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Opinion paper

Pragmatic approach to nutrition in the ICU: Expert opinion regarding which calorie protein target

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SUMMARY

Background & aims: Since the publications of the ESPEN guidelines on enteral and parenteral nutrition in ICU, numerous studies have added information to assist the nutritional management of critically ill patients regarding the recognition of the right population to feed, the energy-protein targeting, the route and the timing to start.
Methods: We reviewed and discussed the literature related to nutrition in the ICU from 2006 until October 2013.
Results: To identify safe, minimal and maximal amounts for the different nutrients and at the different stages of the acute illness is necessary. These amounts might be specific for different phases in the time course of the patient's illness. The best approach is to target the energy goal defined by indirect calorimetry. High protein intake (1.5 g/kg/d) is recommended during the early phase of the ICU stay, regardless of the simultaneous calorie intake. This recommendation can reduce catabolism. Later on, high protein intake remains recommended, likely combined with a sufficient amount of energy to avoid proteolysis.
Conclusions: Pragmatic recommendations are proposed to practically optimize nutritional therapy based on recent publications. However, on some issues, there is insufficient evidence to make expert recommendations.

1. Introduction

This paper aims at reviewing the current evidence regarding energy and protein administration to critically ill patients in the Intensive Care Unit (ICU) which appeared after the publication of the 2006 and 2009 ESPEN guidelines, in order to recommend a pragmatic approach for clinical practice. ICU patients exhibit an increasing spectrum of intertwined pathophysiological processes making an individualized approach to nutrition support essential. In addition, during the ICU stay, nutritional needs are constantly changing, dependent on disease stage. Many questions remain unanswered and should be addressed in future research.

2. Which ICU population should be targeted?

The ICU population is very heterogeneous, and includes mechanically ventilated and non-ventilated patients, patients requiring short or long ICU stays, surgical or medical patients as

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well as obese or malnourished patients. The mode of feeding may also vary according to the clinical condition. The Alberda study[1] showed that 69% of the 2884 patients were fed enterally, 8% parenterally, 17.6% enterally and parenterally, while 5.4% received neither enteral nor parenteral nutrition. Clearly, an elderly, sarcopenic patient with cancer in septic shock has different needs from a young ventilated patient with multiple trauma suffering from a head injury and femur fracture.

In this paper, only studies including patients staying longer than 48 h in the ICU were analyzed and where possible, a distinction was made between surgical and medical, as well as between well- and malnourished patients.

3. Between necessity and side effects: effects of over and undernutrition

Body glycogen energy reserves decrease substantially after 24 h of fasting.[2] In addition, fasting over three days in healthy persons induces insulin resistance. This might be triggered by the "selfish" brain that induces hyperglycaemia in order to receive privileged access to limited energy resources.[3] Proteins are also used as an alternative source for glucose production. A 75 kg human loses 50% of liver glycogen and 1% of muscle mass within 24 h after trauma and fasting.[4] Negative energy balance is associated with increased morbidity and mortality.[5] Undernutrition induces muscle and even heart atrophy, mainly in patients with a long ICU stay. An international large scale survey[1] showed that in patients receiving a maximum of 10 kcal/kg BW/day, the ratio of observed versus expected mortality increased substantially after day 7.

On the other hand, several studies[6,7] have found that the supply of energy above energy needs correlates with an increased rate of complications. These include[8] increased VCO2 and work of breathing.[8] The additional energy needed for the body of storing an excess of 500 kcal leads to 33% increasing in ventilatory workload, fatty liver in the presence of a sustained glucose load whereas parenteral overnutrition may result in fluid overload.[8] Brain and nerves both suffer from hyper- and hypoglycaemia. In particular, during the acute phases of stress metabolism where endogenous substrate mobilization is high and cannot be suppressed sufficiently by nutritional therapy,[9] overnutrition must be avoided to protect respiratory function, reduce the risk of infection and decrease the storage of fat. Autophagia, a cellular repair mechanism, might also be hampered by overnutrition.[10] Finally, adding to the problem of overnutrition, the progressive decrease over time of lean body mass increases the risk of overfeeding when weight-based equations are used and the changes in weight are not taken into account.

Interestingly, numerous recent prospective randomized controlled trials (PRCTs) have compared hypocaloric regimens to "optimal[11] nutritional support", even comparing the so-called "trophic" enteral feeding to full nutritional therapy.[12,13] Enteral nutrition (EN), even when applied in small amounts (trophic feeding) prevents gut atrophy.[12,13] The PRCTs related to metabolic and nutritional support (Table 1) show that for most studies, the calorie and protein intake did not reach the recommended amounts. In the Arabi study,[14] the target group received 1200 kcal/day and 43 g/day of protein, while the so called "permissive undernutrition group" received only slightly less energy (1099 kcal/day) but slightly more protein (47 g/day). It should be highlighted that this study compares two levels of undernutrition. In the Rice study,[11] the authors recruited young overweight patients (mean BMI 28) suffering from single organ failure (acute lung injury) who were randomized to receive either "trophic" enteral feeding or "full-target enteral feeding". No significant difference was found between the 2 groups.

Indeed the majority of studies report the results about patients receiving low calorie and protein intakes, and only 2 studies showed the impact of obtaining an energy balance at 14 days. The intervention group of the TICACOS study[6] and the early PN group from the EPaNIC study[7] have energy intakes above the presumed targets. The intervention group of the SPN study[15] is close to target, while all the other studies have delivered below recommended amounts including the presumed "targeted" regimens in the Rice and Arabi studies. Glucose control studies[16–18] have also provided varying calorie and protein intakes while the recent Doig et al. study[19] was targeted to reach 1500 kcal/day (Table 1).

To define the "danger zone for the optimal administration of nutrients, one has to keep in mind that the substrate metabolism is interlinked (e.g. amino acids and lipids can be transformed into glucose), and that there may be different levels of tolerance for deficiencies of each of them (Fig. 1). The prescription of nutrition is generally based on body weight. When categorized according to their actual body weight, patients with low BMI are often underfed but tolerance to more feeding may be impaired. Yet when categorized according to their ideal body weight, both over- and underfeeding may occur as the respective contribution of fat and lean body compartments may vary greatly. This suggests that physicians do not sufficiently discriminate the differences in nutritional needs (Table 2).

Nutritional prescriptions must take into account many other factors, including age. In fact older patients have been shown to be more vulnerable to overfeeding than younger patients because their lean metabolically active body mass is reduced (sarcopenia), which reduces their energy needs.[20] Patients with a high BMI might need less energy and more protein than patients with normal or low BMI.[21] Substrate utilization can be estimated by indirect calorimetry, but the individual contribution of endogenous and exogenous substrates cannot be discriminated. Thus measured substrate consumption may not indicate exogeneous substrate need.

Statements: *Energy deficits accumulate quickly during the first week in the ICU and are not completely preventable. The ICU-related hypermetabolism is of variable duration, and an indicator to assess its amplitude and duration would be very helpful. The energy expenditure in specific patient subgroups (e.g. elderly, obese, malnourished, paralyzed) remains uncertain if indirect calorimetry measurements are not performed, which makes the prescription of nutrition support difficult. It is necessary to identify safe, minimal and maximal amounts*

Table 1
Recent prospective randomized controlled studies comparing nutritional regimens in critically ill patients. Calories and protein intakes are shown in the intervention and control (Ctrl) groups respectively.

Study reference	Calorie intake intervention	Calorie intake Ctrl	Protein intake intervention	Protein intake Ctrl
Arabi[14] permissive vs target $n = 120 \times 2$	1252	1067	43.6	47.5
Rice[11] trophic vs target	300,149	1,418,686	10.9 ($n = 102$)	54.4 ($n = 98$)
Singer[6] TICACOS	2100 kcal/d	1480 kcal/d	76 g	53
Casaer[7] EPaNIC	6–19 kcal/kg/day	1.25–4 kcal/kg/day	0	0.9
Heidegger SPN[15]	28 kcal/kg	20 kcal/kg/d	79 g	56 g
Doig[19]	1500 kcal/day	750	55	20
Van den Berghe[16]	21.9 kcal/kg/day	22.7 kcal/kg/day	0.84	0.9 g/kg/d

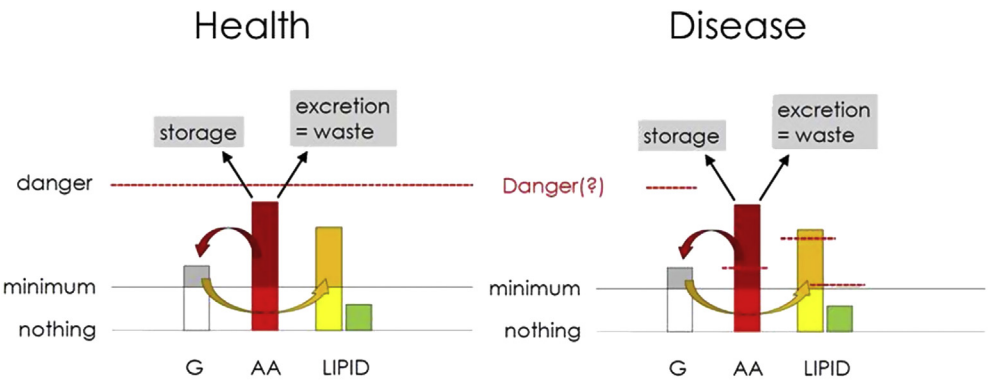

Fig. 1. Minimal and maximal limits for nutrients may are proposed for disease. The lower amounts proposed would be 125 g for carbohydrate, 70 g for amino acids and 15 g for fat while the upper limits would be 275 g for carbohydrates, 150 g for amino acids and 100 g for lipids. Nutrition intakes below the minimum will induce nutrient specific deficits, nutrition above the danger limit will either be stored as fat or will be excreted as waste with additional energy needs. The danger limits may vary between health and disease.

for the different nutrients and at the different stages of acute illness to avoid under and overnutrition. These amounts might be specific for different phases in the time course of a disease.

4. How to manage energy supply?

According to numerous observational studies, most ICU patients suffer from hypocaloric feeding.[5] Indeed, hypocaloric feeding together with bed rest promotes the catabolism of lean body mass.[22] On the other hand, reaching nutritional goals is correlated with improved clinical outcomes in certain groups.[23] Conflicting results resulting from different nutritional strategies have been recently reported.[24]

In a large series with a predominance of cardiac surgery patients who rarely require nutrition support and especially PN, the EPaNIC study[7] compared a carbohydrate load during the first 2 days in the ICU, followed by either early (day 3) or late (day 7) commencement of supplemental PN. The energy prescription was based on the Harris &Benedict equation. The patients who received early supplemental PN had more infectious complications, more days on mechanical ventilation, but no change in mortality, compared to those who received late supplemental PN. This study compared patients with prolonged versus short ICU stay (only 40% of the patients were still in the ICU by day five, 29% by day seven). A number of explanations can be found for these results, including some degree of overfeeding. McClave et al.[25] highlighted various limitations of the study, including its hypercaloric nature and low nitrogen intakes. In addition, the overrepresentation of cardiovascular surgery patients suggests that the findings cannot be generalized. The study is further discussed below.

Heidegger et al.[15] studied patients receiving EN who did not reach 60% of their energy expenditure as measured by indirect calorimetry during the first three days in the ICU in spite of the usual efforts to optimize delivery. By the end of day three after admission in the ICU, patients had accumulated a negative cumulative energy balance of about 4000 kcal. They were then randomized either to continue receiving EN or to receive both EN and supplemental parenteral nutrition (PN) from day 4–8 in order to meet 100 percent of their measured energy needs. Primary outcome was the rate of nosocomial infections after the end of the intervention and until the end of the observation period (i.e. days 9–28). Patients on supplemental PN were in neutral energy balance during the intervention period, while an aggravated energy deficit of about 2200 kcal was noted in those on exclusive EN. A 25% reduction of nosocomial infections was observed in patients on supplemental PN. The number of blood stream infections was similar in both groups. Time on mechanical ventilation was reduced in the SPN group but only significantly for those patients without nosocomial infections. This illustrates the fact that nutrition may prevent complications, but cannot resolve them once they have occurred. The authors concluded that individually optimized energy supplementation with SPN starting 4 days after ICU admission could reduce nosocomial infections, antibiotic usage and time on mechanical ventilation and should be considered as a strategy to improve clinical outcomes in patients in the ICU for whom EN does not meet energy requirements. The study limitations include a limited number of patients per group (i.e. 150), the absence of double blinding, the selection of patients as stated by their degree of tolerance to EN and the rather small difference in energy delivery between groups (due to the fact that EN patients were not intentionally underfed). Therefore the study results cannot be generalized to all ICU patients, in particular to those tolerating EN. This study supports ESPEN guidelines which recommend initiating supplemental PN after 48–72 h in case of intolerance to EN. Such a strategy requires measuring energy expenditure for optimizing feeding, an option that is often neglected due to either the

Table 2
Questions and (un)answers regarding nutritional support in the ICU.

Topics	Answer	Open questions	Suggested solutions
Optimal glucose target	No large confirmation that 80–110 mg/dL is optimal	Role of undernutrition and overnutrition in glucose control	Better control of variability, point of care, trends to reduce hypoglycemia
Energy target	Too little and too much are deleterious	Is matching administered calories to indirect calorimetry optimal?	Universal controls based on large audit (e.g. NutritionDay) should be defined for future PRCT
Protein	1.5 g/kg/day	Enteral bolus versus continuous administration	Choosing the amino acids
Route	EN preferred, progressively	Should we measure gastric residue?	Choosing ICU populations and targeting according to indirect calorimetry
	PN harmful if administered to the wrong population, not harmful if not given in excess	Should we only feed enterally and not give SPN if enteral feeding is not possible during 10 d?	
Glutamine	For exclusive PN addition in patients without MOF	Is glutamine dangerous?	Measure glutamine levels in the plasma

unavailability of indirect calorimeter, or costs related to this technique.

In a recent study, Doig et al.[19] randomized 1372 Australian patients with a temporary contraindication to EN within 24 h of ICU admission to receive either standard care or early PN starting on day one. Caloric requirements were calculated using the Harris & Benedict equation. The early PN strategy resulted in significantly fewer days of invasive ventilation, but did not significantly shorten ICU or hospital stays. It is worth mentioning that Doig et al. did not observe the deleterious effects observed by Caesar et al.[7] in the early PN group and their study supports the findings by Heidegger et al.[13] The prediction, rather than the measurement of energy needs, is a study limitation.[15]

Minimal EN should start soon after admission in the ICU and be increased on day two according to the gut tolerance. This strategy can be seen as a metabolic support or as the first cautious steps of a future full EN and early EN with key substrates, even when applied in small amounts may have specific advantages. The product used for metabolic support should probably include trace elements, vitamins, limited amounts of carbohydrates, anti-inflammatory Ω-3 lipids and amino acids. Despite a theoretical advantage, the clinical benefit of such formula is not yet fully established. Ongoing studies should reveal whether it is safe to initiate EN with much larger amount of food. The measurement of gastric residues during EN administration remains controversial. However, a recent study by Reignier et al.[26] showed that routine gastric volume monitoring does not reduce the risk for developing pneumonia in patients on mechanical ventilation.

Once the patient is hemodynamically stabilized, full nutrition support can be started. It is important to reassess daily patient requirements and the actual amount given since combining PN and EN may increase the risk of overfeeding.

Statements: *A progressive start of EN to reach the calorie target is recommended by the ESPEN guidelines. The best approach is to target the energy goal defined by indirect calorimetry. If this tool is not available, it is recommended to provide 20–25 kcal/kg BW in the early acute phase, which should be increased to 25–30 kcal/kg in the stabilized patients. The administration of supplemental PN in cases of failure of EN after 3 days is a logical option, but its beneficial impact remains to be established.*

5. How much protein is needed?

Metabolic abnormalities associated with stress-related disturbances of protein metabolism in critically ill patients include muscle wasting, glutamine depletion, hyperglycaemia and hypoalbuminaemia. During the first days of sepsis, protein synthesis is severely diminished while protein breakdown is greatly increased[27] and consequently substantial muscle wasting occurs.[28] Glutamine catabolism is accelerated from the onset of illness in septic patients.[29] Amino acid infusions are the main tools to stimulate protein synthesis; however, they cannot reduce protein breakdown.[30] Current evidence supports the early administration of supply of protein, though clinical evidence is scarce. Plank[31] described careful measurements of protein turnover, nitrogen balance or whole-body protein by neutron activation, rather than clinical outcome. A study by this group[32] showed that protein catabolism over a 10-day period soon after ICU admission was reduced by 50% when protein intake increased from an average of 1.1–1.5 g/kg of fat-free mass per day. A higher level of protein intake (1.9 g/kg/day) did not improve the protein sparing effect. The Ishibashi study found an optimal intake of 1.2 g/kg/day but the study was retrospective.[33] Two observational studies found clinical improvement when patients received protein intake close to 1.5 g/kg/d.[34,35] While ESPEN recommends 1.3–1.5 g protein/kg ideal body weight (IBW) per day,[36] studies show that higher infusion rates might further reduce protein catabolism. A protein supply of 1.5 g/kg IBW/day together with an adequate energy intake results in a ratio of non-protein calories to nitrogen of about 80.[19–21] In EPaNIC[7] as in TICACOS[6] this ratio was about 170, and the protein intake was far below the recommended goals.

To define the optimal amount of protein in ICU patients, clinically relevant outcomes should be defined rather than surrogates such as plasma values (e.g. muscle depletion, splanchnic vs. muscle protein synthesis, redox imbalance, glutamine depletion or insulin resistance). The profile of amino acids may also be relevant. It is documented that amino acid administration has less effect on splanchnic protein synthesis than on muscle protein synthesis.[37,38] After abdominal surgery glutathione synthesis is decreased,[39] maybe because of a deficit in cysteine, which is a component of glutathione, as cysteine levels show a linear correlation with glutathione synthesis in erythrocytes. Recently the REDOXS study showed that excessive (twice or more the usual dose) administration of IV supplemental glutamine in severely critically ill patients receiving also glutamine-EN enriched was deleterious and even increased mortality, mainly in patients with multi-organ failure.[40] The recommendations regarding IV glutamine supplementation in patients requiring only PN remain however relevant.[36]

Deficits and excesses in protein supply may also interfere with cellular repair mechanisms such as autophagia. A diet containing 1.4 g protein and 0.16 g branched chain amino acids per kg BW/d prevents insulin resistance in healthy volunteers with 60 days of bed rest.[41] In trauma patients, intravenous alanyl-glutamine dipeptide[42] prevents insulin resistance, and in diabetic patients, oral arginine improves insulin sensitivity.[25] Allingstrup et al. observed that ICU patients receiving protein as recommended by the ESPEN guidelines (average 1.46 ± 0.29 g/kg/day) had a lower mortality than those who received only 0.79 ± 0.29 or 1.06 ± 0.23 g/kg/day independently of energy intake.[43]

While stable isotopes enable precise investigations in research settings, the monitoring of protein metabolism is complicated and nitrogen loss and balance poorly reflect protein turnover.[27] Markers of protein metabolism should be chosen according to the main aims of amino acid provision: a) if lean body mass is targeted, dual X-ray absorptiometry or magnetic resonance imaging measurements might be chosen; b) if glutamine reserves are targeted, plasma protein might be monitored and glutamine plasma levels might be necessary to identify patients with a need for glutamine supplementation.

Statements: *A high protein intake (1.5 g/kg/d) is recommended during the early phase of the ICU stay, regardless of the simultaneous calorie intake. This recommendation may reduce catabolism, but is not supported by strong evidence. Later on during the ICU stay, a high protein intake remains recommended, but it should be combined with a sufficient amount of energy to avoid proteolysis due to fuel energy deficit.*

6. An appraisal of available concepts: glycemia control, early or late enteral or parenteral feeding

ESPEN guidelines[36] recommend early EN (24–48 h), and early supplemental PN (48–72 h) after maximizing the administration of EN. When early EN cannot be increased to the optimal target for energy, an individual decision to supplement EN with PN has to be made, progressing carefully over several days together with glycemic control to maintain the blood sugar below 8.5 mmol/L.

7. Glycemia

Glycemic control has been demonstrated to improve survival, mainly in surgical patients, and has been challenged by numerous

other RCTs and a metaanalysis showing not a clear advantage for all ICU patients. The current recommendations are higher than those previously proposed by Van den Berghe in her original article.[16] Egi et al. [44] showed that practitioners pay great attention to glucose control, in spite of the findings of the NICE −SUGAR study[17] showing an increased mortality using the Leuven approach and of the recent metaanalysis which did not support intensive glucose control for critically ill patients. In fact, the impact of tight glucose control across such a heterogeneous ICU population with diabetes mellitus, previously undiagnosed diabetes or stress-induced hyperglycemia, increased variability in glucose levels and heterogeneous etiologies may explain the differences in the published results. In addition, the incidence of hypoglycemia approached 18% or more and its impact in neurological patients and those with septic shock requires more evaluation. Surgical patients may benefit more from tight glucose control and non diabetic hyperglycemic patients may show a deleterious impact on survival.[45] At present time, some recommendations propose a target glycemia of 100–180 mg/dl.[46,47] In fact, currently used points of care measuring systems are not always accurate enough to target tight glucose control and in addition, the nutritional regimen used in the different studies was very different. Thus EN and PN were provided in the 2001 Leuven study[16] and only hypocaloric EN in the NICE SUGAR study. The EPANIC study showed that excessive early PN administered, mostly in surgical patients (more than 85% of the included patients), significantly increased the complications rate while maintaining glucose control. The Early PN Australian study did not confirm this negative impact.[19]

Accurate or continuous measurements of blood glucose, computerized decision support systems, adequate nutrition support are all essential in optimization of glucose control. Unfortunately, the studies available today do not include all these elements. Until such time, glucose control has shifted from tight glucose control to a more moderate target of up to 150 mg/dl (8.5 mml/L), with the goal of preventing both severe hypo- and hyperglycaemia.

8. Early or late enteral or parenteral nutrition: the barriers to implementation

A number of studies have analyzed the approach of supplemental PN[3,4,13,28,29] and a concept has been proposed for ICU nutrition.[30] In most of these studies EN was started within 48–72 h after ICU admission. PN was started very early in EPaNIC with a high glucose load, while other studies started around 3 days after admission. The step-by-step increase for EN has only been specified for 3 studies (EPaNIC, SPN and TICACOS). For EN, only EPaNIC made such a progression, whereas other trials have compensated for the entire energy deficit only when PN was added to insufficient EN. The need for a careful progression of PN prescription remains to be evaluated, especially for unstable patients. In addition, the energy target determination ideally obtained by indirect calorimetry has some limitations: One of them is the availability of accurate devices since the gold standard Deltatrac II device is no longer available[48] and measurements of resting energy expenditure with other devices may not be accurate enough.

Glucose control has shifted from tight glucose control to a more moderate target of up to 150 mg/dl (8.5 mml/L), with the goal of preventing both severe hypo- and hyperglycaemia. Indirect calorimetry, as the most advanced tool to determine energy needs, was only used in the SPN and TICACOS studies. Malnutrition was only assessed in the EPaNIC trial by the Nutrition Risk Score (NRS-2002),[49] though this score might not be appropriate for cardiac surgery short term ICU patients. None of the studies reported gastrointestinal failure. While patients in the EPaNIC and TICACOS studies were mostly overfeed, underfeeding patients were present in the NICE-SUGAR and most other studies. The provision of protein in the EPaNIC study (0.8 g/kg/d) was considerably below recommendations. The metabolic impact of this protein underfeeding might have been increased by the concurrent energy overfeeding in the early PN group.

The nutrition target has to be adjusted during the acute phase of stress but also in cases of ulterior deteriorations of the clinical status. This includes new bouts of stress, such as in case of new episodes of sepsis, or the adaptation to reduced nutritional needs secondary to the wasting of the metabolically active lean body mass routinely observed during the prolonged ICU stay. Markers of poor tolerance to nutrition include rising glycemia, triglycerides and urea but also a failure to wean from the ventilator.

A concept to simplify nutrition support in ICU patients is based on enteral and parenteral solutions containing 1 kcal per 1 ml of solution.[50] This would ease the prescription since the volume to administer would be equal to the ideal body weight in kilograms multiplied by 20 (acute phase) or 25 (chronic phase) kcal/kg.

The energy target should be set by the physician in charge of the patient. If supplemental PN is prescribed to compensate for insufficient EN, a protocol is needed to give the nurses a sufficient degree of autonomy to adapt the amount of SPN needed to the optimal global amount of energy delivered. This concept is similar to the protocol used to control glycemia: i.e. nurses use insulin and glucose as needed without requiring a new medical prescription constantly. In the absence of such autonomy, it is likely that overfeeding will occur due to the daily and unpredictable variations of enteral energy.

Patients after a prolonged ICU stay generally reach a recovery phase and might benefit from an increased level of energy and protein delivery. Stable euglycemia without increasing insulin doses reflects this metabolic tolerance to a higher level of feeding. In patients with CVVH, active abdominal fistula or burns, an additional supply of protein may be needed.

Statements: *The initial EN prescription is based on gastrointestinal tolerance. Reaching full EN within 2 days by stepwise increases should be the target. If supplemental PN to compensate for insufficient EN is prescribed, a protocol is mandatory to avoid overfeeding. EN and SPN solutions containing 1 kcal per ml would ease the prescription and the administration of nutrition support in the ICU.*

9. Conclusions

Enteral nutrition is the preferred route of feeding in critically ill patients. Progressive increases up to targeted energy needs are suggested within the first 48 h. A high protein administration should be maintained since it contributes to reducing catabolism. If enteral nutrition fails to reach energy and protein goals, supplemental PN should be considered, but a protocol of care is mandatory to avoid overfeeding. Indirect calorimetry is the best available tool to set the energy target and seems useful to optimize the clinical benefits related to nutrition support in ICU patients. Simplified nutrition protocols may be helpful for ICU teams to improve the performance of clinical nutrition.

Contributions of authors

PS, CP, MH, GB and TF participated to the discussion and in the edition of the manuscript. MM, CG, JK and CW participated in the discussion and reviewed the manuscript.

Conflict of interest

The authors were invited by Fresenius Kabi to hold a meeting. The discussion was held and this manuscript was written without any intervention from the company.

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