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Parenteral nutrition in intensive care patients: medicoeconomic aspects

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Purpose of review
Parenteral nutrition (PN) alone or as supplemental parenteral nutrition (SPN) has been shown to prevent negative cumulative energy balance, to improve protein delivery and, in some studies, to reduce infectious morbidity in ICU patients who fail to cover their needs with enteral nutrition (EN) alone.

Recent findings
The optimization of energy provision to an individualized energy target using either early PN or SPN within 3–4 days after admission has recently been reported to be a cost-saving strategy mediated by a reduction of infectious complications in selected intensive care patients.

Summary
EN alone is often insufficient, or occasionally contraindicated, in critically ill patients and results in growing energy and protein deficit. The cost benefit of using early PN in patients with short-term relative contraindications to EN has been reported. In selected patients SPN has been associated with a decreased risk of infection, a reduced duration of mechanical ventilation, a shorter stay in the ICU. Altogether four studies have investigated the costs associated with these interventions since 2012: two of them from Australia and Switzerland have shown that optimization of energy provision using SPN results in cost reduction, conflicting with other studies. The latter encouraging findings require further validation.

Keywords
cost-effectiveness, energy requirements, ICU, infections, supplemental parenteral nutrition

INTRODUCTION

Critically ill patients are characterized by stress-induced catabolism, which includes stress hormones, inflammatory cytokines and other mediators [1]. When relying on enteral nutrition (EN) alone, energy deficits appear frequently during the 1st week following admission to the ICU [2]. Difficulty of initiating efficient feeding results in a cumulated deficit larger than −4000 kcal or 50 kcal/kg during the first week, leading to an increased risk of infection, prolonged duration on mechanical ventilation, longer stay in the ICU and increased mortality [3]. Thus, the 2009 European guidelines have recommended to prevent caloric and protein underfeeding in ICU patients and to initiate early, normocaloric EN [4], including the consideration of supplemental parenteral nutrition (SPN) [5]. In the last 5 years, few multicenter randomized controlled trials (RCTs) have investigated the timing of early parenteral nutrition (PN) and SPN in critically ill patients [6–8]. Contradictory results have been reported, probably explained by the differences in population inclusion criteria (broad or selected), the dose and the type of macronutrients delivered and, most importantly, the use of predictive equations to determine energy target in most of them versus indirect calorimetry targeted in a few. Indeed, predictive equations of energy expenditure based on anthropometric data are inaccurate, when applied to ICU patients. Measured energy expenditure by indirect calorimetry is a key tool to optimize the nutrition therapy of these patients [9].

Long, the PN technique was considered to be more expensive than EN for several reasons: expensive PN solutions (compared with enteral feeds),

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KEY POINTS

- In patients for whom EN alone is insufficient to meet energy requirements, the use of PN or SPN is an alternative.
- Using early PN or SPN optimizes the nutrition therapy in selected ICU patients.
- In selected ICU patients, that is in patients requiring ICU therapy for more than a week and with a clear contraindication to EN or an insufficient EN, using early PN or SPN guided by indirect calorimetry seems to be a cost-saving strategy.
- Further studies evaluating the cost-effectiveness of early PN and SPN in ICU patients are required.

expensive accesses (central catheters), expensive controls (chest radiographs etc.), costly complications (technical and metabolic) and infectious complications [5]. As the 'choosing wisely campaign' of the American Societies of Critical Care that included in 3rd position of five items the recommendation 'do not use PN in adequately nourished critically ill patients within the first 7 days of an ICU stay' [10], this posture has of course not improved the image of PN. But looking at evidence, only few studies have focused on medicoeconomic impact of using early PN or SPN in case of insufficient EN alone [11▪], that is in conditions potentially leading to malnutrition.

Searching for studies addressing this issue of the costs of EN versus PN/SPN, only four studies could be retrieved since 2012 [11▪,12,13▪,14], of which only two were within the time-frame limit imposed by the Current Opinion style, the Harvey *et al.*'s Calories trial comparing EN and PN from admission and the Pradelli *et al.*'s [13▪] SPN trial, evaluating EN versus EN with SPN strategy for 5 days after day 3. Due to the paucity of the data, we will include the four studies. We hereafter analyze the various factors that might have influenced the costs of the different strategies.

COMBINED ENTERAL NUTRITION AND PARENTERAL NUTRITION IN CRITICALLY ILL PATIENTS: RATIONALE

Why would additional PN be required while feeding by the enteral route? Observational studies have repeatedly shown that exclusive EN, despite its potential beneficial effects, is frequently associated with a low-energy delivery, insufficient to cover the measured energy expenditure. EN is difficult in ICU settings, and frequently interrupted. The resultant energy deficit has been associated with a proportional increase in underfeeding-related complications. Moreover it was recently shown in large muticentric French study including 2410 patients in septic shock that EN was associated with more complications, with no advantages over PN [15▪].

In patients for whom EN alone does not cover energy requirements [16–18] for whatever reason, the use of full or partial PN is a validated alternative according to European Society of Parenteral and EN: the upcoming guidelines that will replace the now outdate 2009 guidelines will maintain the position that prolonging absence of feeding beyond 72 h should not be tolerated, and that any feeding route is acceptable for the purpose (communication from the guidelines group that includes M.M.B. and C.P.). Indeed, underfeeding over several days is associated with muscle loss and weakness, increased risk of infection, prolonged duration of mechanical ventilation and length of stay in the ICU, and increased mortality [19▪]. Nevertheless the benefit of SPN in ICU patients remains controversial for several reasons, including that the SPN method is more complex than either EN or PN alone and incurs the risk of overfeeding. A RCT by Heidegger *et al.* showed that the combination of PN with EN for 5 days between days 4 and 8 after ICU admission, in patients for whom EN did not cover 60% of their nutritional goals, resulted in a 35% reduction in the adjusted risk of nosocomial infection compared with continued administration of EN alone (hazard ratio 0.65; 95% confidence interval 0.43–0.97; $P = 0.03$) [8]. Moreover, Singh *et al.* [20] reported that combined EN and PN in patients with severe acute pancreatitis improved clinical outcomes and reduced mortality.

In addition to the classical contra-indications to EN, the presence of profuse diarrhea, which is associated with macronutrient and water malabsorption, may be an indication for supplemental or total PN, although prospective evidence testing this hypothesis is still lacking. Indeed, EN *per se* does not increase the risk of diarrhea, but observations show that in patients receiving more than 70% of their energy needs, the risk of diarrhea is increased 1.7 times [21], and leads to increased length of mechanical ventilation and of ICU stay [22], nurse workload and associated costs [23].

HOW COULD PARENTERAL NUTRITION/ SUPPLEMENTAL PARENTERAL NUTRITION REDUCE COSTS?

The SPN strategy is not a cost-minimization strategy but a cost-efficiency intervention such as tested in the CALORIES trial [11▪]. The first measures and compares the costs of different medical interventions.

The second compares the ratio between the cost of an intervention and the clinical outcomes, and has frequently been applied to malnutrition by international organization such as the International Rescue Committee (viewed on 13 November 2017: https://www.rescue.org/sites/default/files/document/959/nutritiondesignedbrieffinal.pdf). Cost-efficiency evaluations are used to investigate the impact of a potentially more expensive intervention to achieve economic efficiency. Costs are the resources used to conduct the intervention. Benefits are the outcomes realized from the specific intervention. Direct benefits are money saved through reduced length of care (mechanical ventilation, ICU and hospital stay), medications and improved clinical outcomes. Indirect benefits are those which reduce the cost of disease to the society by reducing morbidity and mortality, and improving quality of life.

Optimal nutritional support in ICU patients attenuates the catabolic response to injury, and improves clinical outcomes reflected by a decrease in complication rates and length of stay, likely leading to cost savings [24]. However, nutritional support is associated with side effects and risks. EN is often associated with underfeeding and diarrhea [21], whereas PN has been associated with higher risks of overfeeding and hyperglycemia [5]. Thus, both EN and PN can induce costs. However, few old economic analyses reported cost savings with the use of EN compared with PN in critically ill patients.

Finally, there is currently a broad spectrum of commercial enteral and parenteral feeding products. In general, enteral feeds remain cheaper to administer than PN solutions. Taken together, these previous findings suggest that increased use of EN rather than PN results in cost-savings, particularly in ICU patients. But is it still true, if all cost parameters are included? Only few studies have analyzed the whole picture.

PARENTERAL NUTRITION AND SUPPLEMENTAL PARENTERAL NUTRITION IN ICU PATIENTS: DOES TIMING IMPACT THE COSTS?

In 2013, Doig and Simpson [12] reported cost savings attributable to the use of early PN (day 2) in patients with short-term relative contraindications to EN. Costs of US acute hospital care were reduced by $3150 per patient. However, this medicoeconomic evaluation was based on a cost-minimization analysis [13▪]. Doig *et al.* [6] showed no statistically significant effect of using early PN on 60-day mortality or the incidence of infections, but a significant reduction of mechanical ventilation time was reported in patients receiving early PN, as well as better muscle strength on day 60. Thus, the cost benefit attributable to the use of early PN in patients presenting relative contraindications to EN seems to be favorable.

Recently, a medicoeconomic analysis based on data from the Swiss SPN trial reported that adding SPN to EN in selected ICU patients results not only in significant clinical benefit in terms of infection reduction [8], but also in a cost advantage [13▪]. Of note in this study, the medicoeconomic impacts were included as secondary endpoints of the study. In this RCT, SPN was administrated for 5 days in patients for whom EN by day 3 failed to cover 60% of energy target. This provision of SPN resulted in a mean modest improvement of 2320 kcal in cumulative energy balance compared with EN alone ($P < 0.001$). As a result the risk of nosocomial infection was reduced by 10% for each 1000 kcal decrease in cumulative energy deficit. Association between nosocomial infections and medical resource consumption was established, including antibiotic use, mechanical ventilation, length of stay. Finally, using a cost-effectiveness model, this medicoeconomic analysis showed that the savings achieved by reducing resource consumption clearly exceeded the SPN total cost. Preventing one infection saved 63 048 Swiss franc in the study cohort which was composed of patients with a median ICU length of stay of 11 days: it suggests that the optimization of the energy provision after day 3 may be cost-saving in the sickest ICU patients. Nevertheless, some limitations should be considered before generalizing these findings. First, the subpopulation affected by these cost-savings had a median length of ICU stay of 11 days. Then, this study was conducted in two Swiss university hospitals with nutrition support team, and based on Swiss healthcare costs. Measurement of costs and resource consumption parameters were not exhaustive, as the original study protocol did not include an economic evaluation. Finally, the cost analysis of SPN was based on a single representative product, whereas several EN and PN products were used in the SPN trial: however, the differences in cost between these products are marginal.

These results contrast with previous studies reporting higher costs with PN. A previous study reported that early initiation of PN following ICU admission resulted in higher overall costs compared with late PN [14]. In the latter study, early PN initiation was associated with an increased number of new infections and days of mechanical ventilation, thereby influencing overall costs. It is important to consider some limitations, which challenge the external validity of these findings. First, this trial included many patients without a firm indication

for PN and a short median stay in the ICU (3–4 days). Then, in the early PN group, some degree of overfeeding was likely due to the use of the European Society of Intensive Care Medicine 1998 predictive equation (absence of indirect calorimetry validation of targets), and the early glucose load may have contributed to the higher infection rate and longer ICU stay. In a post-hoc analysis, authors reported that the higher dose of macronutrients, administered parenterally or enterally, was associated with more delayed recovery, irrespective of severity of critical illness [25]. Moreover, the amount of proteins/amino acids rather than of glucose seemed to explain delayed recovery with early PN. These findings suggest that among patients receiving PN, rather than the route of delivery, the dose administered might have been the harmful player, and thus of overall costs. Indeed, avoiding overfeeding in both Doig *et al.* and Pradelli *et al.* studies might have contributed to the costs benefit attributable to the use of early PN and SPN, respectively.

Finally, no differences in clinical outcomes, including infections, were found in the CALORIES trial, which compared the effect of early nutritional support in critically ill patients via either PN or EN [11▪]: the energy target was equation based in both groups which suggests that early overfeeding in both groups might have offset the benefits of early EN. The cost difference between the two groups amounted to 1580£ which compares with 1 day in the ICU. At 1 year, incremental net benefit for the PN compared with the EN was negative. However, considerable uncertainty surrounded the lifetime cost-effectiveness results. Finally, authors concluded that early nutritional support via PN is neither more harmful nor more beneficial than via EN and is unlikely to be cost-effective. In addition, in a recent meta-analysis including RCTs comparing early EN versus early PN, Elke *et al.* [26] also found no mortality difference but decreased infectious complications and ICU length of stay in early EN group. On the contrary, the authors could not examine cost-effectiveness of the two strategies of nutrition due to the inconsistency of reported data in the trials. The recent French trial further shows that pushing EN early on is associated with significantly more complications than PN, some of them being severe (vomiting, diarrhea, bowel ischemia and acute colonic pseudo-obstruction) [15▪].

METHODOLOGICAL CHALLENGES

Drawing firm conclusions from these different studies is challenging due to the differences in methodology and endpoints [27▪]. For each trial, it seems important to note that the relevance of the research aim/question, for example use of early versus late PN, or effects of SPN when EN alone is not sufficient; the characteristics of the patient population (indication of EN and PN, severity of the critical illness); the nutritional support: the route (EN, PN, SPN), the timing (early or late initiation after admission), the dose (overfeeding, underfeeding), the duration, the delivery (continuous or intermittent) and the type of macronutrients delivered.

CONCLUSION

Optimization of energy provision using early PN or SPN in selected ICU patients (i.e. patients not tolerating full EN, having a contraindication to EN), with energy targets measured by indirect calorimetry or using low-energy targets such as Harris–Benedict equation without correction factor or the simple 20-kcal/kg equation, results in clinical benefits. This strategy seems to be a cost-saving due to the reduction of complications. Further studies are needed to validate the cost-effectiveness of early PN and SPN in other categories of ICU patients.

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Conflicts of interest

There are no conflicts of interest.

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