

Intensive Care Nutrition and Postintensive Care Recovery

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KEYWORDS

- Critical illness • Feeding • Parenteral nutrition • Enteral nutrition
- ICU-acquired weakness • Catabolism • Recovery • Autophagy

KEY POINTS

- Critically ill patients are at risk of developing intensive care unit (ICU)-acquired weakness, which aggravates outcome and may persist even years after ICU admission.
- Early full-dose artificial nutrition does not benefit critically ill patients and may even be harmful, especially early parenteral nutrition.
- The ideal timing of artificial nutrition for critically ill patients as well as the optimal dose and composition remain unclear.
- There is no benefit of adding specialized “immunonutrients” to the feeding mixture of critically ill patients, and glutamine administration may be harmful.
- The harmful impact of early parenteral nutrition seems explained by the inability to inhibit muscle wasting and by feeding-induced suppression of autophagy.

INTRODUCTION

Intensive care unit (ICU)-acquired weakness is a devastating complication of critical illness. With time in ICU, the incidence increases and its presence is associated with increased short-term and long-term mortality.^{1,2} In ICU survivors, ICU-acquired weakness often does not recover completely, even years after ICU admission.³ Persistent ICU-acquired weakness is considered to be part of the postintensive care

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syndrome, which encompasses a spectrum of persistent physical, mental, and cognitive impairment seen in survivors of critical illness, especially after prolonged and/or severe critical illnesses.⁴ The mechanisms underlying ICU-acquired weakness are complex and involve structural and functional alterations in both muscles and nerves.⁵ Attributed myofibers show signs of atrophy, which may be triggered by inflammation, immobilization, endocrine and metabolic alterations, impaired microcirculation, denervation, and certain drugs.⁵ Apart from that, relative starvation may also play a role. Indeed, a considerable number of patients have a nutritional deficit on ICU admission and/or cannot receive normal feeding. In healthy volunteers, prolonged underfeeding mimics the severe muscle atrophy as typically observed in prolonged critically ill patients. In these otherwise healthy people, this condition obviously can be reversed by giving nutrition.⁶

TO FEED OR NOT TO FEED?

Several observational studies have associated the accumulation of a caloric and/or protein deficit in critically ill patients with an increased risk of ICU-acquired weakness and mortality. Hence, for a long time, early full nutritional support has been recommended for critically ill patients.⁷ However, whether the relationship between feeding deprivation and ICU-acquired weakness and decreased survival is causal or not cannot be deduced from observational studies. Indeed, because tolerance of feeding, especially of enteral nutrition (EN), is affected by the severity of illness, the association of enhanced feeding with improved outcome could be explained by a better feeding tolerance in less sick patients.⁸ Establishing a causal relationship can only be done by a randomized controlled trial (RCT). Because of the long-lasting dogma of starvation harming critically ill patients and the resultant ethical constraints, RCTs randomizing patients to artificial feeding or no feeding have not been performed. Instead, in the last years, several large RCTs have investigated the impact of different doses (and routes) of artificial feeding.^{9–17} These studies have substantially changed the insights in the effects of nutritional support in critical illness (**Table 1**). Indeed, recent RCTs have not confirmed the hypothesized benefit of early, enhanced artificial feeding of critically ill patients and several trials have indicated potential harm.^{9,10,15} This article reviews the evidence obtained from these studies, the underlying mechanisms potentially explaining the results, and the remaining questions.

IS EARLY SUPPLEMENTATION OF INSUFFICIENT ENTERAL NUTRITION WITH PARENTERAL NUTRITION BENEFICIAL?

In patients unable to eat by mouth, early EN has been recommended over early parenteral nutrition (PN).¹⁸ Often, however, full EN is not tolerated or even contraindicated. Hence, the question arises when to initiate or associate PN to ensure the intended nutritional target. Because of the lack of adequately powered RCTs, clinical practices have varied widely. Proponents of early PN have referred to the avoidance of a caloric and protein deficit by this approach, whereas opponents referred to the potentially increased risk of complications, especially infectious complications.⁸

In the last years, several RCTs have investigated whether early supplementation of insufficient or failing EN with PN offers clinical benefit.^{9–13} In contrast to the expectations, none of these RCTs showed benefit on the primary endpoint and the 2 largest RCTs, the Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients (EPaNIC) and Early versus Parenteral Nutrition in the Pediatric Intensive Care Unit (PEPaNIC) trial, demonstrated harm.^{9–13,19} Indeed, as compared with withholding PN until 1 week after ICU admission, early supplementation of insufficient EN

Intervention	Impact	References
Early vs late supplementation of insufficient EN with PN	No benefit of early supplemental PN; increased morbidity in the 2 largest RCTs	9–13
Early EN vs isocaloric early PN	No benefit of early EN (more bowel ischemia in patients with severe shock)	14,15
Early full vs hypocaloric EN	No benefit of full feeding, also not on the long-term	16,17,22–25,27,29,30
Early amino acid supplements vs regular amino acid dose	No benefit of early amino acid supplements, increased ureagenesis	13,39
Indirect calorimetry–based feeding vs formula-based feeding	No benefit of indirect calorimetry	43
Immunonutrients vs no immunonutrients	No benefit of immunonutrients; possible harm by glutamine	44–50

Abbreviation: EN, enteral nutrition; PN, parenteral nutrition; RCT, randomized controlled trial.

with PN resulted in a prolonged ICU dependency in both critically ill children and adults, with a prolongation of organ failure and a prolonged dependency on mechanical ventilation.^{9,10} Harm occurred in all studied subgroups, including subgroups with the highest perceived risk of underfeeding, being critically ill neonates, patients with the highest nutritional risk score, and patients unable to receive early EN.^{9,10} In a prospectively planned subanalysis of the EPaNIC study including mostly long-stay ICU patients, ICU-acquired weakness was increased by early supplemental PN, and recovery from ICU-acquired weakness was impaired.²⁰ Importantly, in the EPaNIC and PEPaNIC trial, withholding PN was only applied to the macronutrients (carbohydrates, lipids, and amino acids). All patients received a sufficient supply of micronutrients (vitamins and trace elements) throughout ICU stay, also during the acute phase of illness, to prevent refeeding syndrome. In the EPaNIC study, blood glucose was maintained in the normal range for all patients (80–110 mg/dL).⁹ In the PEPaNIC study, the blood glucose target was center specific, going from a strict, age-adjusted normal target range in one center to more liberal blood glucose control in other centers (up to 180 mg/dL).¹⁰ The results of this study did not reveal a center difference.

IS EARLY ENTERAL NUTRITION BETTER THAN EARLY PARENTERAL NUTRITION?

Theoretically, the potential harm of early supplemental PN could be explained by a different feeding dose and/or by a different feeding route. Indeed, traditionally, EN has been recommended over PN because of its lower degree of invasiveness and potentially less complications, its lower cost, and its potential trophic effects on the intestinal mucosa.⁸ Hence, harm by early supplemental PN observed in the EPaNIC and PEPaNIC trials could theoretically be explained by the fact that more nutrition was delivered through the parenteral route. However, until recently, EN and PN were not directly compared in large RCTs. Hence, the perceived superiority of EN largely originated from observational studies, which may be confounded by indication, because sicker patients tend to have a lower tolerance to EN.⁸ In addition, PN may cause severe hyperglycemia, and prevention of this condition with insulin therapy

may have rendered PN safer in current ICU practice.²¹ Two recent RCTs have investigated whether administering early EN affects outcome as compared with early PN in current practice.^{14,15} The CALORIES trial found no major difference between 1 week of early EN and an isocaloric amount of PN in a general ICU population.¹⁴ However, more patients in the early EN group had signs of gastrointestinal intolerance (vomiting), whereas there was a nonsignificant trend toward more liver dysfunction in the early PN group. The NUTRIREA-2 study randomized patients with severe shock to receive early PN or early EN. In the early PN group, PN was administered for at least 72 hours and could be switched to EN after resolution of shock.¹⁵ In this sick patient population, early EN, at a nearly isocaloric dose as early PN, induced significant clinical harm, with a 4-fold increased incidence of bowel ischemia and acute colonic pseudoobstruction. Hence, these studies show that in current ICU practice and during a short time period, EN is not superior to PN and may even be harmful when administered to patients with severe shock.^{14,15} Importantly, because the intervention window in both studies was restricted to maximum 1 week, the outcome effects of longer administration of EN versus PN in patients with less severe illness remain unclear.

IS EARLY FULL ENTERAL NUTRITION BENEFICIAL?

In recent years, several large RCTs have investigated whether early full EN provides benefit as compared with hypocaloric EN in the acute phase.^{16,17,22–24} Relatively small single-center RCTs have shown mixed results, with some studies being neutral,^{22,24} one study showing less infectious complications,²⁵ and another RCT suggesting increased mortality by early enhanced EN.²³ Two larger multicenter RCTs did not find a benefit of early EN as compared with hypocaloric feeding.^{16,17} The EDEN trial randomized patients with acute lung injury to full or hypocaloric EN during the first week in ICU, with restriction of all macronutrients in the hypocaloric arm.¹⁶ There was no difference in short-term clinical endpoints, and after 1 year, physical function and mortality were unaffected.^{16,26,27} Likewise, the PermiT trial did not find a benefit of early enhanced EN in patients with an expected ICU stay of minimum 3 days.¹⁷ In the latter trial, the intervention window was extended to 2 weeks, but both groups were isonitrogenous, meaning that macronutrient restriction only applied to carbohydrates and lipids. A secondary analysis of the PermiT trial also revealed no benefit of full EN in patients with the highest nutritional risk.²⁸ In line with this, a recent meta-analysis did not find benefit of early enhanced EN as compared with hypocaloric EN.²⁹ A second meta-analysis, which included RCTs in which a different dose of EN was achieved, also revealed no difference in mortality, but associated a lower caloric intake with a lower risk of bloodstream infections and incident renal replacement therapy.³⁰ Hence, combining these results with the results from the early EN versus PN trials suggests that the harm observed by early supplemental PN may be explained by the higher feeding dose rather than by the different route. This is confirmed by a secondary analysis of the EPaNIC study, which suggested a negative dose-dependent impact of early feeding on outcome.³¹ In line with this, a recent meta-analysis of EN versus PN trials only found benefit by EN in the subset of RCTs in which a lower dose of nutrition was provided through EN.³² These findings may also explain why 2 cluster RCTs did not find benefit of a protocol that aims to enhance nutritional intake.^{33,34} One small RCT even found greater in-hospital mortality with such a protocol.³⁵

DO HIGH DOSES OF AMINO ACIDS PROVIDE BENEFIT?

Critics have argued that the absence of a beneficial impact of early supplemental PN is explained by the relatively low amount of administered amino acids.³⁶ In the early

PN group of the EPaNIC study, patients on average received amino acid dosage of 0.8 g/kg/d, whereas some observational studies have suggested beneficial effects with amino acid dosage of 1.2 to 1.5 g/kg/d.^{9,37} However, recent RCTs have not confirmed this hypothesis.³⁸ In the Nephro-Protective trial, administration of amino acid supplements did not lead to clinical benefit, with patients receiving on average amino acid dosage of 1.75 g/kg/d in the intervention group, as compared with 0.75 g/kg/d in the control group.³⁹ Instead, the higher amino acid dose increased ureagenesis, with a trend toward an increased need for renal replacement therapy.³⁹ Also, in 3 RCTs of early supplemental PN, ureagenesis increased by an increase in amino acid dose in the early PN group.^{9,10,13,40,41} The increased ureagenesis observed with amino acid supplements, which was disproportional to changes in plasma creatinine, likely points to catabolism of the supplementary provided amino acids. The stimulatory effect of amino acids on glucagon could mediate at least part of such an effect.⁴² Indeed, during critical illness, elevated plasma glucagon has shown to drive amino-acid breakdown in the liver, a phenomenon that is further aggravated by infusing amino acids, which further increased plasma glucagon but did not protect against muscle wasting.⁴²

IS INDIRECT CALORIMETRY–BASED FEEDING SUPERIOR TO CALCULATION-BASED FEEDING?

A second point of critique that has been suggested to explain the negative impact of the recent feeding RCTs is the absence of indirect calorimetry guidance in most studies. Indeed, for most studies, the energy target in the intervention group was calculated by a fixed formula and hence not “individualized”. Several observational studies have shown that the calculated energy target may substantially differ from the measured energy expenditure by indirect calorimetry.³⁷ Some experts have suggested that indirect calorimetry–based feeding is superior to formula-based feeding.³⁷ However, only 1 single-center RCT directly compared the impact of indirect calorimetry–based feeding with formula-based feeding.⁴³ The study found no significant impact on the primary endpoint (in-hospital mortality) but more infections and a prolongation of mechanical ventilation in the indirect calorimetry group.⁴³ Other recent RCTs also do not support the use of indirect calorimetry. Indeed, in 3 of the multicenter RCTs comparing early versus late supplemental PN, indirect calorimetry was used at least in a subgroup of patients.^{10,12,13} In the PEPaNIC study, which showed harm by early supplemental PN, indirect calorimetry was a standard practice in 1 of the 3 participating centers. Because the trial found harm without any center difference, this RCT does not support the critique that feeding guided by indirect calorimetry benefits critically ill patients.¹⁰

IS THERE A ROLE OF ADDING IMMUNONUTRIENTS?

Certain nutrients may have immune-modulating properties, including glutamine, arginine, omega-3 fatty acids, gamma-linolenic acid, L-carnitine, taurine, and pharmacologic doses of selected vitamins (vitamin C, vitamin E, and beta-carotene) and trace elements (selenium, zinc, copper, and manganese).⁸ Despite promising pilot studies, large RCTs have been disappointing. Indeed, large multicenter RCTs have been neutral or even demonstrated potential harm by adding selected immunonutrients.^{44–50} The largest RCT, the REDOXs study, found in a 2 × 2 factorial trial increased mortality by glutamine administration to critically ill patients with multiple organ failure, whereas high doses of micronutrients (selenium, zinc, beta-carotene, vitamin E, and vitamin C) did not provide any benefit.⁴⁵ As in the RCTs on amino

acid supplements, glutamine supplements also increased ureagenesis.⁴⁵ Besides the REDOXS trial, the METAPLUS study also did not show a beneficial impact of immunonutrient-enhanced feeding, with a trend toward increased mortality.⁴⁶ In this study, the intervention group received supplements of glutamine, omega-3 fatty acids, vitamin C, vitamin E, selenium, and zinc. Hence, glutamine may have contributed to the potential harm observed in this study. However, other presumed immunonutrients may be harmful as well, because the OMEGA trial also found harm by immunonutrition not containing any glutamine.⁴⁸ In the latter study, patients with acute lung injury were randomized to immunonutrient-enhanced enteral feeding or isocaloric control feeding. The study found an increased dependency on ICU care in the immunonutrient group, with fewer ventilator-free days and more days with organ failure. There was also a trend toward increased mortality. As the intervention group received supplements of several presumed immunonutrients (omega-3 fatty acids, gamma-linolenic acid, vitamin C, vitamin E, beta-carotene, zinc, selenium, L-carnitine, and taurine), but no glutamine, the culprit compound remains unclear.⁴⁸ With regard to selenium, large RCTs specifically investigating high-dose selenium administration to critically ill patients have been neutral, as was a recent meta-analysis.^{44,49,51} In summary, current evidence does not support administration of these immunonutrients to critically ill patients, and some of these compounds may even be harmful, as shown for glutamine.

MECHANISMS EXPLAINING THE ABSENCE OF A BENEFIT OF EARLY FULL FEEDING

Several mechanisms may explain why early enhanced feeding, especially early supplemental PN, has failed to benefit patients and may even increase ICU-acquired weakness and ICU dependency: the inability to suppress muscle catabolism and feeding-induced suppression of autophagy (Fig. 1). Several RCTs have shown that increased amino acid supplementation in the acute phase of critical illness increased ureagenesis.^{13,39–41,45} In the EPaNIC study, over 2 weeks, almost two-third of the supplementary amino acids provided by early PN were net wasted in urea.⁴⁰ This suggests that the supplementary amino acids are broken down to urea instead of incorporated into proteins. In line with this, detailed mechanistic studies have shown that early supplemental PN did not counteract microscopic or macroscopic muscle wasting.^{20,52} On the other hand, in a prospective subanalysis of the EPaNIC study mainly including long-stay ICU patients, ICU-acquired weakness was increased by early supplemental PN, which cannot be explained by the equal loss of myofibers.²⁰ Detailed mechanistic studies put forward feeding-induced suppression of autophagy as a potential mechanism.^{20,53} Indeed, autophagy is an important housekeeping process that selectively removes damaged organelles and intracellular microorganisms.⁵⁴ In normal physiology, the process is activated by a variety of stress signals but is strongly inhibited by nutrients. Over recent years, increasing evidence has implicated autophagy as essential recovery process necessary to survive critical insults.⁵⁴ Both animal and human studies have shown that early supplemental PN indeed suppresses autophagy in muscle and vital organs of critically ill patients and animals.^{20,53} The degree of autophagy suppression even correlated with the severity of organ failure and ICU-acquired weakness.^{20,55} Of note, of the 3 macronutrients, in particular amino acids are known to be powerful suppressors of autophagy.⁵⁴ Although speculative, this may explain why secondary analyses of the EPaNIC and PEPaNIC studies statistically attributed the clinical harm of early PN to the supplementary administered amino acids and not to the extra glucose or lipids.^{31,41}

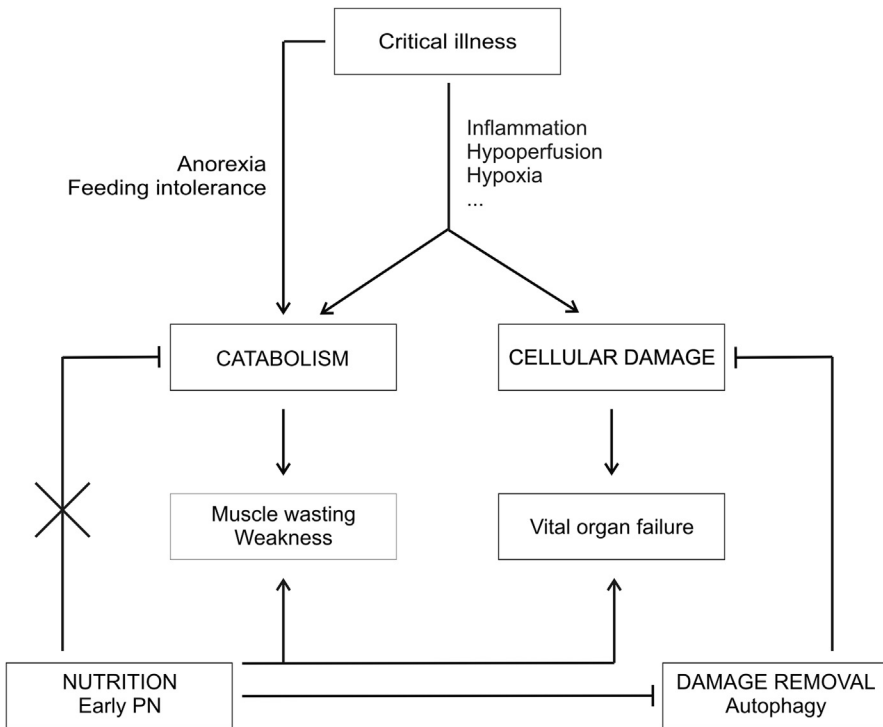


Fig. 1. Potential mechanisms explaining why early full nutrition has failed to benefit critically ill patients. In critical illness, numerous stressors may induce cellular damage and catabolism, which leads to muscle wasting and ICU-acquired weakness, as well as vital organ failure. Critical illness–induced anorexia and feeding intolerance may further aggravate catabolism. Early nutritional support, in particular early supplemental parenteral nutrition (PN), which used to be administered in an effort to reduce muscle catabolism and ICU-acquired weakness, seemed inefficient to do so and actually aggravated ICU-acquired weakness and prolonged organ failure. Mechanistically, the harmful impact of early PN seems explained by feeding-induced suppression of autophagy, a crucial damage removal pathway.

NUTRITION DURING RECOVERY AND AFTER INTENSIVE CARE UNIT STAY

Limited information is available regarding the nutritional management of prolonged critically ill patients and patients recovering from critical illnesses. All large RCTs have been performed in the acute phase of critical illness, so the neutral or negative results cannot be extrapolated beyond the first week or beyond ICU and hospital stay. Also in the post-ICU setting, underfeeding is common and associated with increased mortality.⁵⁶ However, a recent Cochrane review, involving 28,619 patients from 244 RCTs, did not identify a beneficial impact of nutritional support on mortality or serious adverse events in hospitalized adults at nutritional risk, although the studied population was heterogeneous and most included RCTs were at high risk of bias.⁵⁷ On the other hand, enhanced and early oral feeding has been a cornerstone of enhanced recovery after surgery programs, which have lowered postoperative morbidity and hospital length of stay.^{58,59} However, the relative contribution of enhancing nutritional intake to the observed benefit remains unclear, because these programs typically involve multimodal management including, among others, early mobilization, medical counseling, and smoking cessation.⁵⁹

SUMMARY

Despite the association of a nutritional deficit with poor outcome, recent large RCTs have not shown benefit of early full nutritional support. Two large studies showed harm by early supplementation of insufficient EN with PN with more infections, more ICU-acquired weakness, and a prolongation of organ failure, hereby prolonging ICU dependency. Likewise, early full EN delivered to patients with severe shock and glutamine administration to patients with multiple organ failure was found to be harmful. The harmful effect of early full nutritional support may at least partially be explained by feeding-induced suppression of autophagy. The ideal timing, dose, and composition of artificial nutrition remain unclear.

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