ICU

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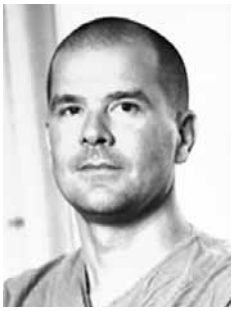
New ESPEN Guidelines for Nutrition in the Critically Ill: Help, What Happened!?



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ESPEN guidelines for nutrition in critical illness have shifted from optimistic anticipative nutritional pharmacotherapy towards cautious and balanced metabolic support. This important new orientation in ICU nutrition management is a consequence of recent strong RCT-based evidence.

Introduction

Recently, the new ESPEN guidelines for critically ill patients have been published. They are the result of two years of data collection, analysis, discussion, rewording, voting, and writing, under direction of Dr. Pierre Singer (Singer et al. 2018). The recommendations have shifted from early enhanced feeding towards more restricted feeding in the acute phase of critical illness. In this contribution we explain what provoked this major shift in the recommendations. We focus on how to interpret these new guidelines, distinguishing "should" from "can" and, likewise, "level A evidence" from "a strong agreement." High quality comparative clinical research of the last decade has resulted in steady progress towards novel, evidence-based nutrition management. Moreover, translational investigations within these trials have increased our understanding of the impact of nutritional management on recovery and functional outcome. These insights allow to design more individualised and dynamic time-adaptive feeding strategies, to be validated in future RCT's.

ESPEN GL for the ICU 2018: A Landslide in Nutrition Support for the Critically Ill

Table 1 summarises the major differences in recommendations between the ESPEN 2006 (Enteral Nutrition) and 2009 (Parenteral Nutrition) and 2018 (Nutrition) guidelines for the critically ill (Kreymann et al. 2006; Singer et al. 2009; Singer et al. 2018). A layman summary would be *"from optimistic anticipative nutritional pharmacotherapy towards cautious and balanced metabolic support."* Indeed, while the previous guidelines were built on preventing cumulative energy and protein debt and attenuating the inflammatory response to critical illness-induced stress, the recent guidelines focus primarily on avoiding iatrogenic harm. Initiation of PN is postponed, the energy target is lower in the acute phase, parenteral glutamine is abandoned, and the use of immune-modulating lipids is no longer recommended, but only suggested. More than ever, the importance of the refeeding syndrome is underscored.

How to Interpret the New ESPEN Guidelines for the Critically Ill?

The new ESPEN guidelines rely –wherever possible- on meta-analyses, conducted by a dedicated and independent epidemiologist, Rd. Waleed Alhazzani. The level A and level B evidence supported recommendations thus rely on statistically sound estimations of treatment effect.

Summarising the level A and B-evidence-supported recommendations, novel nutritional strategies are built on prioritising Enteral Nutrition (EN) rather than Parenteral Nutrition (PN), progressive (slow and titrated) build-up of nutrition doses and accepting hypocaloric feeding for up to 1 week if the gut doesn't tolerate more (Singer et al. 2018). The concept of nutrition as a drug, so-called pharmaconutrition, early in critical illness has been tested and was abandoned (Heyland et al. 2013; Manzanares et al. 2013).

For domains/topics where no reliable

evidence was available yet, e.g. the optimal protein dose or feeding in patients with extremely low BMI (<17), the ESPEN-GL-panel aimed at providing some pragmatic guidance to clinicians. Such recommendations are worded in statements with "can" or "may" and level 0 evidence, leaving their implementation at the clinicians' discretion.

At the end of the data retrieval, analysis, and discussion process, the experts finally voted in favour or against every recommendation. The result of these votes is summarised as "strong consensus" (>90% agreement) or "consensus" (75-90% agreement). Importantly, strong consensus should not be confused with "strong recommendation." Indeed, strong consensus on a level zero recommendation "1.3 g/kg protein can be delivered" implies that the majority of the experts agreed that this might be a target but that the supporting evidence is extremely weak.

What Drove Experts to Write Guidelines So Different From the Previous Versions?!

For many ICU clinicians and nutritionists, these new guidelines may have been upsetting. Indeed, for many years, they have been striving to reach energy and protein targets early in critical illness. They might be wondering whether the current paradigm shift is just the pendulum of clinical guidelines and expert opinion swinging from the left to the right and back, from early –generous- to late –reluctant- nutritional support. The discrepancy between the older and new nutrition guidelines, however, are the consequence of a large body of novel strong evidence. Indeed, over the last decade, *approximately 20000 patients have been included in high-quality randomised controlled trials,* contributing to the generation of reliable clinical data. The lack of such data, unavoidably, resulted in the 2006 and 2009 guidelines, relying largely on physiological and epidemiological evidence. Indeed, numerous observational studies have associated an increased or optimal energy and protein delivery with an improved outcome. Such observations, however, are confounded by severity of illness. Indeed, it is easier to feed patients who are less severely ill. More generally, as SS Young and A Karr explain in a provocative and inspiring paper *"Any claim coming from an observational study is most likely to be wrong"* unless strict rules reducing bias of such analyses are applied (Young and Karr 2011).

Table 1. New evidence changing guidelines (Kreymann et al. 2006; Singer et al. 2009; Singer et al. 2018).

	ESPEN-2006/2009	ESPEN-2018
Time to initiate EN	Early EN (within 24h)	Early EN (within 48h)
Amount	Up to 25 kcal/kg over 2-3 days	Hypocaloric in the early phase; progressive increase until target within 3-7 days
Patients with shock	No contraindication for EN (monitor tolerance)	No EN in uncontrolled shock
In case of insufficient or contraindicated EN	Consider PN within 1-2 days	PN within 3-7 days
Glutamine	PN should contain glutamine	No parenteral glutamine

> "early enhanced feeding does not improve outcome and may evoke harm"

The recent Nutrition-RCTs are heterogeneous regarding their size and design, which increases the validity and generalisability of the aggregated data. Most large trials have been pragmatic, randomising thousands of patients to standardised feeding strategies (Arabi et al. 2015; Casaer et al. 2011; Chapman et al. 2018; Harvey et al. 2014; Reignier et al. 2018; Rice et al. 2012). Some smaller RCTs have elegantly provided labour-intensive titrated nutritional support, guided by indirect calorimetry and/or nitrogen balances (Allingstrup et al. 2017; Heidegger et al. 2013; Singer et al. 2011). All these different studies unanimously revealed that early enhanced feeding does not improve outcome and may evoke harm.

Hence, over the last years, metabolic support in critical illness has been enriched by the principles of modern comparative research and data aggregation, which generated novel and reliable guidelines, particularly regarding early nutrition management in critical illness.

These "Negative" RCTs on Nutrition - Aren't They All About Overfeeding? No

Several recent multicentre RCTs finding harm by early enhanced feeding have been criticised for having administered excessive energy and insufficient protein. Both the EPaNIC RCT in critically ill adults and the PEPaNIC RCT in critically ill children found prolonged ICU dependency by early PN supplementing insufficient EN, as compared to withholding supplemental PN until one week after ICU admission. In both RCTs, early PN evoked more infections and prolonged dependency on vital organ support (Casaer et al, 2011; Fivez et al 2016). In critically ill adults, early PN was also found to increase ICU-acquired muscle weakness and –in both children and adults- health care-related costs (van Puffelen et al. 2018b; Vanderheyden et al. 2012). Hence, both RCTs found that accepting a macronutrient deficit in patients with failing or contraindicated EN is superior

to administering early PN. Pre-planned secondary analyses of both RCTs did not support the hypothesis that harm by early PN would be driven by excess energy intake (Mcclave et al. 2012; Casaer et al. 2013; Vanhorebeek et al. 2017). Indeed, in both EPaNIC and PEPaNIC, harm related to the administered amino acid dose, and not to the glucose and/or lipid dose.

A meta-analysis of studies comparing EN versus PN in critically ill patients suggested, however, that harm is evoked by the dose of nutrition given rather than the route (Elke et al. 2016). Indeed, Gunnar Elke and co-investigators revealed that PN in the first ICU week provoked more infections as compared to EN, but this was not the case for "isocaloric" studies providing EN and PN at comparable doses, such as the CALORIES and Nutritrea-2 trials (Harvey et al. 2014; Reignier et al. 2018). Likewise, RCTs evaluating supplemental PN tend to be neutral if the separation between nutrition doses in both arms was rather modest (Allingstrup et al. 2017; Heidegger et al. 2013). In none of the trials revealing harm by early up-to-target feeding, however, the energy or protein target was "excessive," considering the targets recommended at the time they have been conducted (Braunschweig et al. 2014; Casaer et al. 2011; Doig et al. 2015b; Singer et al. 2011). As a consequence, the beneficial effect in the control arm is more likely to be brought about by temporary nutrient restriction (Braunschweig et al. 2014; Casaer et al. 2011; Doig et al. 2015b). This is why the current guidelines recommend a more progressive (slower) build-up of energy provided (Singer et al. 2018).

Is Indirect Calorimetry the Solution to Prevent all These Nutrition-Related Complications? No

Indirect Calorimetry (IC) provides the best estimation of Resting Energy Expenditure, closest to Direct Calorimetry quantification of the amount of energy burned by a patient. IC is more accurate than equations based on biometrics and disease state (Reid 2007). ESPEN guidelines, thus, recommend relying on an indirect calorimeter when determining REE (level B Recommendation). Uncertainty remains, however, regarding how to apply measured REE in nutritional management. In the early phase of critical illness, the guidelines recommend keeping caloric intake below 70% of either measured or calculated REE (level B). The recommendation to target measured REE thereafter was graded "evidence level 0" reflecting the lack of evidence in support of IC-guided nutrition therapy. Indeed, Early Goal-Directed Nutrition (EGDN), initiated on ICU Day 1 and guided by IC and nitrogen balance did not improve functional outcome in the EAT-ICU trial (Allingstrup et al. 2017).

> "current guidelines recommend a more progressive (slower) build-up of energy provided"

Despite careful titration, EGDN actually increased ureagenesis and ICU length of stay. The TICACOS trial of early IC-guided PN revealed similar results (Singer et al. 2011), while the SPN trial evaluating later initiation of a low dose of IC-guided SPN together with EN revealed no impact on hard clinical endpoints (Heidegger et al. 2013). Importantly, in the PEPaNIC trial, Early-PN was equally detrimental in participating ICU's applying IC as in units relying on calculated REE (Fivez et al. 2016).

These discouraging results of IC early in critical illness may be explained by anabolic resistance. Indeed, in the acute phase of critical illness, nutrient mobilisation from endogenous reserves through catabolism is not suppressed by feeding (Schwarz et al. 2000). Hence, even when REE is measured very accurately, the nutrition provided comes "on-top" of this, increasing metabolic burden.

The impact of REE-guided nutrition therapy in prolonged critical illness may be more important, and deserves to be listed as a research priority. Nevertheless, even in expert hands, conducting repeated REE measurements in critical illness remains challenging and confounded by high FiO2, chest tubes, and continuous renal replacement therapy. This is reflected by the important proportion of study-patients in which no REE value could be obtained in recent RCTs (Heidegger et al. 2013).

Do all Patients Respond Equally to Nutritional Interventions?

Obviously, ICU patients are a very heterogeneous population including well-nourished patients admitted after major surgery and chronically underfed patients treated for sepsis. Pre-planned subgroup analyses in some of the larger RCTs determined whether patients respond differently to enhanced nutrition interventions (Arabi et al. 2016; Casaer et al. 2011; Fivez et al. 2016). In summary, no differential response was detected in patients with or without sepsis, medical versus surgical patients, different BMI categories or high versus low nutritional risk scores. Also in critically ill children, patients deemed to be at the highest nutritional risk (neonates and patients with a high nutritional risk score) were significantly harmed by early supplemental PN (Fivez et al. 2016; van Puffelen et al. 2018a; van Puffelen et al. 2018c). Finally, in the pilot TOP-UP RCT, early PN had no benefit when provided only to patients presumed to be at high nutritional risk (Wischmeyer et al. 2017).

The differential effect of temporary nutrient restriction on long-term rehabilitation as compared to acute outcomes is another common concern. However, in none of the trials studying long-term functional outcome, lower protein and/or energy intake had any untoward effect

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(Allingstrup et al. 2017; Doig et al. 2015a; Needham et al. 2013). Moreover, in the EPaNIC RCT, early PN actually increased weakness, and hampered recovery thereof. Mechanistic studies have implicated feeding-induced suppression of autophagy, a crucial cellular recovery process, as a culprit (Hermans et al. 2013). In the PEPaNIC RCT, finally, Early-PN compromised neurocognitive development, as assessed 2 years after randomisation (Verstraete et al. 2019).

The Time-to-Start-Feeding Indicator

The 2018 version of the ESPEN GL recommends waiting 3 to 7 days before initiating PN when EN fails and before increasing energy intake up to target (Singer et al. 2018), which highlights the remaining uncertainty on how long caloric restriction can be tolerated. Even the 7-day cut-off may not be strict since a more prolonged nutrient restriction has never been studied. The ideal time when patients do benefit from artificial nutrition may vary, and may depend on the severity of illness and its evolution over time. A more individualised determination of when a patient may benefit or at least not experience harm from enhanced nutrition support would be very welcome. A reliable real-time indicator of the organism converting to anabolism is yet to be identified. Such insights may be helpful in designing a "ready-to-feed" monitor and a novel dynamic feeding strategy, to be evaluated in future RCTs.

Conclusion

Recent RCTs in ICU have allowed to design evidence-based nutrition strategies for the acute critically ill. Since none of the available nutritional risk parameters identified patients benefiting from early or enhanced feeding, most recent feeding guidelines promoting hypocaloric feeding in the acute phase of critical illness can be applied to all ICU-patients. Future research, particularly focusing on the post-acute and prolonged critically ill patients and identifying the time of anabolic switch would allow to further improve patient care.

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Abbreviations

BMI	Body Mass Index
EGDN	Early Goal Directed Nutrition
EN	Enteral Nutrition
ESPEN	European Society of Parenteral and Enteral Nutrition
IC	Indirect Calorimetry
ICU	Intensive Care Unit
PN	Parenteral Nutrition
RCT	Randomised Controlled Trial
REE	Resting Energy Expenditure

Key points

- Novel nutritional strategies are built on prioritising enteral nutrition rather than parenteral nutrition, progressive build-up of nutrition doses and accepting hypocaloric feeding for up to 1 week.
- Over the last years, metabolic support in critical illness has been enriched by the principles of modern comparative research and data aggregation, which generated novel and reliable guidelines.
- Recent feeding guidelines promoting hypocaloric feeding in the acute phase of critical illness can be applied to all ICU-patients.

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