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CLINICAL COMMENTARY

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Is it now time to promote mixed enteral and parenteral nutrition for the critically ill patient?

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Abstract *Background:* Intensive care outcome measured by morbidity and mortality is altered in the severely malnourished ICU patient, and nutritional support of the critically ill is accepted as a standard of care. Current recommendations suggest starting enteral feeding as soon as possible whenever the gastrointestinal tract is functioning. The disadvantage of enteral support is that inadequate energy and protein intake can occur. The present commentary focuses on some recent findings regarding the nutritional support of critically ill patients and proposes to promote mixed nutrition support by enteral nutrition (EN), and by parenteral nutrition (PN) whenever EN is insufficient. *Recent findings:* An increasing nutrition deficit during a long ICU stay is associated with increased morbidity (increased infection rate or impaired wound healing). Evidence shows that EN can result in underfeeding and that nutrition goals are reached only after 5–7 days. Contrary to former beliefs, recent meta-analyses of studies in the ICU showed that PN is not related to excess mortality but may even be associated with improved survival. *Conclusions:* Optimising the increased substrate requirement for the critically ill by initiating timely nutrition support and ensuring tight glycaemic control with insulin is now considered central for improved intensive care outcomes. Supplemental PN combined with EN could be an effective alternative to achieve 100% of energy and protein targets at day 4, when EN alone fails to achieve goals greater than 60% by day 3. Whether such combined nutrition support provides additional benefit on overall outcome has to be ascertained in further studies.

Keywords Nutritional support · Critical care · Human · Practice guidelines · Standards · Enteral nutrition · Parenteral nutrition · Outcome · Combined nutrition

Introduction

For many years the major concern of physicians caring for critically ill patients was to stabilise vital signs, including haemodynamic and respiratory function, and to control infection. Nutrition was often a second priority. During the past decade, however, increasing evidence in critical care medicine suggests that optimal nutritional management of critically ill patients could positively influence clinical outcome. The rationale for nutritional support is based on the observation that critically ill patients undergo an obligatory catabolic phase. This is associated with protein breakdown to produce energy and amino acids, a metabolic condition resulting in protein-energy malnutrition and with an increased rate of complications, including infections, multiple organ failure, poor outcome and prolonged length of stay [1–7]. In ICU patients, the cumulated deficit has been associated with increased morbidity [8]. In addition, up to 50% of patients admitted to European hospitals have various degrees of malnutrition [9]. Thus, standards of care for ICU patients should include nutritional support.

Over the years, opinion on the best nutritional support administration route has evolved. This was demonstrated

by Berger et al., who described the change in nutritional support techniques in a surgical ICU over a 10-year period [10]. A considerable change was observed, evolving from the predominant use of total parenteral nutrition (TPN) to the wide use of enteral nutrition (EN). However, when EN is systematically used in ICU patients, a protein-energy deficit is often observed. First, the full coverage of nutritional needs by EN is often reached only after 5–7 days. This is due to relative gastrointestinal intolerance and temporary cessation of feeding during patient care or investigations [11, 12]. Second, EN delivery frequently differs from the amount prescribed by the physician [13, 14]. Moreover, there is still some confusion regarding the optimal timing for initiation of nutritional support. In practice, it commonly takes up to 7 days before full coverage of energy needs is achieved [15]. With these limitations in mind, in order to prevent both protein and calorie deficits, we propose a comprehensive clinical approach, as summarised in Fig. 1.

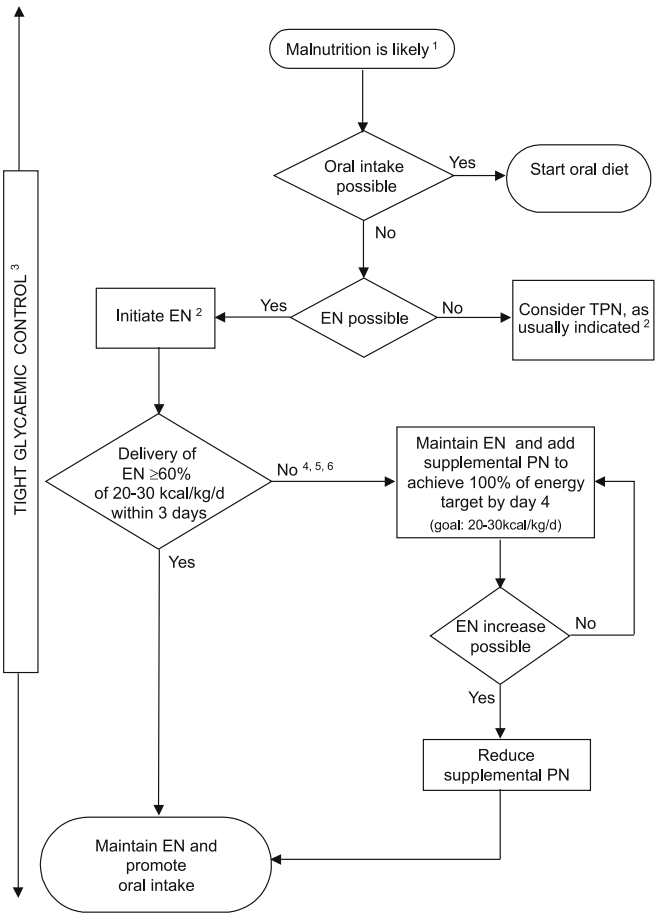

Fig. 1 Nutrition in critically ill patients: revisiting the approach to nutrition with enteral (*EN*) and supplemental (*PN*) support maintaining glycaemic control. Notes: *1* At admission, 30–50% of patients have pre-existing malnutrition and are at risk of developing acute malnutrition in the ICU [9]; *2* EN reduces morbidity in ICU patients [54]; *3* glycaemic control reduces morbidity and mortality [49]; *4* inadequate EN is frequent [12]; *5* inadequate EN increases morbidity and length of stay [8]; *6* early TPN reduces mortality [44]

Enteral nutrition support in ICU patients

For the purpose of this commentary, we use the term "critically ill" to designate patients receiving mechanical ventilation for at least 48 h. Patients requiring prolonged mechanical ventilation generally suffer from acute severe illness (SAPS III score > 40; $\geq 10\%$ expected mortality) and are expected to have a prolonged ICU stay. Our discussion will not refer to patients routinely managed in ICUs for a short time, such as post-operative cardiovascular patients.

In patients with an intact and functional gastrointestinal tract, when oral feeding is impossible, enteral feeding is thought to be more physiological than TPN and is also cheaper [16]. It is also accepted that EN may maintain intestinal integrity, immune and gut-barrier functions. Several studies have demonstrated consistent benefit of EN in decreasing septic morbidity, hospital and ICU length of stay, and mortality [17, 18]. Moreover, the timing of initiation of EN is also important, as indicated by a retrospective cohort study conducted in a medical ICU that found greater mortality with delayed than with early EN [19].

The ESICM Working Group on Nutrition and Metabolism proposed relevant indications and contraindications as well as a pragmatic approach for prescribing EN [20]. These principles are summarised in Table 1. In their recommendations, early EN is proposed within 3 days of injury. However, achieving targeted nutritional goals with EN is often difficult, at least during the early phase after ICU admission [11–14]. Several studies reported failure to deliver adequate energy intake in clinical practice if only EN is used [14, 21–24]. The inability to deliver adequate energy intake, resulting in energy deficit, has been associated with increased morbidity and mortality in ICU patients [8, 25].

The implementation of feeding protocols has been proposed as a strategy to successfully deliver adequate nutritional support [26–28]. The ACCEPT study, a Canadian study conducted in 14 hospitals [29], showed that survival from intensive care was improved when evidence-based guidelines for nutrition were followed and larger amounts of nutrition were delivered more consistently. Other recent studies have shown that despite implementation of feeding protocols, nutritional requirements in the critically ill remain difficult to meet. Genton et al. studied 494 patients with a daily target caloric prescription of 20–25 kcal/kg (women) and 25–30 kcal/kg (men) of admission body weight [12]. On day 5, less than 30% of the patients received $\geq 90\%$ of the prescribed calories and their protein delivery reached only about 70% of requirements—clearly an under-nutrition situation. Another study showed that only 14% of ICU patients achieved 90% of prescribed

Table 1 Indications, contraindications, and timing of enteral nutrition (*EN*) in critically ill patients

General statement
Whenever nutritional support is indicated, the enteral route is preferred to parenteral nutrition
Practical indications
Malnutrition present, whatever the aetiology, in a patient unable to eat
Prolonged fasting (more than 3–4 days)* in a well-nourished patient unable to resume oral nutrition
Supplementation of insufficient oral intake for > 3–4 days*
Severe trauma and burns: there is accumulating evidence that early EN is beneficial
Maintenance of gut mucosa, prevention of atrophy, stimulation of compensatory hypertrophy after small bowel resection
Opening of digestive tract and preparation of oral feeding
Contraindications
Absolute
Non-functional gut: anatomic disruption, obstruction, gut ischemia
Generalised peritonitis
Severe shock states
Relative
Expected short period of fast, except in severely injured patients
Abdominal distension during EN
Localised peritonitis, intra-abdominal abscess, severe pancreatitis
Patient with terminal disease
Comatose patients at risk of aspiration (especially gastric feeding)
Extremely short bowel (less than 30 cm)
Timing
Early EN (within 24–48 h): severe trauma, burns, highly catabolic state
Standard EN (after 2–3 days): moderate stress in a patient unable to eat

Adapted from reference [20], Table 3, p. 855, with kind permission of Springer Science and Business Media
* Evidence-based elements demonstrate clinical efficacy after delay as long as 7 days. However, clinical practice and experimental evidence strongly suggest that earlier onset of administration is warranted

calories within 3 days, based on a 25–35 kcal/kg/day need [13]. Spain et al. [30] also analysed the effect of implementing a nutritional support protocol. They demonstrated that only 58% of ICU patients included in an enteral feeding protocol achieved their targets. It is worth mentioning that when good compliance to the enteral feeding protocol was maintained over 80% of the prescribed volume was administered by day 3.

How can we achieve the target values of nutritional needs?

Generally speaking, under- as well as over-feeding should be avoided [31, 32]. Various complications of overfeeding have been reported in several studies: hyperglycaemia, hyperlipidaemia, hepatic dysfunction, ventilation weaning difficulties [33–36]. However, the critically ill patient is more often at risk of hypocaloric than hypercaloric feeding. A recent study including medical ICU patients showed that hypocaloric feeding is associated with increased risk of bloodstream infection [37]. Another investigation demonstrated a reduction in the duration of mechanical ventilation associated with improved nutritional support [38]. A prospective study on the nutritional support in 48 critically ill patients staying ≥ 5 days in the surgical ICU revealed that despite following a nutrition protocol, negative energy balance was very common during critical illness, with the lowest energy delivery during the first week, creating an important cumulative energy debt (5,000–9,000 kcal) [8]. Additionally, there was an association between the cumulated energy deficit and the number of complications (infection rate, impaired wound healing), and the deficit was not compensated during the ICU stay. Another study by Dvir et al. also found a correlation between negative energy balance and complications in ICU patients [25].

Given the various patient presentations and conditions determined by the underlying nutritional status, extent of stress response, diagnosis, and severity of illness, different increasingly aggressive options of nutrition support can be considered, including: (1) allowing hypocaloric EN; (2) EN with slow augmentation until achievement of target delivery; (3) EN supplemented by PN by day 3 of attempts at maximisation of EN delivery; (4) early combination of EN plus PN started at admission. With the first two options, there would be a high risk of underfeeding in most critically ill patients. With a combined approach of EN plus PN initiated by day 3 of ICU admission, if the daily caloric goal is not achieved, most ICU patients would be fed adequately without accruing a large caloric debt. Although even more aggressive approaches are possible,

Ibrahim et al. [39] showed that a too rapid initiation of nutrition therapy is associated with a poorer outcome. It is, however, important to note that in this study, using bolus feeds, even the early-feeding group received less than 28% of the estimated caloric and protein requirements. In our opinion, the conclusions of this study cannot be generalised. Therefore, it seems that the available evidence, along with financial considerations, would presently support an approach of initiating supplemental nutrition support by day 3 of attempts at maximisation of EN delivery.

Enteral versus parenteral nutrition

Until recently, early PN was not believed to be beneficial, due to its metabolic and infectious complications, more frequently observed during the early post-injury phase. There has been also reluctance to use PN because of concerns regarding complications related to hyperglycaemia, hypertriglyceridaemia, and gut mucosal atrophy [40, 41]. In a meta-analysis comparing EN to EN supplemented with PN, Dhaliwal et al. [42] recommended against starting PN at the same time as EN, arguing the absence of data suggesting a benefit from using EN and PN combined, and potential harm from PN in critically ill patients. However, it is important to note that (1) the study population was heterogeneous, with two of the five studies included investigating patients with burns; (2) all of the five studies included were conducted before 1998, at a time when the benefits of tight glycaemic control had not been shown; and (3) overfeeding was also commonly practised, frequently resulting in TPN-induced hyperglycaemia. This last point could explain the difference in the risk of infection. The concept of nutritional support has evolved since then: the recently published ESPEN guidelines #8 [43] state that patients who fail to reach the lower target for intake using EN should receive additional PN. In daily practice the initiation of PN is often delayed, and only if after 7–10 days the patient is still unable to receive at least 60% of the caloric and nitrogen requirements with enteral feeding is supplementary PN then indicated. However, this concept must be revisited. Indeed, Simpson et al. in a meta-analysis of 465 publications, compared the use of TPN versus EN [44]. The results, based on nine trials with complete follow-up, showed decreased mortality with the use of TPN [odds ratio (OR) of death 0.51, 95% confidence interval (CI) 0.27–0.97, $p = 0.04$] despite an increase of infectious complications in the TPN group (OR 1.66, 95% CI 1.09–2.51, $p = 0.02$).The benefit

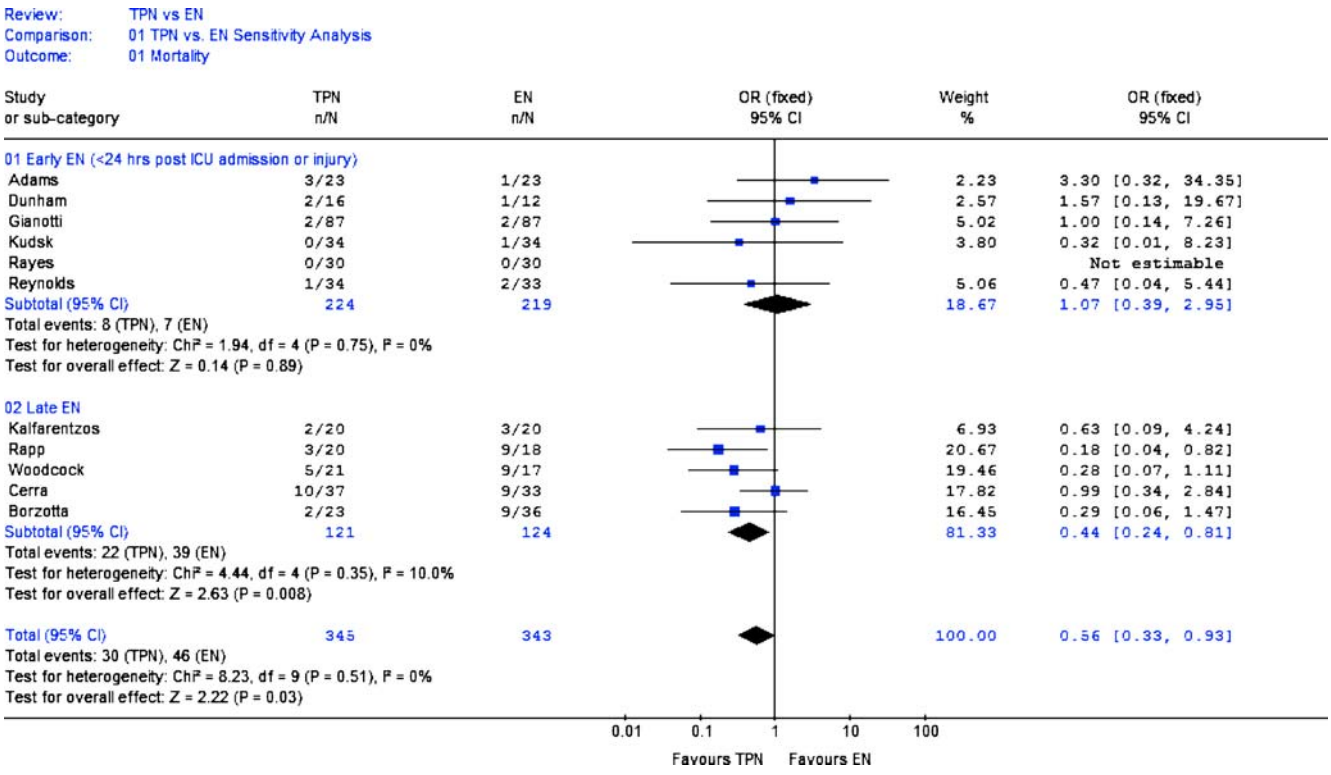

Fig. 2 Total parenteral nutrition (*TPN*) versus enteral nutrition (*EN*): effect on mortality, sensitivity analysis and subgroup analysis. *OR* Odds ratio; *N* total number of patients in the group; *n* number of patients who died in the group. Adapted from reference [44], Fig. 4, p. 19, with kind permission of Springer Science and Business Media

was even more important when trials compared the use of early TPN with delayed EN (> 24 h), (OR 0.29, 95% CI 0.12–0.70, $p = 0.006$) (Fig. 2). The authors recommended the administration of TPN in patients in whom EN could not be initiated within 24 h of ICU admission or injury, concluding that early TPN may be superior to delayed EN.

Another meta-analysis in critically ill patients is consistent with the finding that TPN is not associated with incremental mortality despite an increase of infection [45].

As an alternative to central administration of TPN, some advocate the use of peripheral PN (PPN), when a central line access is not available. PPN could be of benefit in ICU patients without the risks associated with venous central catheterisation [46–48]. Although PPN might be an effective alternative to central venous administration of TPN, the short-term tolerance of PPN might be limited to 5–7 days. More prospective documentation is needed before any conclusion can be reached regarding wider use of this modality in clinical practice.

Contemporary metabolic and nutritional issues: tight glycaemic control is mandatory!

Recognising the presence of altered and increased metabolic requirements is central to understanding why nutrition is so important for ICU patients. It is likely that some of the side effects related to TPN observed in studies over the past decade were due to inadequate glycaemic control. Indeed, trauma and/or septic ICU patients have increased substrate turnover of carbohydrates, lipids and amino acids and altered end-organ perfusion combined with peripheral insulin resistance, all processes linked to systemic inflammation. The increased demand for glucose and amino acids derives from protein breakdown, and the huge increase in skeletal muscle catabolism is the most evident consequence. Optimising the particularly increased substrate requirements and overcoming insulin resistance is considered central to positively affect clinical outcomes. Since the landmark Leuven study, tight glycaemic control with the use of insulin is considered central to improving morbidity and mortality in critically ill patients [49]. The survival benefits of intensive insulin therapy seem to depend mainly on the maintenance of normoglycaemia rather than glycaemia-independent insulin effects [50]. New preliminary evidence, however, questions tight glycaemic control due to a possible increase in hypoglycaemia (Preiser JC, Tight glycemic control in real life: results of the Glucontrol Study, presented at the 19th Annual ESICM meeting, Barcelona, Spain, 24–27 September 2006) [51]. As hypoglycaemia has been associated with increased mortality, the need for adequate energy intake may be crucial to obtain the beneficial effects of tight glycaemic control. Van den Berghe et al. reported an incidence of hypoglycaemia of about 19% without increased morbidity or mortality, but the patients in that study were aggressively fed enterally and parenterally from the time of ICU admission [52].

As the majority of the parenteral feeding trials were accomplished before the era of tight glucose control, it seems likely that their unfavourable outcomes were due to hyperglycaemia and not exclusively to TPN.

A revision of the dogma is needed: We should apply EN with supplementary PN when EN alone fails to reach the nutrition goal

As we have seen, and contrary to former beliefs, recent meta-analyses show that TPN does not involve excess mortality [44, 45]. These reports convey a concept that is a major breakthrough in current routine nutritional support in ICU patients by promoting a much wider use of PN. Current evidence suggests that enteral feeding is the preferred route. Unfortunately, underfeeding due to insufficient delivery is repeatedly reported and is related to an increased risk of developing or aggravating an existing malnutrition state and associated with increased morbidity [8, 53]. This can be prevented by proper nutrition protocols that include timely and adequate enteral feeding. When EN delivery is inadequate, PN supplementation usually allows immediate 100% coverage of these needs. We propose that if EN fails to meet the patient's nutritional needs within 3 days, immediate PN must be initiated to achieve 100% of energy and protein targets by day 4. A sequential approach should be considered, with de-escalation of PN as EN is approaching the goals. Simultaneously, glycaemic control, avoiding hypoglycaemia by appropriate nutritional support along with insulin administration, is necessary [49]. By implementing such protocols, improved matching between energy requirements and delivery can be achieved. Combined nutritional support will also allow the protein needs to be met sooner during critical illness. A randomised controlled trial is warranted to confirm the outcome benefits of the proposed approach.

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