections or overall mortality. (106) A recent Cochrane review of enteral and parenteral glutamine supplementation in critical illness or major surgery (53 RCTs, 4671 participants) found moderate evidence for glutamine supplementation to reduce the hospital infection rate and days on mechanical ventilation, low quality evidence for reduced length of hospital stay and little or no effect on mortality.(107)

The largest RCT including glutamine as an intervention is the REDOXS trial, a 2x2 factorial design study conducted in 1223 patients from 40 ICUs in Canada, the USA and Europe.(108) Combined parenteral and enteral administration of high-dose glutamine (0.35 g/kg/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), beta-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 in in-hospital and 6-month mortality in subjects whom received glutamine supplementation, with or without supplemental antioxidants.(88) 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) may have provoked the significant increase in mortality risk; further the enteral plus parenteral dose of glutamine was higher than previously administered in ICU patients and then recommended in nutrition guidelines. (106;109) Initial glutamine levels were available in a very limited number of patients precluding interpretation of their impact on the observed effects.

Endogenous glutamine release from muscle is not attenuated by glutamine administration in critical illness.(111) It has been speculated that low blood glutamine levels early in critical illness may be an adaptive response in some patients; although this is not evidence-based, if true, correction with exogenous glutamine will be ineffective.(110;111) Relevant to this discussion is the recent Metaplus trial 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 stable critically ill patients compared to a standard high-protein tube feed. The supplemented formula did not reduce infectious complications or other hospital morbidity or mortality, yet unexpectedly increased 6-month mortality in the pre-specified septic subgroup.(8) Taken together, these recent data caution against relying on the results of meta-analyses of multiple smaller studies unless confirmed by subsequent larger high quality RCTs to define approaches to therapy.(112) Based on the mixed data to date, 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.(3)While awaiting results of new RCTs, glutamine supplementation of PN and high-dose supplementation of EN should be avoided in multiple organ failure and/or shock.

Nutrition during recovery and after the *ICU stay*

Little information is available on the impact of nutrition support in the post-ICU hospital or home setting after a prolonged ICU stay.(29) Although the effect of early and enhanced EN and/or PN during acute critical illness is unclear to date(3), it is not possible to extrapolate these findings to nutrition therapy beyond day 7 and outside the ICU to the floor or home-rehab setting. A Cochrane analysis (2011) of dietary advice and/or complete oral nutrition supplements(ONS) in a mixed but largely outpatient population (N=3186) at nutritional risk revealed no difference in morbidity, mortality or quality of life but an increase in weight, muscle mass and handgrip

strength in some of the comparisons.(113) ONS or tube feeding reduced the incidence of pressure ulcers in 1224 high risk hospitalized patients.(114) Enhanced and early oral feeding is also a cornerstone (together with other interventions) of Enhanced Recovery After Surgery (ERAS) strategies, which have shown to shorten hospital stay.(115) Likewise, multimodal interventions, including nutritional intervention, in patients recovering from hip fracture reduce disability, nursing home admissions and mortality in a dramatic way.(116) Current limited data preclude identifying the relative contribution of nutritional interventions to the observed clinical benefit to ERAS strategies, as these are co-administered with resistance training, medical counseling, smoking cessation and much more. However, in sarcopenic outpatients, combined exercise and oral protein supplements improved functional indexes more than only protein or exercise or placebo alone.(116) In stable chronic obstructive pulmonary disease, growth hormone administration during rehabilitation improved muscle mass but not function(117) All these results together, suggest that clinical outcome is more easily modified by nutrition support in patients who are not critically ill and thus avid for nutrient repletion.

Most patients do not achieve adequate oral intake on the post-ICU hospital ward and this is associated with increased mortality.(118) Meals delivered to hospital patients provide complete nutrition but are typically only partially consumed by hospitalized patients, due to illness-associated anorexia, gastrointestinal symptoms and meals interruptions for diagnostic tests or therapeutic procedures.(118;119) In this regard, multimodal and multidisciplinary institution-wide practice change strategies have been proposed to improve the early identification of patients at risk for malnutrition, the continuous evaluation of nutrition adequacy and eventual action. These strategies should now be validated in cluster randomized trials.(120)

General conclusion

The prevention or attenuation of early energy and macronutrient deficiencies in critical illness has been a cornerstone in many ICU nutrition strategies. Results of recent RCTs challenged the effectiveness of such interventions and cautioned against possible harm. It is unclear today whether the dose (full feeding versus moderate feeding), route of administration (EN versus PN) or a specific macronutrient (e.g. higher dose glucose, protein or glutamine) is responsible for these unexpected findings. These disappointing results should not be extrapolated beyond the acute phase of critical illness, probably, once acute disease resolves, the eventual metabolic burden of early nutritional interventions is outweighed by their anabolic benefits. Unfortunately, very limited evidence-based guidance is available for feeding beyond the first week in ICU. Therefore, future studies evaluating 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 given during the first ICU-week, particularly in severely ill patients with high illness severity scores and multiple organ failure and/or hemodynamic instability. Thus, prudence with regard to administration of conventional doses of energy, glutamine and other amino acids, carbohydrate and fat may be important in the first ICU-week, when the benefit/risk ratio is not well established, especially for PN. However, in patients requiring artificial nutrition therapy pre-ICU admission, there are little data. The use of micronutrients (e.g. vitamins, trace elements) is even less evidence based, but the consequences of occasional deficiencies particularly upon 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 given the available limited 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 hemostasis.

Author Contributions and conflict of interest

MPC wrote the first draft of this review, TRZ edited the drafts and both authors finally reviewed and approved the manuscript. MPC and TRZ have no conflict of interest.

Both authors have seen and approved for this revised version.

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