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Review article

Parenteral nutrition in the ICU: Lessons learned over the past few years

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ABSTRACT

Since the early 1990s enteral nutrition (EN) has been considered the optimal route of feeding rather than parenteral nutrition (PN), which was considered harmful in critically ill patients with intense inflammation. The aim of this review was to summarize recent developments and progress in PN, which have changed the view on this feeding technique. PubMed and personal databases were searched for studies and reviews reporting historical development of PN, and for clinical trials conducted after 2010 investigating PN in critical illness, comparing it to EN or not. Trials from the past decade have explored modalities and timing of artificial feeding. Trials based on equation-estimated energy targets and applying an early full feeding strategy have generally had negative results in terms of complications (infections, prolonged ventilation, and intestinal complications with EN). The few trials that based their targets on measured energy targets have achieved reduction of complications regardless of the route. Opposing enteral and parenteral feeding is no longer rational in the critical care setting. A pragmatic and reasonable approach offers better options for the individual patient. Although PN is simpler to deliver than EN, its metabolic consequences are more complicated to handle. A combination of both techniques may be a more reasonable approach in the sickest patients.

Introduction

Complete parenteral nutrition (PN) in its modern form was invented by Arvid Wretlind in 1961 in Sweden [1] and almost simultaneously by Stanley Dudrick in the United States [2]. Nearly 60 y later, PN has become a well-established therapy that has enabled the survival of thousands of patients with gastrointestinal (GI) failure [3]. Although having evolved significantly with major improvements over the past 20 y, its use in the critically ill continues to generate debate. Being easier to deliver than enteral nutrition (EN), PN became overused in many intensive care units (ICUs), and was associated with more metabolic and infectious complications than EN. Since 2013, after the publication of trials showing a negative effect of early PN on clinical outcome, the medical community is left with great uncertainty as to the place and optimal timing of PN initiation in the treatment of critically ill patients [4].

The most important concern comes from the indication that bypassing the gut increases the inflammatory response. Fong et al. [5] showed that feeding PN rather than EN to healthy patients for 5 d exacerbated the inflammatory response to endotoxin. The simultaneous publication of several studies showed that infectious complications were more frequent with PN than with EN. This proved to be mainly due to poor catheter policy, but also to hyperalimentation, which was the standard at that time. These observations led to a worldwide reduction of the use of PN in favor of EN, a change that was followed by a significant increase in malnutrition in ICU patients [6]. Indeed the deliberate initial historical aim of PN was to achieve a *hyperalimentation*. This term was first used by Jonathan Rhoads [7,8]: Cancer patients should receive on purpose more than their "normal" nutrient requirements. Delivering 3000 to 4000 kcal/d with PN was common in the 1980s, whereas glucose metabolism was left to its spontaneous evolution. It became obvious that PN was associated with increased infectious complications [9] compared with EN [10].

The availability and rapid technical improvement of PN, as well as its easy delivery compared with EN [6], was associated with its

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wide use in northern Europe, often in patients without complete GI failure. Although PN has obviously saved many lives, the historical hyperalimentation and associated hyperglycemia certainly contributed to worsening outcomes in many patients. However, in absence of indirect calorimetry (IC) in most studies, it is difficult to define precisely the amplitude of the overprescription. On the other hand, enteral feeding is generally left to the nurses, and feeding protocols have been shown to be unsuccessful in many ICUs, resulting is serious underfeeding [11,12].

In light of changes in clinical practice, such as the introduction of glucose control and the availability of more balanced PN solutions, only those studies published after 2000 were included in the present discussion. PubMed was searched for observational studies after 2000 and for randomized trials after 2010. Personal databases were searched for historical papers: Keywords included PN and critical illness. In 64 AC, Seneca wrote "the past must advice the future": Hence to understand the progress that has been made, a reminder of the development of PN is necessary.

The evolution of PN solutions

The development of PN solutions was a stepwise process: Glucose solutions were available first, followed by the amino acid solutions and finally lipid emulsions [3].

Carbohydrates

Glucose administration was long considered safe, and large hyperosmolar doses were delivered via central venous catheters, aimed at protein sparing. Glucose loading was supposed to suppress endogenous glucose production and to prevent amino acid oxidation, both hypothesis having since been proven wrong [13]. The discovery of a maximal glucose oxidation capacity of 4 to 5 $mg \cdot kg \cdot min^{-1}$ in both adults and children raised questions as to the glucose tolerance. The question was even more important in the United States, as dietitians did not dispose of lipid emulsions for decades, forcing them to deliver large (possibly excessive?) amounts of dextrose (the D-isomer of glucose) to cover estimated energy requirements. In the 1980s and 1990s, hyperglycemia in the range 10 to 15 mmol/L was considered normal and adaptive, and generally not treated. The high glucose loads generated complications such as excessive carbon dioxide production, respiratory failure, fever, high metabolic stress with significant elevations of endogenous cortisol epinephrine and glucagon, and liver complications with steatosis and cytolysis [14]. In Germany, a glucose load reduction was attempted by integrating fructose, another hexose. Studies observed a less pronounced increase in insulin activity during fructose compared with glucose infusion, and fructose was assumed to facilitate the mobilization of endogenous lipid stores and lipid oxidation [15]. Fructose was banned to prevent fatal complications in patients with undiscovered hereditary disturbances in fructose metabolism.

It was only after the 2001 Leuven trial [16] that the medical community became aware of the importance of controlling blood glucose levels by means of continuous intensive insulin therapy. The first trials aimed at blood glucose levels between 4.1 and 6 mmol/L: It was subsequently demonstrated in two large trials that such tight glucose control was dangerous in the critically ill fed by the enteral route (Nice Sugar [17], and Glucontrol [18] trials). Due to the interruptions of EN while insulin was infused continuously, many patients experienced severe hypoglycemia episodes that contributed to mortality. A more reasonable target was proposed, resulting in the now prevailing 5 to 8 mmol/L glucose range; however, it was not really understood that overfeeding might be the primary cause of hyperglycemia.

Amino acids

The preparation of the amino acids (AA) solutions was complex and remains unsatisfactory in 2018. In the 1930s, William Rose determined the essential AA in humans from plasma and proposed the ideal mixture of AA that could support protein synthesis in healthy individuals (published in 1949) [1]. The incomplete processing of the proteins and resulting di- and tripeptides were responsible for low nitrogen utilization and hyperammonemia. Arvid Wretlind refined the technique using an enzymatic hydrolysis, further dialyzing the solution to get rid of the di- and tripeptides. However, this form of AA production had the disadvantage of delivering solutions with a fixed composition, determined by the composition of the "mother protein." Interestingly, the initial solutions, contaminated with small peptides, contained glutamine. It took until the 1960s to develop the crystalline AAs [19]. These purified solutions did not contain glutamine or trace elements anymore, which led to the development of a series of micronutrient deficiencies. For stability reasons, tyrosine, cysteine-cystine, and glutamine could not be incorporated in the solutions. Fürst and Stehle finally solved the glutamine stability issue in the early 1980s with the concept of the alanyl-glutamine (GLN) dipeptides [20]. The actual amino acid compartments of the industrial triple-chamber bags remain deprived of GLN: such incomplete AA solutions have been shown to be less efficient in terms of nitrogen balance [21]. GLN is essential for maintaining intestinal integrity and function, sustaining immunologic response, and maintaining antioxidant balance. However, critical illness is characterized by a GLN depletion, and insufficient endogenous availability of GLN may impair patient outcomes. GLN should therefore be an obligatory component of any PN at nutritional doses [21]. This is despite the one negative trial using pharmacologic doses of GLN [22]. The industrial solutions are, therefore, still not "complete" or "total." There is still room for progress and for the elaboration of AA profiles adapted to different life stages.

Lipids

Lipid emulsions have been extremely challenging in terms of safety and composition, and their optimization requires intensive research. Thanks to the development of the soybean solution (Intralipid, Kabi-Vitrum, Stockholm, Sweden) using egg yolk phospholipids as the emulsifying agent by Arvid Wretlind and his team, PN was nutritionally complete from 1962 in Europe (i.e., it was considered a "total PN" from the start regarding macronutrients) [23]. Philip Calder reviewed the latest developments in lipid emulsions with the availability of a variety of fatty acids (medium-chain triacylglycerols, ω-9 and ω-3 fatty acids) [24]. Focus has been put on the ω-3 polyunsaturated fatty acids (PUFAs) that might act as pharmaconutrients with modestly supranutritional doses being able to achieve independent anti-inflammatory effects [25]. The issues now are to find the optimal combination of fatty acids and the optimal proportion of the total energy to be provided as fat, a proportion that might vary depending on different patient conditions, possibly being lower in critically ill than in stabilized hospital patients, or those on home PN.

Micronutrients

As a result of the availability of crystalline AA solutions, the first zinc deficiencies were observed by Kays et al. in 1976 [26]. In 1977, Jeejeebhoy et al. showed that long-term PN caused a reversible chromium deficiency [27]. Then Jacobson et al. conducted trace element (TE) balance studies, indicating that the majority of the 20

TEs included in the study were lost, resulting in the need for a systematic additional prescription. Indeed, these first demonstrations of TE deficiency were followed by several others (copper, selenium, iron, and zinc [28–32]), as well as observations of vitamin deficiencies. It took several years (late 1970s) for the industry to finally produce balanced vitamin and TE solutions that prevented deficiencies. The latter issue remains unresolved, as there is still no ready-to-use TE solution adapted to the specific requirements of critically ill patient at high risk for deficiency [33,34]. TEs have some characteristics that complicate their prescription and delivery by enteral and intravenous (IV) routes [35]: When delivered at higher than standard doses, copper and zinc compete for absorption at the intestinal level, whereas their peripheral IV administration causes phlebitis, requiring central venous access for higher doses.

Of importance, hydrosoluble vitamins, especially ascorbic acid, are quickly inactivated in the PN admixture at normal room temperature and light exposure. Further development of PN bags is required to optimize vitamin delivery [36].

From the Christmas tree to triple-chamber bags

The components of PN were available as separate glass bottles until the 1980s, which made PN very technically complex (Fig. 1). As a result, the routine administration of PN was a succession of glucose and AA solutions, followed by a separate short perfusion of lipids, often over a 6- to 8-h period. Hyperglycemia and hypertriacylglycerolmia were frequently observed. In the 1990s, major advances in plastic technology made it possible to develop double- and triple-chamber bags, separating all the needed macronutrients until administration to the patient, allowing for better shelf-life. They provided the necessary guaranties regarding both the stability and sterility of solutions, reducing contamination and errors in prescription to a minimum, as well as costs [37]. One disadvantage, however, is the fixed substrate composition.

Needs in perspective of the effects of disease on lean body mass

Critical illness elicits a cascade of redox, inflammatory, immune, endocrine, metabolic, and physical responses [38]. In response to these changes, patients remaining acutely ill beyond the first 72 h experience proteolysis increases in excess of protein synthesis, a condition called catabolism, which causes a rapid loss of lean body mass (LBM), mostly controlled by the ubiquitin-proteasome pathway [39].

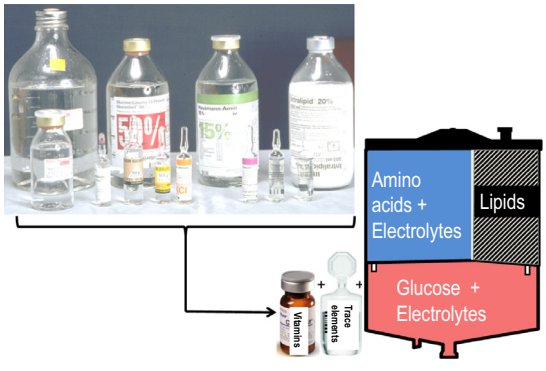

Fig. 1. Parenteral nutrition has evolved from a complex combination of glass bottles and ampoules to triple-chamber bags requiring only the addition of micronutrients (trace elements and vitamins).

In the 1990s, it was shown that critically ill patients require more proteins than healthy individuals. It was also observed that a daily protein delivery >1.3 g/kg did not further increase protein accretion [40]. In critically ill trauma patients, PN providing 120% of the measured energy expenditure (EE) did not have a positive effect on protein metabolism, but only generated deleterious hypermetabolism [41]. Furthermore, bed rest studies conducted in healthy individuals under the umbrella of the European Space Agency and National Aeronautics and Space Administration demonstrated an intense protein catabolism related to physical immobilization [42], which was further increased by hypocaloric feeding. Critically ill patients combine both intense stress and physical immobilization [42], which causes a rapid decrease of lean tissues: This in turn has an effect on respiratory and peripheral muscle function. The International Body Composition Project demonstrated a strong association between the lowering of the phase angle, reflecting a reduction of lean tissues, and the 28-d mortality after the ICU stay [43]. After acute disease, the recovery of muscle alterations is associated with an improved global functioning and quality of life [44,45]. However, this requires the adaptation of feeding toward higher protein intakes, not only higher energy [46]. How much exercise is required and its optimal timing remains an unknown [47].

Pharmaconutrition

The development and availability of the separate components of PN, such as GLN on the AA side, and ω-3 PUFAs on the lipid side resulted in attempts to use them as drugs modulating metabolism and immunity. The strategy seemed successful, as shown by beneficial results observed in several trials, and meta-analysis that were conducted indicating reduction of infectious complications and of costs associated with inclusion of GLN [48,49] and of ω-3 PUFAs [50]. The effect was strongest in the critically ill for GLN and in surgical patients for the ω-3 PUFAs.

Recently, however, two large preclinical randomized controlled trials (RCTs) have raised questions: The doses of GLN as well as the timing and duration of its administration have largely explained the negative results. The Scottish trial (SIGNET) enrolled 502 patients with GI failure [51]. The patients were randomized to receive daily 20.2 g GLN, or 500 mcg selenium, or both, versus placebo for up to 7 d, but few patients actually received those doses. No overall effect of GLN was observed on any outcome variable, and selenium had only a modest effect when delivered for >5 d. Several shortcomings of the study, including a very short administration time (mean <5 d) and a "one-size-fits-all" prescription of the ready-to-use PN bags resulted in the delivery of a very low GLN dose (0.1 g/kg daily, below the ESPEN recommendation) [52]. On the non-effect side, a small U.S. RCT study 44 patients randomized to three groups to receive either an iso-nitrogenous EN, or GLN 0.5 g/kg daily by IV or enteral route for 8 d. No difference in antioxidant status or other marker of oxidative stress was detected [53]: Importantly, about one-third of the patients had normal baseline GLN levels.

The REDOXS (Reducing Deaths Due to Oxidative Stress) trial reported data in 1223 patients receiving the highest daily doses used to date of GLN (0.78 g/kg supplied as 0.35 g/kg IV + 30 g/d enterally), about twice the recommended doses. In these patients with severe organ failure (93% of patients in shock state and 33% with renal failure), intervention was started within the first 24 h of admission, independently of nutrition [22], that is, earlier than in any previous trial. Plasma GLN concentration was determined in a subset of patients: Only 31% presented with a low baseline GLN (<420 μmol/L), whereas 15% of these patient had supranormal

plasma GLN values at baseline. The latter finding has been shown to be associated with increased mortality [54]. Pharmacologic doses of GLN in unstable patients should therefore not be used. But GLN, being a normal component of nutrition in ranges of 8% to 10% of AAs, as is the case in EN solutions, should be part of PN [55].

Toward the end of the EN versus PN controversy

Recent RCTs have shown that although there are some specific advantages to using the gut when it works, using either route does not really matter. For those who are unconditional users of EN, it is important to recall that forcing EN despite limited GI tolerance results into significant occurrence of diarrhea, and other complications, associated with additional costs [56] and increased workload for nurses [57]. It is more important to avoid under- and overfeeding by either route [58], to respect substrate proportions, and to target the individual patient's energy needs. Difficulties in appreciating the real energy requirements in acute conditions with the use of inexact predictive equations [59] is an important issue and the relation between measured EE and overall body metabolic needs during the first 3 to 4 d after ICU admission deserves more research [60].

The Swiss supplemental parenteral nutrition (SPN) trial [61] based the SPN intervention on energy goals determined by IC and precise delivery of the measure energy values. The study achieved a reduction of infectious complications. The investigators intended

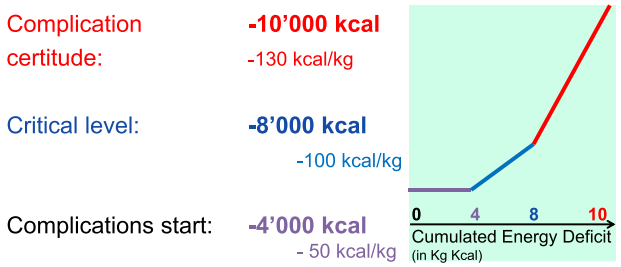

Fig. 2. Conceptual representation of the increasing number of underfeeding related complications with growing cumulated energy deficit: the cutoffs bar based on observational studies [63,64]. As patients do not tolerate catch up feeding, reaching the cut-off level of -8000 kcal should be prevented.

Table 1
Trials investigating PN or SPN and comparing it with EN

Acronym [Reference] First author	Trial year	Trial type (N)	Outcome and comments	Goal tool*/Energy deficit before PN
EPaNIC [12] Casaer et al.	2011	RCT (N = 4640)	Intervention (early PN) was initiated with a carbohydrate load for 48 h followed by PN using ESICM equation. Faster recovery and fewer infections in late feeding group	Equation/No
TICACOS [72] Singer et al.	2011	RCT (N = 112)	Patients randomized to receive feeding to measured EE or to 25 kcal/kg. More infections in EE directed group, but less mortality	IC/No
PEPaNIC [77] Fivez et al.	2015	RCT (N = 1440)	Same design as the EPaNIC adult trial	Equation/No
Early PN with EN contraindication [78] Doig et al.	2013	RCT (N = 1372)	Target was moderate and based on Harris–Benedict equation No increase in infectious complications. Significant reduction of ventilation time and better strength at 60 d	Equation/N
Swiss SPN [61] Heidegger et al.	2013	RCT (N = 305)	Comparison of pure EN with supplemental PN to measured EE target. Reduction of infectious complications, Mortality ns	IC/Yes 72 h
CALORIES [79] Harvey et al.	2014	RCT (N = 2388)	Comparison of EN and PN with target 25–30 kcal/kg: Mortality ns. Less hypoglycemia and vomiting in PN	Equation/No
Renal AAs [80] Doig et al.	2015	RCT (N = 474)	Multicenter, phase II comparing 100 g of IV AAs or standard care (maximum total daily protein intake of 2 g/kg with nutrition). This was not a nutritional study. Estimated GFR was improved in AA groups	Equation/No
Hypo-Normo Energy [73] Petros et al.	2016	RCT (N = 100)	Patients were randomized to 50% or 100% of EE, and received 40% of measured EE target or 80%: More infections in the hypocaloric group	IC/No
EAT-ICU [74] Allingstrup et al.	2017	RCT (N = 199)	Comparison of patients receiving full measured EE from day 1. No outcome differences	IC/No
NUTRIREA [81] Reignier et al.	2017	RCT (N = 2410)	Comparison of full EN and PN within 24 h in septic shock patients with targets 20 –25 kcal/kg: Mortality ns; more digestive complications in EN	Equation/No
TOP-UP pilot [82] Wischmeyer et al.	2017	RCT (N = 120)	PN and EN vs EN alone in underweight and obese ICU patients to an estimated target with a difference of 30% in energy. No outcome differences	Equation/No
SPN – pilot [83] Ridley et al.	2018	RCT (N = 100)	Patients randomized to PN titration 48–72 h after admission to estimated target. Higher energy and protein delivery. Outcomes similar	Equation/Yes 48 h

AA, amino acid; AKI, acute kidney injury; EAT-ICU, Early Goal-Directed Nutrition in ICU Patients; EE, energy expenditure; EN, enteral nutrition; EPaNIC, Early versus Late Parenteral Nutrition in Critically Ill Adults; ESICM, European Society of Intensive Care Medicine; GFR, glomerular filtration rate; IC, indirect calorimetry; ICU, intensive care unit; IV, intravenous; ns, non-significant; NUTRIREA, Impact of Early Enteral vs. Parenteral Nutrition on Mortality in Patients Requiring Mechanical Ventilation and Catecholamines; PEPaNIC, Early versus Late Parenteral Nutrition in the Pediatric Intensive Care Unit; PN, parenteral nutrition; RCT, randomized controlled trial; SPN, supplemental parenteral nutrition; TICACOS, Tight Calorie Control Study; TOP-UP, Trial of Supplemental Parenteral Nutrition in Under and Over Weight Critically Ill Patients.
*Tool used for goal determination.

to use the available ready-to-use industrial solutions, which did not enable giving the 1.2 g·kg·d^{-1} protein targets specific attention: Nevertheless 1.1 g·kg·d^{-1} were delivered [62]. The SPN study is hence one of the few trials having delivered such doses of proteins. These proteins requirements >1 g·kg·d^{-1} now seem to have reached a consensus among experts, higher doses ≤2.5 g·kg·d^{-1} being advocated by some.

Importantly, the Swiss group interpreted its previous results regarding energy deficit [63], not as if a deficit needed to be completely prevented, but as if some degree of extrinsic deficiency was acceptable (roughly −4000 kcal, or −50 kcal/kg) during the first week: Hence the group set its intervention on day 4. The message was that a cumulated deficit increasing beyond the −4000 kcal cutoff exposed the patient to a risk for complications. This cutoff was confirmed by another group's study conducted with the same methodology including IC, that confirmed that complications from underfeeding were starting at −4000 kcal, increasing steeply by −8000 kcal, and becoming nearly certain by −10 000 kcal [63,64]. Interestingly, the SPN intervention started by day 4, at about −4000 kcal of cumulated extrinsic deficit, therefore leaving space to accommodate to the body's endogenous energy production, which is maximal during the first days, and cannot be suppressed by extrinsic feeding (Fig. 2) [60].

Overfeeding and hypocaloric feeding

As overfeeding is a threat, some authors have proposed the prescription of hypocaloric feeding (i.e., 70 to 80% of the calculated target [65], or even less). This strategy has been developed mainly for obese patients, in whom all the equations invariably fail, the Penn State equation adapted for the obese being among the closest to measured EE [66].

The use of industrial formula implies that delivering low amounts of calorie reduces the protein delivery—a minimum of energy is required to be able to benefit of proteins [67]. The trend toward lower energy targets observed over the past 10 y is associated, in absence of close monitoring, with an increased risk for insufficient protein delivery. This has deleterious clinical consequences with prolongation of length of mechanical ventilation and ICU stay [68]. Moreover, the international surveys show that underfeeding remains a serious threat [11], with patients with body mass index <18 kg/m^2 experiencing a maximal variability of energy delivery [69].

Recent research has focused on autophagy, associated with the healing process, aiming at the removal of mitochondria damaged during the acute phase of sepsis. This mechanism is a two-edged sword, however, that may result in cell death [70]. Overfeeding and insulin are well documented inhibitors of autophagy [71], hence PN driven by equation-based targets (that favor overfeeding [4]), and not by measured EE are more likely to generate overfeeding.

Indeed until now, only four trials to our knowledge, have based their nutritional intervention on measured EE by IC (Table 1): TICACOS (Tight Calorie Control Study) [72], the Hypo- versus Normocaloric Nutrition trial [73], the Swiss SPN trial [61], and the EAT-ICU (Early Goal-Directed Nutrition in ICU Patients) trial [74]. Although TICACOS and EAT-ICU initiated feeding to target on day 1, the other two trials started intervention later and progressively, and were associated with a reduction in infectious complications. Considering the recent data, the ESPEN and ESICM societies propose a progressive ramping up of feeding by either enteral or parenteral route (Fig. 3).

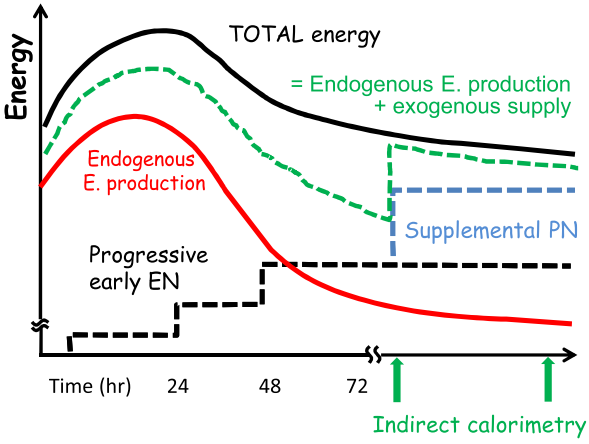

Fig. 3. Schematic representation of the proposed progressive feeding strategy that accommodated integrates endogenous energy provision: EN should be started at a low rate within the first 48 h and completion with PN considered from day 4 in those patients not covering 50% of their needs. (Adapted and reproduced with permission from Oshima et al. [60]). EN, enteral nutrition; PN, parenteral nutrition.

Conclusion

From the past decade's trials, we have learned that an unequivocal approach (i.e., one opposing enteral and parenteral feeding) is no longer a rational approach in critically ill patients [75]. An early "aggressive" feeding strategy, that is, the delivery from day 1 of full calculated or measured energy goals, has been shown to be inappropriate regardless of the route. The term *aggressive* should be banned from vocabulary, and from feeding strategies. Although PN is simpler to deliver than EN, its metabolic consequences are more complicated to handle. A pragmatic and reasonable attitude requires patient observation and individual adaptation, using moderate targets during the first 72 h, with progression to measured EE from day 4. The eventual use of SPN should be based on the clinical observation of the intestine's capacity to accommodate (or not) enteral feeds. This strategy requires tight monitoring and dedicated resources such as dietitians or nurses in the ICU [76].

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