Meeting Nutritional Targets of Critically Ill Patients by Combined Enteral and Parenteral Nutrition: review and rationale for the EFFORTcombo trial

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Abstract

While medical nutrition therapy is an essential part of the care for critically ill patients, uncertainty exists about the right form, dosage, timing and route in relation to the phases of critical illness. As enteral nutrition (EN) is often withheld or interrupted during the ICU stay, combined EN and parenteral nutrition (PN) may represent an effective and safe option to achieve energy and protein goals as recommended by international guidelines. We hypothesize that critically ill patients at high nutritional risk may benefit from such a combined approach during their stay on the intensive care unit (ICU). Therefore, we aim to test if an early combination of EN and high-protein PN (EN+PN) is effective in reaching calorie and protein goals in patients at high nutritional risk, while avoiding overfeeding. This approach will be tested in the here presented EFFORTcombo trial. Nutritionally high-risk ICU patients will be randomized to either high (≥2.2 mg/kg/d) or low protein (≤1.2 mg/kg/d). In the high protein group, the patients will receive EN+PN, in the low protein group, patients will be given EN alone. EN will be started in accordance to international guidelines in both groups. Efforts will be made to reach nutrition goals within 48–96 hours. The efficacy of the proposed nutritional strategy will be tested as an innovative approach by functional outcomes at ICU- and hospital-discharge, as well as at a 6-month follow-up.

Registration:

EFFORT Trial: NCT03160547

EFFORTcombo Trial: EudraCT-No.: 2018-003703-19

Introduction

During the past decades, the optimal amount of nutrition and route of feeding in critically ill patients has been debated controversially in the literature[1]. It is currently unclear what the optimal protein energy targets should be and exactly when they should be reached[2]. Current international nutrition guidelines recommend the initiation of medical nutrition therapy in the form of **enteral nutrition (EN)** within 24–48 hours in the critically ill patient who is unable to maintain sufficient oral intake[3; 4; 5; 6]. However, EN alone is often insufficient to achieve energy and protein targets particularly in the early phase of critical illness due to frequent interruptions for procedures and metabolic or gastrointestinal (GI) intolerance[7].

Parenteral nutrition (PN) provides advantages in achieving target nutrition goals earlier, which might be particularly relevant in patients at high nutrition risk. In fact, the **combined use of EN and PN (EN+PN)** may reduce large nutrition deficits in critically ill patients and might be attractive in those patients who cannot achieve their energy and protein goals during their ICU stay from EN

alone[8]. One strategy to optimize protein intake is to combine EN and PN (EN+PN) early after admission to the ICU to reach nutrition targets in patients at nutritional risk as soon as possible. Another approach would be the early initiation of EN with the addition of supplemental PN if the nutritional targets cannot be reached by EN alone (SPN) after several days.

For critically ill patients, achieving the protein goal is perhaps more important than achieving the calorie goal, as several large-scale randomized controlled trials (RCTs) have not been able to demonstrate any benefit from near goal caloric delivery [9; 10; 11]. The few RCTs evaluating protein targets will be discussed in this manuscript, but clear evidence is still lacking. In fact, determining the optimal protein dose and timing for critically ill patients is a high priority research question[12]. Even with a combined enteral and parenteral nutrition approach, it may remain challenging to reach the currently recommended protein goals with available nutrition products.

The EFFORT trial investigates the influence of higher prescription of protein (≥2.2 g/kg/day) versus usual protein prescription (≤1.2 g/kg/day) on the outcome of nutritionally-high-risk critically ill patients[13]. One of the biggest challenges in this trial will be continuously achieving adequate amounts of protein in the higher dose group[14; 15]. Since this might be more consistently achieved through an early combination of EN+PN, we plan to conduct a sub-study in the EFFORT trial wherein patients randomized to the higher dose group automatically receive combined EN+PN versus EN alone in the usual care group, known as the EFFORTcombo trial. The purpose of this paper is therefore to critically review the current evidence, to generate hypotheses and thus, to provide the scientific rationale for the concept of combining EN+PN applied in the early phase of critical illness in nutritionally-high risk critically ill patients and to present the details of trial methods.

Current evidence and discussions about enteral and parenteral nutrition

EN is the most common route of feeding in the ICU[16] and is uniformly recommended in current international nutrition guidelines[3; 4; 5; 6]. However, recent data demonstrated that EN is still often withheld or started with significant delay after admission to the ICU in the clinical routine[7; 17]. The progression of EN into a full feed is highly subjective to the clinician[7; 17] and often takes several days due to feeding intolerance and common interruptions of EN[18; 19; 20]. **Thus, EN may lead to protein-calorie deficiency with a possible negative impact on patient outcome– especially in the patient´s first ICU-week[21; 22; 23]**.

For years, PN was thought to be associated with neutral or even harmful effects, as older studies suggested that the risk/benefit ratio for use of PN in the ICU-setting may be much narrower than that

for use of EN[24; 25]. Few studies indicated that the use of PN was associated with more infectious complications, most likely related to hyperalimentation and hyperglycaemia, as consistently shown in earlier meta-analyses[26; 27; 28; 29]. The "Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients (**EPaNIC**) study by Casaer et al. demonstrated some potentially harmful effects of early PN in critically ill patients [24; 30; 31; 32; 33]. In this study, patients were randomized to early supplementation of insufficient EN with PN versus withholding PN for one week[24]. Patients in the early PN group received intravenous glucose under conditions of intensive insulin therapy for the first three days, when EN was still insufficient, and then, if the patient was still in the ICU, PN was started on day three. In the late PN group, PN was only initiated at day eight. The major findings demonstrated that early PN led to a prolonged dependency on intensive care treatments and an increased infection-rates. In contrast, withholding PN improved clinical outcomes, which was associated with relevant cost saving effects. Importantly, in the large subgroup with a contraindication for EN upon admission, harm by early PN was even more pronounced, whereas the authors suggested a suppression of the physiological response mechanism autophagy by feeding in the PN group as reason for the observed negative effects. Yet, there are several limitations, that limit the validity and generalizability of the findings. For example, the application of glucose instead of PN under conditions of tight glycaemic control within the first few days is rather rare at other ICUs. As evidenced by the primary publication, the harm signal was evident in the early group even before PN started on day 3, so the harm cannot be attributed to the introduction of PN on day 3. Furthermore, the majority of patients underwent surgery (90%) and within these 60% cardiac surgery, resulting in an overall short ICU-stay (3–4 days) with a rather low mortality. Enrolled patients were thus very low nutritional risk and would not have received any artificial nutrition in many ICUs around the world. Thus, the results of the EPANIC trial cannot be expanded to nutritionally high-risk patients in other settings.

Nevertheless, based on the EPaNIC findings and because EN was thought to be cheaper, safer, and more physiologic, international nutrition guidelines recommend that the enteral route should be preferably used in critically ill patients without a contraindication to EN [3; 34; 35; 36] and did not support the routine use of PN in the early phase of critical illness [37]. However, the more recent evidence from randomized studies about the safety and efficacy of PN might make physicians more comfortable with prescribing PN earlier [38; 39].

The **CALORIES** trial by Harvey et al. involved 2388 critically ill patients receiving exclusive PN or EN as soon as possible within 36 hours after admission. No significant differences were found in

adverse events, mortality or in the infectious complications, demonstrating the equivalence of EN and PN. However, this study included less severely ill patients[38]. More recently, Reignier et al. investigated the effects of EN vs. PN in the **NUTRIREA-2** trial including 2410 patients receiving invasive mechanical ventilation and vasopressor support for shock[39]. In this isocaloric trial, early EN did not reduce mortality or the risk of secondary infections, but was associated with an increased risk of digestive complications such as vomiting, diarrhoea and bowel ischemia when compared with early PN[39]. Both the NUTRIREA-2 and CALORIES studies contrasted previously mentioned safety concerns about PN and overall challenged the paradigm that EN is superior to PN with respect to clinical outcomes in critical illness. The rather low amount of delivered protein in the EN and PN group, as well as the short duration of these studies may represent the main reasons why no clinical advantages could be detected either in the EN or in the PN group.

Given the fact that GI-dysfunction is commonly observed in severely ill patients, and that PN was demonstrated to be safe in the more recent trials, early high-protein PN may help to securely and rapidly achieve the recommended nutrition goals during feeding intolerance and GI-symptoms. The described concerns about EN-safety and EN-progression illuminate a promising opportunity for PN as alternative nutrition strategy to bridge the gap between the nutritional goals and delivered calories/proteins, whenever EN is withheld or reduced, at any time point during the ICU stay.

Experience in combining enteral and parenteral nutrition

Pichard and colleagues systemically investigate the concept of EN and PN in the ICU to reduce the overall nutrition deficiency[40]. The pragmatic concept was introduced with the idea to start PN in patients with proven intolerance to EN and defined as supplemental PN (SPN). In an RCT, patients who were EN-intolerant, and therefore were unable to reach their nutritional target by day three were randomized to control group (EN alone) or SPN. Nutritional targets were measured by indirect calorimetry. Only patients receiving less than 60% of their target during the first three days were enrolled, therefore leading to a considerable protein-energy debt in all enrolled patients. In this trial, increased nutritional adequacy and a reduced number of nosocomial infections was observed in the SPN group[41].

In a different but related concept, the effect of a combined EN+PN strategy was tested in the recent **TOP-UP pilot** trial, where PN was started immediately after randomization without testing for EN intolerance to achieve the prescribed nutrition goals, referred to as combined EN+PN[42]. The energy targets were calculated in a pragmatic approach based on the actual body weight, with the overall goal to reach the full energy target at day one post randomization. The proposed nutrition strategy

was feasible and effective regarding the separation of protein-calorie intake between the two groups. Considering the clinical relevance, no overall benefit could be demonstrated in this small pilot study, however, the results revealed some encouraging trends of improved functional outcomes in the combined EN+PN group, which needs to be evaluated in following confirmatory studies.

The most recent **EAT-ICU trial** tested the effects of an early goal-directed nutrition vs. standard nutritional care in adult critically ill patients[11]. In the early goal-directed nutrition-group, the nutritional requirements were estimated by indirect calorimetry and 24-hour urinary urea. This group received an intense EN+PN therapy to cover 100% of the calculated target. Patients randomized to the control group received standard care, providing 25 kcal/kg/day by EN alone. While the feasibility of this strategy was demonstrated by a significant separation of both treatment groups with respect to energy and protein uptake, no significant effect was detected regarding the clinical relevance. However, frequent hyperglycaemia despite extraordinarily high dosages of administered insulin demonstrated rather poor metabolic control, which overall might have influenced the evaluated physical outcome assessment as primary endpoint.

Table 1 gives a short summary of the characteristics of the above-mentioned trials.

What can we learn from recent trials?

Focus on the right patients

One of the reasons why recent trials aiming at high amounts of calories or protein in the ICU-setting have failed to demonstrate a positive outcome might be inappropriate patient populations. For example, well-nourished patients following elective surgery, with a short ICU-LOS, such as those studied in the EPaNIC trial are unlikely to benefit from augmented feeding approaches (or requiring artificial feeding at all). Critically ill patients are a heterogenous group of patients with respect to the extent to which they will benefit from artificial nutrition therapy.

The patients` previous **nutritional state** is of paramount importance as it determines the availability of self-defence mechanisms such as endogenous antioxidant mechanisms[43; 44]. On the other hand, patients who are either previously malnourished or at risk of malnutrition – either under- or overweight –, or with expected prolonged ICU-stay will most likely benefit from an intense nutrition therapy[45; 46; 47; 48; 49].

In extension to the assessment of nutritional risk, increasing attention is paid to the presence of sarcopenia, frailty and the associated impaired physical functioning, as they have been demonstrated to be important predictors of a longer ICU- and hospital-length of stay, post-discharge mortality,

quality of life and lower likelihood to return to home, as summarized in greater detail in recent reviews[50; 51; 52]. Notably, sarcopenic patients might benefit from an intense nutritional therapy, as recently demonstrated by Koga et al. in a retrospective analysis, where sarcopenic patients supplied with early EN showed a reduced hospital-mortality compared to those who did not receive early EN, while that effect was not visible in non-sarcopenic patients[53].

Focus on Protein

The influence of protein on the outcome of critically ill patients has been discussed in controversially [13; 54], but the above-displayed evidence leads to the conclusion that nutrition interventions targeting only the energy adequacy did not show statistically significant improvements in many studies. Increased protein intake however, was associated with improved long-term physical recovery and lower mortality in observational trials[47; 55; 56; 57] and did not influence duration of renal dysfunction [58].

One systematic review performed by Davies et al. showed no relationship between protein delivery and mortality whereas both the low and high protein groups in this review were protein-malnourished (0.67 g/kg/d and 1.02 g/kg/d)[59]. However, even in nutrition trials targeting the adequate provision of protein, enteral nutrition failed to provide more than 1.5 g/kg day[15], highlighting the need for high-protein nutrition products or effective strategies to reach the protein goals. Heyland et al recently performed a meta-analysis assessing the effect of higher vs. lower protein intake but the effect could not be analysed in detail due to high heterogeneity of the existing trials and incomplete datasets. The authors were only able to aggregate the effect of higher protein dosing on mortality (risk ratio: 0.89; 95% confidence interval: 0.66–1.19, p= 0.42)[13]. Despite the current lack of evidence and controversial discussion, current guidelines recommend the daily provision of 1.2–2.5 g/kg protein[3; 5; 60].

Focus on functional outcomes

Outcome measures should be patient-cantered, reliable, accurate, and simple to measure in ways that minimize bias. The majority of large RCTs trials are measuring “hard” outcomes, because they are objective, comparatively easy to obtain and clearly observable by researchers. Major outcome parameters, such as mortality have been used in nutrition-trials despite observed decreasing overall mortality rates and therefore many nutrition trials have remained nonsignificant. Although these parameters are undoubtedly important, they do not adequately capture the patients’ perspective after discharge from hospital and might not be sensitive enough for nutrition interventions[61]. With the paradigm **“add life to years, not years to life”** more and more interventions aim to increase the quality of life after critically illness [62; 63; 64; 65]. In this connection, the evaluation of mid- and long-

term survival by functional outcomes are increasingly considered, because they evaluate muscle mass, muscle function and physical function closely connected to the patient's quality of life in the longer-term[66]. Furthermore, functional outcomes reflect the overall state of the patient and are affected by a variety of treatments, not only nutrition and mobilization.

More recent nutrition studies have used physical outcome assessment, or surrogate parameters and some have revealed trends of improved functional outcomes intense nutrition therapy groups[11; 16; 42; 67]. In addition, Wu et al. observed unchanged "classic" parameters such as hospital-LOS, postoperative morbidity rates, and standard blood biochemistry profiles, in a patient cohort after esophagectomy. However, these patients had better physical functioning and less fatigue[68].

On the other hand, physical outcome assessment is complex, and its performance requires adequate teaching of study sites to receive reliable data for a rigorous knowledge transfer. Poor metabolic control for example reflected by hyperglycaemia and a low number of patients, might have confounded the physical outcome assessment as primary endpoint in the EAT-ICU trial[11]. Additionally, the primary endpoint in this study showed some weakness as a) little evidence exists about its use, as it has rarely been used before, b) the assessment at 6 months after ICU-discharge bares the risk, that the effects may be influenced by other relevant aspects than the ICU-treatment itself and c) the physical outcome showed a large variance in the assessment, emphasizing the need for strict adherence to standardized operation protocols. Based on these findings received from rather smaller clinical studies, a well-timed physical outcome assessment matching the study intervention is encouraged to be evaluated in following confirmatory studies[69].

Conclusion

Based on the evidence gathered from recent trials the authors conclude as follows:

1. Targeting energy adequacy only might not be enough to improve the outcome of critically ill patients. Increasing attention should be paid on effective supplementation strategies to achieve recommended protein goals.
2. In iso-energetic trials, the route of administration might not influence "standard" outcome parameters as mortality and hospital-LOS
3. PN, as well as EN+PN seem to be safe, feasible and effective to achieve the prescribed nutritional targets in critically ill patients.
4. Without consideration of metabolic tolerance, early aggressive EN+PN may not be effective in improving patient outcomes in unselected patients.

5. In nutritionally high-risk patients, combined EN+PN may improve functional and other patient-reported outcomes.

From the EFFORT trial to the EFFORTcombo trial

Based on our review of the current evidence, we hypothesize that a combination of EN+high-protein-PN vs. EN alone in nutritionally high-risk patients can improve the functional outcomes. **To test this hypothesis, we plan the nested sub-study "EFFORTcombo" in the context of the EFFORT trial.**

The **EFFORT Trial** (clinicaltrials.gov/NCT03160547) was developed as multi-centre pragmatic volunteer driven, registry based RCT in which 4000 patients will be randomly assigned to either a higher prescribed dose of protein (≥2.2 g/kg/d) or usual protein prescription (≤1.2 g/kg/d) [13]. However, the EFFORT trial does not specify how these determined protein dosages can be achieved. As protein delivery has been challenging in the past and only 55% of prescribed protein (equal to 0.7 g/kg/d) are actually delivered as reported in the International Nutrition Survey (INS)[14], we propose that the addition of high-protein-PN to EN compared to EN alone, represents a promising nutrition strategy to increase nutritional adequacy to achieve the goals set in the original EFFORT trial. In comparison to the EFFORT trial, in the proposed multicenter EFFORTcombo substudy a) patients randomized to the high protein dosage will receive a combination of high-protein PN and EN and b) the main outcome for this substudy is short-term physical function as assessed by the six-minute walk test.

In addition, we will use a high-protein PN product and thus expect to reach the nutrition goals faster and more securely through this combination as shown in Figure 1. We hypothesize that the augmented protein delivery to these nutritionally high-risk-patients will translate into improved functional and patient-reported outcomes. Written informed consent will obtained from all patients or their legal representatives before enrolment. The ethic committee of the RWTH Aachen University approved the study (EK339/19) and local jurisdictional approval will be obtained for each centre.

Inclusion and exclusion criteria

As a nested sub-study within the EFFORT trial, the EFFORTcombo study includes mechanically ventilated critically ill adult patients (≥18 years), who are at high nutritional risk as defined in detail in our published EFFORT protocol[13]. **Table 2** illustrates in detail all in- and exclusion criteria.

Investigational high-protein product

To provide high-protein-PN in patients randomized to the EN+PN group, we will use Olimel® N12 with electrolytes provided by Baxter® International Inc. Olimel is a 3-in-1 parenteral admixture solution containing the following drug substances: dextrose solution, amino acid solution with

electrolytes (sodium, potassium, magnesium, phosphate) and lipid emulsion with an olive oil/soybean oil ratio of 80:20 and 12 g nitrogen per litre. This product will be similar in energy density to the standard EN solutions (1–1.4 kcal/ml). Olimel® N12 will be administered via central venous line until the daily target of ≥2.2 g/kg/d is reached.

Peri-Olimel is a PN-product that can be used either peripherally or centrally and will be used whenever a central venous line for PN is not available. Both products are indicated for parenteral nutrition for adults.

Nutrition protocol

As soon as the patient is hemodynamically stable and there is a nasogastric tube or feeding tube in place, EN will be started within 24–48 hours after admission to ICU, as per local standards. If the patient has not been started on EN but there is an indication and intention to start on EN in the first 7 days, the patient will still be considered eligible for this study. The type of enteral formula should be of similar caloric density (1–1.5 kcal/ml), but otherwise used in accordance to local standards. In both groups, targets will be set using pre-ICU known weight (e.g. dry actual weight). For patients with BMI >30 kg/m^2, ideal body weight based on a BMI of 25 kg/m^2 will be used. As per current guidelines, we recommend monitoring for metabolic and GI-tolerance as well as the provision of usual nutritional therapy by credentialed clinicians with expertise in directing the feeding of critically ill patients. **If equipoise regarding the nutritional regimen or protein dosage is not given in the clinician's prescription for an individual patient, the patient will not be included in the trial.** Metabolic and feeding tolerance will be assessed by blood glucose, insulin dose, glucose infusion rates, phosphate, urea, triglycerides and electrolytes, which will be monitored frequently, as clinically indicated and consideration of recent guidelines for monitoring of nutrition therapy will be endorsed [70].

Those patients randomized into the high-protein group will receive EN+PN, with **PN added as soon as possible** following randomization. While the identification and randomization of appropriate patients will take 24-48 hours, the PN should be started within 48-96 hours. The study PN solution will be started at 25 ml/hr and increased if tolerated (e.g. the infusion rate can be increased by 25 ml every 4–6 hours) so that >80% of protein nutrition goals will be reached within 48–96 hours of starting PN. We aim to avoid overfeeding calories and if the protein target cannot be met by combined EN+PN, protein supplements (enteral protein supplements or intravenous amino acids) should be added as per local standards to reach the goal of ≥2.2 g/kg/d. The **PN-rate will be adjusted** in a compensatory fashion to ensure that patients receive >80% of their target goal rate on a continuous

basis, for example if EN infusion rates change due to GI-intolerance or interruption. Therefore, PN should be continued for a minimum of 7 days even at a minimal rate (10 ml/h).

Both EN and PN will be **continued for a minimum of 7 days post randomization** and be continued on the ward. PN should be continued at a minimum of 10 ml/h until the 7th day to enable easy compensations of the fluctuation in oral nutrition and/or EN-rates as well on the normal ward. The EN-rate will be always adjusted to the individual patients, while considering the minimum PN-rate of 10 ml/h. At 7 days post randomization, if the patient is still in the ICU, and PN is clinically indicated to achieve high-protein goals, Olimel® N12E will be used in the high dose group. In the low dose group, if a patient develops a contraindication to EN, after day 7, PN can be used with product selection and duration determined by local standards but protein goals should not be above 1.2 g/kg/day. In either group, after the end of the 7 days post randomization study period, if the patient has been discharged from the ICU and PN is clinically indicated, standard PN solutions can be used. Olimel® N12E will be discontinued at ICU-discharge (unless it occurs before day 7 as explained below), day 28 (maximum of PN treatment if the patients are still on ICU), or until death, whichever comes first.

The primary endpoint - functional outcome assessment

The primary objective of this sub-study is to demonstrate improved short-term physical function by a 6-minute walk test at hospital discharge. We also will assess in-hospital secondary outcomes and patient-reported 6-month outcomes similar to the NEXIS trial (Clinicaltrials.gov, NCT03021902). These secondary outcomes include the overall strength of upper and lower extremity (Medical Research Council sum score), quadriceps- and handgrip-strength (dynamometry), body composition (ultrasound and available CT-scans), overall physical function (Short Physical Performance Battery and Functional Status Score for the ICU), which will be assessed longitudinally while the patient is still in the hospital. The physical functioning (Katz activities of daily living and Lawtons instrumental activities of daily living) as well as health related quality of life (Short Form-36 and EQ-5D5L) will be assessed while the patient is in the hospital and 6 months after discharge. All outcome assessment will be performed by trained outcome assessors strictly following detailed standard operating protocols. All assessors will be blinded to the treatment group.

Summary

Taken together, international observational studies revealed considerable practice variations, and the existing clinical trial data, albeit weak and outdate, did not always support the routine use of PN in the early phase of critical illness. Importantly, the more recent evidence about the safety and efficacy

of PN might make physicians more comfortable with prescribing PN earlier to bridge the gap between nutrition goals and actual delivery of calories and protein. This might be especially for patients at high nutritional risk, or patients with an increased risk for prolonged ICU-stay. In this context, we are proposing the EFFORTcombo trial that evaluates the effects of an early combined EN + high-protein PN nutrition strategy to decrease the nutritional deficiencies in the critically ill patients at nutritional risk. We hypothesize that this nutritional strategy will improve the functional outcomes of these nutritionally high-risk patients.

List of Abbreviations

EN	Enteral Nutrition
EN+PN	Combined Enteral and Parenteral Nutrition
GI	Gastrointestinal
ICU	Intensive Care Unit
LOS	Length of Stay
PN	Parenteral Nutrition
RCT	Randomized Controlled Trial
SPN	Supplementary Parenteral Nutrition

Declarations

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Conflicts of Interest

Gunnar Elke has received lecture fees and travel expenses by Baxter Healthcare Corporation, Fresenius Kabi and consulting fees from Fresenius Kabi and Nutricia.

Christian Stoppe has received lecture fees and travel expenses by Fresenius Kabi and consulting fees from Fresenius Kabi and biosyn. Christian Stoppe received a co-funding grant from Baxter Healthcare Corporation to realize this investigator-initiated trial and Baxter Healthcare Corporation provides the investigational product for the here presented EFFORTcombo study.

Stefan J Schaller received research support from MSD (Haar, Germany) not related to this manuscript. He holds stocks from Rhoen-Klinikum, Bayer AG and Siemens AG and held stocks in the recent past from GE Healthcare, Merck & Co Inc, and Fresenius SE.

Danielle E Bear reports receiving advisory board fees, speaker fees or conference attendance support from Nutricia, Nestle Nutrition, BBraun, Baxter Healthcare Corporation, Fresenius Kabi, Abbott Nutrition, Cardinal Health and Avanos.

Ulrich Suchner reports on receiving personal fees of Fresenius-Kabi and on having received lecture-fees as well as refunds of travel expenses from the BA. Akademie, whereas all these revenues are not related to the submitted work.

The other authors declare no conflicts of interest that may be perceived as inappropriately influencing the representation or interpretation of reported research results.

Author contributions

A.H., C.S. and D.K.H. equally contributed to the conception and design of the research together with, S.J.S., R.S., C.H., C.L., G.E. and P.M. A.H. and C.S. drafted the manuscript together with D.K.H. Figures were provided by A.H. and C.S.. A.H., C.S., K.C.C., J.N., L.S., J.B., S.L. and T.L. contributed to the acquisition of data and to the study selection. All authors contributed to analysis and interpretation of the reviewed data, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Figures

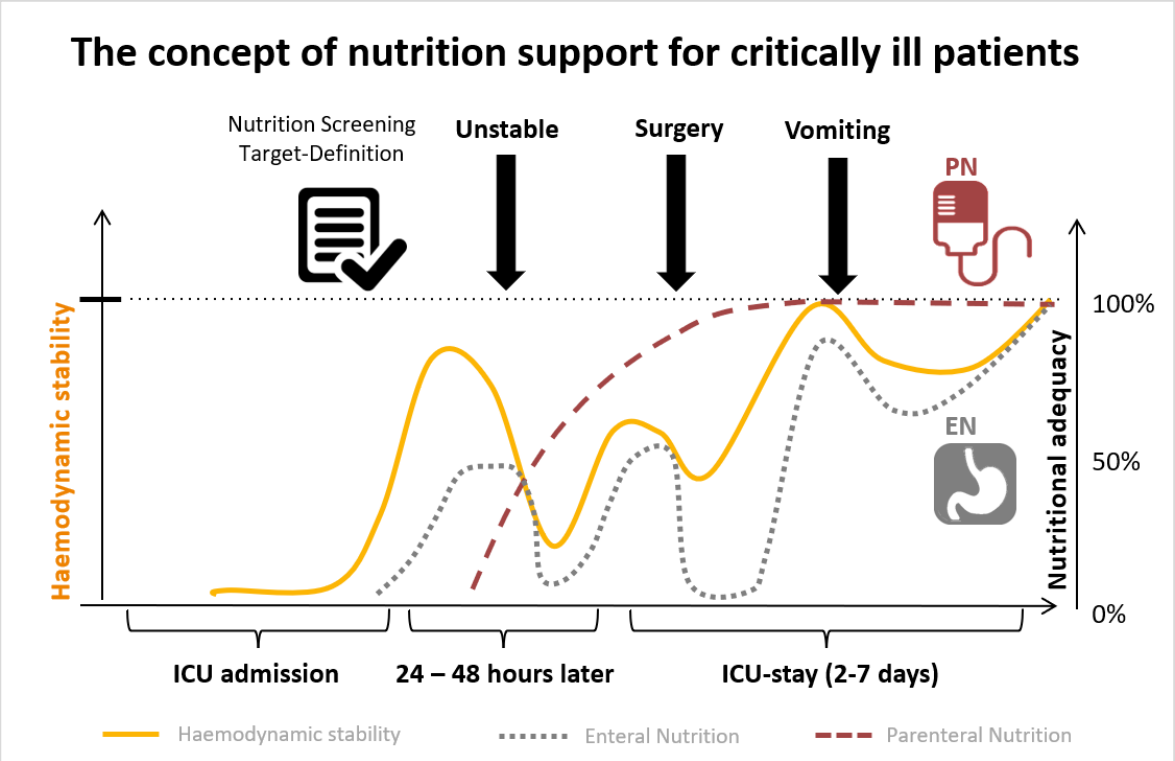

Figure 1: The concept of nutrition support for critically ill patients

Tables

Table 1: Comparison of recent trials combining enteral nutrition and parenteral nutrition, abbreviations: EN= enteral nutrition, PN= parenteral nutrition, SPN= supplemental parenteral nutrition, EGDN=early goal directed nutrition, BMI= body mass index, BW= body weight IBW= ideal body weight, APACHE II= Acute Physiology and Chronic Health Evaluation II Score, SAPS II= Simplified Acute Physiology II Score, SOFA= Sequential Organ Failure Assessment Score

Trial	Heidegger 2013 [41]	Wischmeyer [42]	Allingstrup 2017 [11]
Trial focus	EN vs. SPN	EN vs. EN+PN in over- or underweight patients	EGDN vs. standard of care PN to reach target: • EGDN group: <24 hours • Standard group: > 7 days
Enrolled patients	305	125	203
Mean Age in years	60.5	55.4	65.5
Mean BMI in kg/m²	25.9	33.3 (52% BMI < 25 48% BMI > 35)	22
Mean baseline disease severity scores	• APACHE II Score= 22.5 • SAPS II = 48	• APACHE II Score= 20.7 • SOFA= 6	• SAPS II Score =47.5 • SOFA Score =8
Calculation of Energy	• 25 kcal/kg/d (for women) and 30 kcal/kg/d (for men), using IBW or anamnestic BW for patients with a BMI ≤ 20 • Indirect calorimetry in 65% of patients	• BMI <25: ≥25 kcal/kg/d actual BW • BMI > 35: ≥20 kcal/kg/d adjusted BW (= IBW + [actual weight – IBW] x 0.25, where IBW is based on a BMI of 25)	• EGDN group: indirect calorimetry • Standard group: 25 kcal/kg/d
Energy delivered	Days 4–8: • SPN group: 28 kcal/kg/d (103%) • EN group: 20 kcal/kg/d (77%)	First 7 days: • EN+PN group: 95% • EN group: 68% First 27 days: • EN+PN: 90% of target • EN group: 67% of target	• EGDN group: 97% • Standard group: 64%
Calculation of protein	1–2 g/kg/d using IBW	≥1.2/kg/d Using actual body weight for patients with BMI <25 and adjusted body weight for patients with BMI >35	• EGDN group: ≥1.5 g/kg/day, calculated by urea excretion using Bistrian´s equation • Standard group: 1.2 g/kg/d
Protein delivered	Not reported	First 7 days: • EN+PN: 86% of target • EN group: 61% of target First 27 days: • EN+PN: 82% of target • EN group: 60% of target	• EGDN group: 97% • Standard group:45%

413 *Table 2: In- and exclusion Criteria - comparison between EFFORT and EFFORTcombo, modified from [13]*

Inclusion Criteria for the EFFORT and EFFORTcombo trials	

• ≥18 years old
• Nutritionally high-risk:
  ○ Low (≤25) or high BMI (≥35)
  ○ Moderate to severe malnutrition (as defined by local assessments)
  ○ Frailty (Clinical Frailty Scale, ≥5 or more)
  ○ Sarcopenia (SARC-F score, ≥4 or more)
  ○ From point of screening, projected duration of mechanical ventilation >4 days.
• Requiring mechanical ventilation with actual or expected total duration of mechanical ventilation >48 hours	

Exclusion Criterion	Rationale for Exclusion
Criteria from the original EFFORT trial	
>96 continuous hours of mechanical ventilation before screening	Intervention is likely most effective when delivered early
Expected death or withdrawal of life-sustaining treatments within 7 days from screening	Patients unlikely to receive benefit
Pregnancy	Unknown effect on the fetus
The responsible clinician feels that the patient either needs low or high protein	Uncertainty about protein dosage does not exist, patient safety issues
Patient requires PN only, and sites do not have the products to reach the high-dose protein group	Site will be unable to reach high-protein-dose prescription
Additional criteria in EFFORTcombo	
Patients in hospital >5 days prior to ICU admission or severe pre-existing weakness	Confounding of results
Pre-existing severe neuromuscular, cognitive or language impairment	Patient will be unable to perform physical outcome assessment
Lower extremity impairments that prevents the patient from walking (previously or newly acquired)	Patient will be unable to perform physical outcome assessment
Absolute contraindication to EN	Randomization impossible
Severe metabolic disorders including electrolyte disorders, uncontrolled hyperglycaemia, hyperlipidaemia, hypophosphatemia, or impaired nitrogen utilization	Intervention potentially hazardous
Severe chronic liver disease (MELD-score >20) or acute fulminant hepatitis.	Protein supplementation may be harmful in patients with severe liver disease

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References

1. Preiser J-C, van Zanten ARH, Berger MM *et al.* (2015) Metabolic and nutritional support of critically ill patients: consensus and controversies. *Critical care (London, England)* **19**, 35.
2. Elke G, van Zanten ARH, Lemieux M *et al.* (2016) Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials. *Critical care (London, England)* **20**, 117.
3. McClave SA, Taylor BE, Martindale RG *et al.* (2016) Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN Journal of parenteral and enteral nutrition* **40**, 159-211.
4. Weimann A, Braga M, Carli F *et al.* (2017) ESPEN guideline: Clinical nutrition in surgery. *Clinical nutrition (Edinburgh, Scotland)*.
5. Singer P, Blaser AR, Berger MM *et al.* (2018) ESPEN guideline on clinical nutrition in the intensive care unit. *Clinical Nutrition*.
6. Reintam Blaser A, Starkopf J, Alhazzani W *et al.* (2017) Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. *Intensive care medicine* **43**, 380-398.
7. Heyland DK, Schroter-Noppe D, Drover JW *et al.* (2003) Nutrition support in the critical care setting: current practice in canadian ICUs--opportunities for improvement? *JPEN Journal of parenteral and enteral nutrition* **27**, 74-83.
8. Bost RB, Tjan DH, van Zanten AR (2014) Timing of (supplemental) parenteral nutrition in critically ill patients: a systematic review. *Annals of intensive care* **4**, 31.
9. Rice TW, Mogan S, Hays MA *et al.* (2011) Randomized trial of initial trophic versus full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure. *Critical care medicine* **39**, 967-974.
10. Arabi YM, Aldawood AS, Al-Dorzi HM *et al.* (2017) Permissive Underfeeding or Standard Enteral Feeding in High- and Low-Nutritional-Risk Critically Ill Adults. Post Hoc Analysis of the PermiT Trial. *American journal of respiratory and critical care medicine* **195**, 652-662.
11. Allingstrup MJ, Kondrup J, Wiis J *et al.* (2017) Early goal-directed nutrition versus standard of care in adult intensive care patients: the single-centre, randomised, outcome assessor-blinded EAT-ICU trial. *Intensive care medicine*.
12. Arabi YM, Casaer MP, Chapman M *et al.* (2017) The intensive care medicine research agenda in nutrition and metabolism. *Intensive care medicine*.
13. Heyland DK, Patel J, Bear D *et al.* (2018) The Effect of Higher Protein Dosing in Critically Ill Patients: A Multicenter Registry-Based Randomized Trial: The EFFORT Trial. *JPEN Journal of parenteral and enteral nutrition*.
14. Heyland DK, Weijs PJM, Coss-Bu JA *et al.* (2017) Protein Delivery in the Intensive Care Unit: Optimal or Suboptimal? *Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition* **32**, 58S-71S.
15. van Zanten ARH, Petit L, De Waele J *et al.* (2018) Very high intact-protein formula successfully provides protein intake according to nutritional recommendations in overweight critically ill patients: a double-blind randomized trial. *Critical care (London, England)* **22**, 156.
16. Ridley EJ, Peake SL, Jarvis M *et al.* (2018) Nutrition Therapy in Australia and New Zealand Intensive Care Units: An International Comparison Study. *JPEN Journal of parenteral and enteral nutrition* **42**, 1349-1357.
17. Cahill NE, Dhaliwal R, Day AG *et al.* (2010) Nutrition therapy in the critical care setting: what is "best achievable" practice? An international multicenter observational study. *Critical care medicine* **38**, 395-401.
18. Heyland D, Cook DJ, Winder B *et al.* (1995) Enteral nutrition in the critically ill patient: a prospective survey. *Critical care medicine* **23**, 1055-1060.

19. Adam S, Batson S (1997) A study of problems associated with the delivery of enteral feed in critically ill patients in five ICUs in the UK. *Intensive care medicine* **23**, 261-266.
20. McClave SA, Sexton LK, Spain DA *et al.* (1999) Enteral tube feeding in the intensive care unit: factors impeding adequate delivery. *Critical care medicine* **27**, 1252-1256.
21. Berger MM, Chiolero RL (2009) Enteral nutrition and cardiovascular failure: from myths to clinical practice. *JPEN Journal of parenteral and enteral nutrition* **33**, 702-709.
22. Berger MM, Revelly J-P, Cayeux M-C *et al.* (2005) Enteral nutrition in critically ill patients with severe hemodynamic failure after cardiopulmonary bypass. *Clinical nutrition (Edinburgh, Scotland)* **24**, 124-132.
23. Villet S, Chiolero RL, Bollmann MD *et al.* (2005) Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. *Clinical nutrition (Edinburgh, Scotland)* **24**, 502-509.
24. Casaer MP, Mesotten D, Hermans G *et al.* (2011) Early versus late parenteral nutrition in critically ill adults. *The New England journal of medicine* **365**, 506-517.
25. Kelly DG, Tappenden KA, Winkler MF (2014) Short bowel syndrome: highlights of patient management, quality of life, and survival. *JPEN Journal of parenteral and enteral nutrition* **38**, 427-437.
26. Braunschweig CL, Levy P, Sheean PM *et al.* (2001) Enteral compared with parenteral nutrition: a meta-analysis. *The American journal of clinical nutrition* **74**, 534-542.
27. Gramlich L, Kichian K, Pinilla J *et al.* (2004) Does enteral nutrition compared to parenteral nutrition result in better outcomes in critically ill adult patients? A systematic review of the literature. *Nutrition (Burbank, Los Angeles County, Calif)* **20**, 843-848.
28. Heyland DK, Montalvo M, MacDonald S *et al.* (2001) Total parenteral nutrition in the surgical patient: a meta-analysis. *Canadian journal of surgery Journal canadien de chirurgie* **44**, 102-111.
29. Peter JV, Moran JL, Phillips-Hughes J (2005) A metaanalysis of treatment outcomes of early enteral versus early parenteral nutrition in hospitalized patients. *Critical care medicine* **33**, 213-220; discussion 260-211.
30. De Vlieger G, Ingels C, Wouters PJ *et al.* (2018) Impact of supplemental parenteral nutrition early during critical illness on invasive fungal infections: a secondary analysis of the EPaNIC randomized controlled trial. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*.
31. Hermans G, Casaer MP, Clerckx B *et al.* (2013) Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. *The Lancet Respiratory medicine* **1**, 621-629.
32. Vanderheyden S, Casaer MP, Kesteloot K *et al.* (2012) Early versus late parenteral nutrition in ICU patients: cost analysis of the EPaNIC trial. *Critical care (London, England)* **16**, R96.
33. Casaer MP, Langouche L, Coudyzer W *et al.* (2013) Impact of early parenteral nutrition on muscle and adipose tissue compartments during critical illness. *Critical care medicine* **41**, 2298-2309.
34. Dellinger RP, Levy MM, Rhodes A *et al.* (2013) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Critical care medicine* **41**, 580-637.
35. Dhaliwal R, Cahill N, Lemieux M *et al.* (2014) The Canadian critical care nutrition guidelines in 2013: an update on current recommendations and implementation strategies. *Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition* **29**, 29-43.
36. Singer P, Berger MM, Van den Berghe G *et al.* (2009) ESPEN Guidelines on Parenteral Nutrition: intensive care. *Clinical nutrition (Edinburgh, Scotland)* **28**, 387-400.
37. Heyland DK, Dhaliwal R, Drover JW *et al.* (2003) Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN Journal of parenteral and enteral nutrition* **27**, 355-373.

514 38. Harvey SE, Parrott F, Harrison DA *et al.* (2014) Trial of the route of early nutritional support in
515 critically ill adults. *The New England journal of medicine* **371**, 1673-1684.
516 39. Reignier J, Boisrame-Helms J, Brisard L *et al.* (2018) Enteral versus parenteral early nutrition in
517 ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study
518 (NUTRIREA-2). *Lancet (London, England)* **391**, 133-143.
519 40. Heidegger C-P, Romand J-A, Treggiari MM *et al.* (2007) Is it now time to promote mixed enteral
520 and parenteral nutrition for the critically ill patient? *Intensive care medicine* **33**, 963-969.
521 41. Heidegger CP, Berger MM, Graf S *et al.* (2013) Optimisation of energy provision with
522 supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial.
523 *Lancet (London, England)* **381**, 385-393.
524 42. Wischmeyer PE, Hasselmann M, Kummerlen C *et al.* (2017) A randomized trial of supplemental
525 parenteral nutrition in underweight and overweight critically ill patients: the TOP-UP pilot trial.
526 *Critical care (London, England)* **21**, 142.
527 43. Chow CK (1979) Nutritional influence on cellular antioxidant defense systems. *The American*
528 *journal of clinical nutrition* **32**, 1066-1081.
529 44. Khare M, Mohanty C, Das BK *et al.* (2014) Free radicals and antioxidant status in protein energy
530 malnutrition. *International journal of pediatrics* **2014**, 254396.
531 45. Heyland DK, Dhaliwal R, Jiang X *et al.* (2011) Identifying critically ill patients who benefit the
532 most from nutrition therapy: the development and initial validation of a novel risk assessment tool.
533 *Critical care (London, England)* **15**, R268.
534 46. Kondrup J, Allison SP, Elia M *et al.* (2003) ESPEN guidelines for nutrition screening 2002.
535 *Clinical nutrition (Edinburgh, Scotland)* **22**, 415-421.
536 47. Alberda C, Gramlich L, Jones N *et al.* (2009) The relationship between nutritional intake and
537 clinical outcomes in critically ill patients: results of an international multicenter observational study.
538 *Intensive care medicine* **35**, 1728-1737.
539 48. Artinian V, Krayem H, DiGiovine B (2006) Effects of early enteral feeding on the outcome of
540 critically ill mechanically ventilated medical patients. *Chest* **129**, 960-967.
541 49. Khalid I, Doshi P, DiGiovine B (2010) Early enteral nutrition and outcomes of critically ill
542 patients treated with vasopressors and mechanical ventilation. *American journal of critical care : an*
543 *official publication, American Association of Critical-Care Nurses* **19**, 261-268.
544 50. Bear DE, Wandrag L, Merriweather JL *et al.* (2017) The role of nutritional support in the physical
545 and functional recovery of critically ill patients: a narrative review. *Critical care (London, England)*
546 **21**, 226.
547 51. Friedman J, Lussiez A, Sullivan J *et al.* (2015) Implications of sarcopenia in major surgery.
548 *Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral*
549 *Nutrition* **30**, 175-179.
550 52. Jolley SE, Bunnell AE, Hough CL (2016) ICU-Acquired Weakness. *Chest* **150**, 1129-1140.
551 53. Koga Y, Fujita M, Yagi T *et al.* (2018) Early enteral nutrition is associated with reduced in-
552 hospital mortality from sepsis in patients with sarcopenia. *Journal of critical care* **47**, 153-158.
553 54. Heyland DK, Stapleton R, Compher C (2018) Should We Prescribe More Protein to Critically Ill
554 Patients? *Nutrients* **10**.
555 55. Heyland DK, Stephens KE, Day AG *et al.* (2011) The success of enteral nutrition and ICU-
556 acquired infections: a multicenter observational study. *Clinical nutrition (Edinburgh, Scotland)* **30**,
557 148-155.
558 56. Heyland DK, Cahill N, Day AG (2011) Optimal amount of calories for critically ill patients:
559 depends on how you slice the cake! *Critical care medicine* **39**, 2619-2626.
560 57. Ferrie S, Allman-Farinelli M, Daley M *et al.* (2016) Protein Requirements in the Critically Ill: A
561 Randomized Controlled Trial Using Parenteral Nutrition. *JPEN Journal of parenteral and enteral*
562 *nutrition* **40**, 795-805.

58. Doig GS, Simpson F, Bellomo R *et al.* (2015) Intravenous amino acid therapy for kidney function in critically ill patients: a randomized controlled trial. *Intensive care medicine* **41**, 1197-1208.
59. Davies ML, Chapple L-AS, Chapman MJ *et al.* (2017) Protein delivery and clinical outcomes in the critically ill: a systematic review and meta-analysis. *Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine* **19**, 117-127.
60. Elke G, Hartl WH, Kreymann KG *et al.* (2018) DGEM-Leitlinie:„Klinische Ernährung in der Intensivmedizin ". *Aktuelle Ernährungsmedizin* **43**, 341-408.
61. Poolman RW, Swiontkowski MF, Fairbank JCT *et al.* (2009) Outcome instruments: rationale for their use. *The Journal of bone and joint surgery American volume* **91 Suppl 3**, 41-49.
62. Dowdy DW, Eid MP, Sedrakyan A *et al.* (2005) Quality of life in adult survivors of critical illness: a systematic review of the literature. *Intensive care medicine* **31**, 611-620.
63. Needham DM, Dowdy DW, Mendez-Tellez PA *et al.* (2005) Studying outcomes of intensive care unit survivors: measuring exposures and outcomes. *Intensive care medicine* **31**, 1153-1160.
64. Hopkins RO, Suchyta MR, Kamdar BB *et al.* (2017) Instrumental Activities of Daily Living after Critical Illness: A Systematic Review. *Annals of the American Thoracic Society* **14**, 1332-1343.
65. Dinglas VD, Faraone LN, Needham DM (2018) Understanding patient-important outcomes after critical illness: a synthesis of recent qualitative, empirical, and consensus-related studies. *Current opinion in critical care* **24**, 401.
66. Parry SM, Huang M, Needham DM (2017) Evaluating physical functioning in critical care: considerations for clinical practice and research. *Critical care (London, England)* **21**, 249.
67. Chen F (2011) Influence of different routes of nutrition on the respiratory muscle strength and outcome of elderly patients in respiratory intensive care unit. *Chinese journal of clinical nutrition*.
68. Wu W, Zhong M, Zhu D-M *et al.* (2017) Effect of Early Full-Calorie Nutrition Support Following Esophagectomy: A Randomized Controlled Trial. *JPEN Journal of parenteral and enteral nutrition* **41**, 1146-1154.
69. Devlin JW, Skrobik Y, Gélinas C *et al.* (2018) Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Critical care medicine* **46**, e825-e873.
70. Berger MM, Reintam-Blaser A, Calder PC *et al.* (2019) Monitoring nutrition in the ICU. *Clinical nutrition (Edinburgh, Scotland)* **38**, 584-593.