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Review

When is parenteral nutrition indicated?

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ABSTRACT

The indications and contraindications of parenteral nutrition (PN) are discussed in view of recent clinical findings. For decades, PN has been restricted to patients unable to tolerate enteral nutrition (EN) intake owing to the perceived risk of severe side-effects. The evolution of the PN substrate composition and delivery of nutrition via all-in-one bags has dramatically improved the application prospects of PN. Recent studies show similar complication rates of nutrition therapy administered through enteral and intravenous routes. Therefore, indications of PN have, based on evidence, extended beyond complete gastrointestinal (GI) failure to include conditions such as insufficient EN generating persistent negative energy balance and insufficient protein intakes, malabsorption, or specific needs that are impossible to cover with EN feeds.

Introduction

Nutrition therapy is required in cases where oral feeding is not possible for several days[1] to not only maintain a desirable body composition and the potential for physical and mental activity but also enable therapeutic measures. The choice of feeding route depends on the condition of the patient and function of the gastrointestinal (GI) tract [Figue 1]. The proportion of enteral and parenteral nutrition (PN) required to cover the needs of individual patients is determined based on the severity of failure of the GI tract, as discussed below.

PN was developed in the 1960s to feed patients presenting with major malnutrition in the context of short bowel or advanced cancer cachexia with bowel obstruction, i.e., complete GI failure.[2] The first name of the intravenous feeding strategy was “hyperalimentation,” as it was mainly used in patients with severe malnutrition. In the 1980s and 1990s, prescription of PN became widespread and was considered to be a common alternative to enteral nutrition (EN), particularly in Scandinavian countries, because of its ease of use, with very broad indications. However, until the late 1990s, PN was associated with several complications (predominantly infections) and its utility is a heated subject of debate,[3] with some authors even describing it as “poison.” The analysis of the complications attributed to PN allowed the inference that they were caused by overfeeding, by the use of elevated proportions of glucose without glucose control, and by poor catheter policy.[2] Lately, indications of PN have increased again after the PN ban was shown to result in malnutrition. The contraindication and indication pendulum is back in the middle. The recent randomized trials, CALORIES[4] and NUTRIREA-2,[5] have demonstrated equivalence between EN and PN regarding complications and outcomes, leading American specialists to state that the “gap is closing regarding outcome detriments between EN and PN”.[6] In clinical settings, the different feeding routes are currently utilized in a complementary manner [Figure 1]. Since their introduction into the marketplace in the 1990s,[2]] the tri-compartmental industrial PN bags have become easier to handle, reducing the manipulations and costs, and their composition more physiological, which contributes to the equivalent outcomes of EN and PN. In particular, development of lipid emulsions with optimal combinations of fatty acids[7] and availability of glutamine as a dipeptide for combination with amino acids in the most sick patients have led to improvement of prognosis.[2,8]

This review addresses the most common conditions observed in critically ill patients leading to indications for PN in 2022 based on literature and guidelines published in English after 2000.

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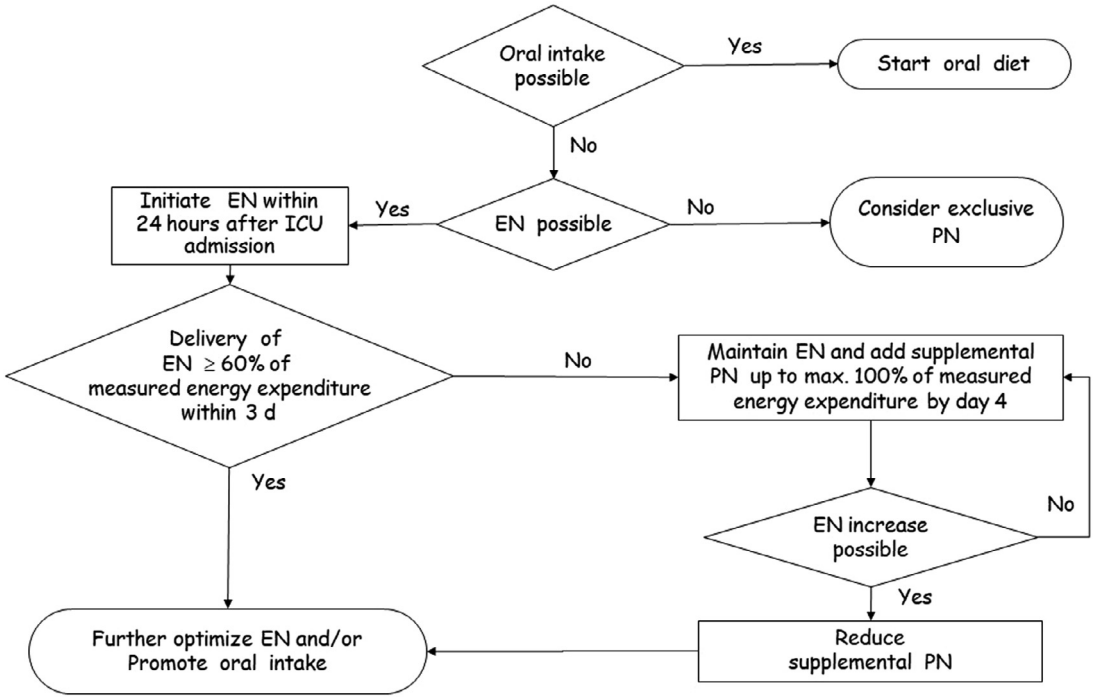

Figure 1. When oral or gastric EN becomes inefficient or is contraindicated post-pyloric and supplemental PN or total PN are the preferred options. Different feeding routes are no longer opposed but act in a complementary manner (adapted from Heidegger et al.[52]) EE: Energy expenditure; EN: Enteral nutrition; ONS: Oral nutrition supplements; PN: Parenteral nutrition.

Defining Energy and Protein Needs

Determination of the specific needs of critically ill patients over the different periods of their intensive care unit (ICU) stay poses a major challenge. Due to the widespread absence of measured values and use of predictive equations, rational evaluation of feeding goals for both energy and protein has been a subject of considerable debate. Regarding energy delivery, both overfeeding and underfeeding have been shown to be deleterious, narrowing the therapeutic window. The determination of energy goals is currently based on a rational strategy of measuring energy expenditure (EE) to facilitate the deduction of needs based on the hypothesis that EE is equivalent to nutritional needs, at least after the hyperacute phase of the disease. Indirect calorimetry is the accepted gold standard for measurement of EE. EE includes thermogenesis, i.e., energy dissipated by metabolic processing of protein, carbohydrates, and fat, as well as diet-induced thermogenesis.

Unfortunately, indirect calorimetry devices are mostly unavailable outside of metabolic research centers. Therefore, most ICU departments continue to use predictive equations, which have proven inexact in the majority of patients.[9] Indirect calorimetry measures oxygen consumption and carbon dioxide production for calculation of EE. Newly developed devices introduced into the market are easy to use, accurate, and affordable. Measurement of EE traditionally takes 40–60 min while novel measurement tools have provided reliable values to set individual energy goals in recent years after only 5–15 min.[10] An alternative technology is continuous measurement with a device on the ventilator. However, while this method is easy to use, overestimation of EE has been proven.[11]

EE is reduced or normal during most chronic diseases due to reduction in the lean body mass and spontaneous physical activity. During acute illness requiring admission to the ICU, EE may increase because of physiologic alterations, such as fever, pain, muscle contractions, or stress hormones levels. In view of this finding, progress in ICU therapy during the last 20 years has been associated with attenuation of the amplitude of hypermetabolism: the latter persists although less marked for 1–2 weeks. These measurements should be repeated as the EE changes with evolving clinical conditions such as fever, physical agitation, surgical procedures, and weaning off the ventilator. In practice, the first measurement should occur between days 3 and 5 after admission, followed by at least once weekly. A recently developed indirect calorimeter facilitates measurement of EE within 10 min.[10,12] Repeated short measurements to capture metabolic changes related to clinical evolution are preferable to longer, less frequent measurements.

Energy balance represents the difference between intake and EE. Cumulative energy balance is particularly important during the first 10 days and determines later outcomes, but should be considered throughout the ICU stay. The energy input is easy to establish. The calculated energy balance can be applied to determine whether the energy of the patient is in equilibrium, deficit, or excess. A cut-off of −6000 kcal of cumulative energy deficit is a reliable number associated with worse outcomes, such as length of hospital stay, mortality, and capacity for home discharge.[13,14]

Regarding protein requirements, the target has been set at 1.2–1.5 g • kg^{-1} • day^{-1} by different societies.[1] Unfortunately, at the time of this review, no measurable clinical variables were available to indicate specific individual needs. An increasing blood urea value >20 mmol/L is considered an indication to re-

duce intake by some groups, while others consider 30 mmol/L as the cut-off for reduction. Limited physiological data are available on the effects of increasing protein delivery on metabolic utilization.[15] On the low intake side, cumulative deficit of about −300 g[13] or persistent delivery of <75% of the above goal[16] are associated with poorer outcomes.

Clinical Situations Potentially Requiring PN

The clinical situations that may be an indication of PN or supplemental PN (SPN) requirement are summarized in Table 1.

Complete GI failure

PN was first used in patients with complete intestinal failure [2] defined as "the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth".[17] This condition remains the principal indication for PN and is accepted worldwide by all nutritional societies.[18–22] However, PN may be required in a number of other situations (summarized in Table 1). The comparative advantages of each feeding route are presented in Table 2.

Bowel ischemia is a life-threatening condition that may result from either anatomic occlusion of mesenteric vessels (blood clots or atherosclerosis) or insufficient blood flow to the intestinal area, such as that occurring during shock of any etiology or in the context of abdominal compartment syndrome.[23] Bowel damage can vary from minimal lesions in the framework of reversible ischemia to transmural injury, with subsequent necrosis and perforation.[24] In the latter case, intestinal resection is necessary. Usually, feeding with EN becomes impossible in this situation, leading to the need for PN.

Anatomic GI obstruction or discontinuity and paralytic ileus are classical indications for PN, as is pseudo-obstruction.[25] Paralytic ileus may also be an indication, particularly in the context of severe abdominal sepsis.

Partial GI failure

In critically ill patients, variable degrees of GI failure are frequently observed, resulting in enteral feeding intolerance in ~60% cases.[26] This intolerance is often evolutionary and mostly resolves completely after 5–7 days. However, over the period of resolution, several days of inadequate feeding below the goal level or even starvation can occur, contributing to acute malnutrition and deleterious consequences. Tolerance to partial or total starvation is variable depending on nutritional status on admission, presence of sarcopenia, and age.

Furthermore, partial GI failure may complicate appreciation of the functional capacity of the gut, particularly in short bowel patients. Hyperphagia may enable partial coverage of needs, reducing the requirement for PN.[6] Enteral feeding often becomes difficult with frequent interruptions, compromising the delivery of sufficient amounts of energy and proteins.[27] Some of these situations are associated with risk of malnutrition and may be an indication for initiation of either supplemental or full PN. Clinical criteria have been proposed to identify situations where EN is likely to fail.

Introduction of PN or SPN should be based on increasing deficit with a cumulative energy balance of between −4000 kcal and −6000 kcal[13,14,28] or cumulative protein deficit exceeding −300 g or persistent delivery of <75% of the goal.[16] It is important not to wait beyond these numbers, which are associated with non-recoverable clinical consequences.

Vomiting and nausea

Recurrent vomiting is a contraindication of gastric EN, as it increases the risk of aspiration and decreases the chance to cover nutritional needs. Utilization of a post-pyloric or direct intestinal access is sometimes possible, but not always successful.

Hyperemesis gravidarum rarely requires hospitalization, but in the worst cases of weight loss, electrolyte abnormalities, and severe or persistent vomiting after rehydration,[29] PN may be required.

Diarrhea

Diarrhea is diagnosed in cases reporting ≥3 liquid stools/day, a condition observed in a large proportion of ICU patients.[30] Diarrhea episodes are related to infections and antibiotic treatments, intestinal resection, or malabsorption. Unfortunately, establishing the precise etiology is frequently impossible as the causes of diarrhea are generally multifactorial. Data suggest that antibiotics, including antifungal drugs, and EN are the most frequent underlying causes.[30] Persistent diarrhea translates into dehydration, electrolyte imbalance, and increased risk of bedsores. We recently reported that diarrhea causes a significant nursing burden, leading to an increase in the number of investigations and considerable additional costs.[31]

ESPEN guidelines recommend the use of continuous EN instead of bolus feeding to prevent diarrhea. In the event of diarrhea, a temporary reduction (e.g., 50% of the initially prescribed energy delivery) is recommended for 1–3 days.[1] If resumption of the initial level of feed administration is not possible afterwards, PN should be considered to avoid a progressive energy deficit and ensure substrate bioavailability, as malabsorption is frequent.

While diarrhea lasting for 4–5 days has limited metabolic consequences other than the increased nurses' workload, in persistent critically ill patients on EN, prolonged diarrhea is likely

Table 1
Non-exhaustive list of the most common indications for PN.

Indications
Inadequate absorption resulting from short bowel syndrome
GI fistula (high output)
Bowel obstruction or discontinuity
Prolonged bowel rest
Paralytic ileus
Severe malnutrition under conditions where EN is not possible
Severe abdominal sepsis
Not meeting 60% of the energy requirement for >4–5 days
Cumulative energy balance less than −6000 kcal or cumulative protein deficit <300 g
Hyperemesis gravidarum
Severe persistent diarrhea

EN: Enteral nutrition; GI: Gastrointestinal; PN: Parenteral nutrition.

Table 2
Advantages of PN or SPN compared to EN.

Situation	Respective advantages	References
Complications	Similar frequencies of complications in patients randomly assigned to receive EN or PN Less hypoglycaemia and GI complications with PN Physiological reasons support the use of the GI tract with EN and to pave the way to resume oral feeding	[4,5,28,45]
Risk of underfeeding	Larger with EN: Securing full coverage of nutritional needs with EN is difficult as the patient's tolerance is often altered during the first week in the ICU	[28,46]
Risk of overfeeding	Larger with PN and SPN: Topping up an insufficient EN with PN (SPN) is rational and safe if EE is measured	[14,28]
Nursing efforts and manpower	Less in PN compared to EN	[30,31]
Diarrhea	EN is more highly associated with diarrhea than PN especially when >60% of the patient's energy needs are covered, which generates hidden costs (manpower and etiology investigations)	[30,31]
Costs	Use of SPN to cover measured EE after day 4 has been shown to reduce hospital costs	[47]
Modulation of inflammation	EN attenuates the inflammatory response via non-nutritional mechanisms Omega-3-containing lipid emulsions of PN attenuate the inflammatory response and reduce infectious complications and costs	[48–51]

EE: Energy expenditure; EN: Enteral nutrition; GI: Gastrointestinal; PN: Parenteral nutrition; SPN: Supplemental parenteral nutrition.

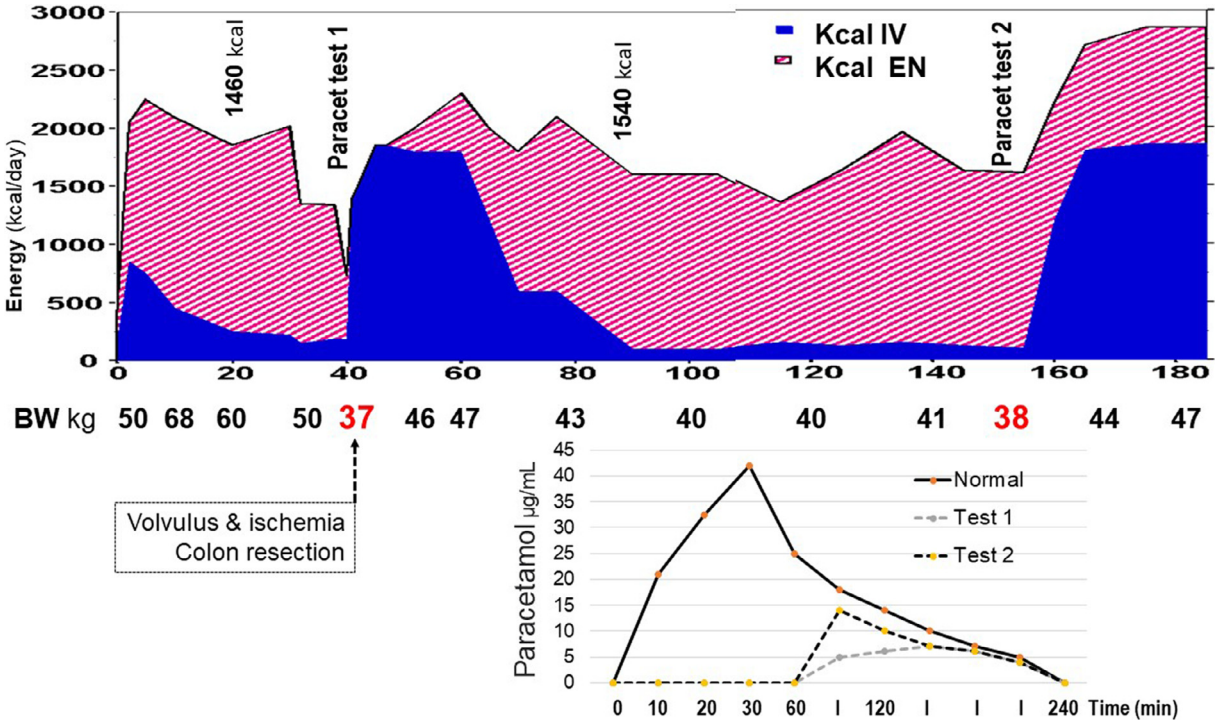

Figure 2. Case of a young critically ill burn patient (55% body surface area burns), presenting with partial intestinal failure due to persistent diarrhea and volvulus. Despite provision of around 2000 kcal, i.e., more than the measured EE of 1470 kcal, the patient continued to lose weight from 53 kg to 37 kg). During the first episode, the paracetamol test was conducted, which confirmed extremely low absorption. The patient subsequently received PN, which led to stabilization of weight. After reintroduction of EN, the patient underwent weight loss again. The second paracetamol test showed modestly higher absorption values, which were still within the abnormal range. PN was reintroduced for 30 days, leading to restoration of both weight and wound healing. During the second episode, the energy from EN was maintained but not counted as absorbed, resulting in total energy delivery of 2800 kcal, while EE was around 1550 kcal. Ultimately, the patient regained weight and was discharged. EE: Energy expenditure; EN: Enteral nutrition; PN: Parenteral nutrition.

to cause energy deficit, as discontinuation of EN is generally prescribed for control of the condition. Generally, supplemental PN is prescribed and initiated after a time lag. Moreover, diarrhea related to high small bowel flow may be associated with direct energy loss, as shown from calorimetric measurement of diarrheic feces,[32] and malabsorption due to rapid intestinal transit. Demonstration of nutritional consequences requires specific monitoring. Figure 2 presents the case of a young burn patient who became critically ill and suffered partial intestinal failure with persistent severe diarrhea and volvulus. Despite feeding above the measured EE, the patient consistently continued to lose weight. A paracetamol test disclosed nearly no absorption (15 mg/kg via the gastric route with measurement of blood levels over 4 h.[33]) Subsequent introduction of PN stabilized the weight of the patient. After a while, EN was reintroduced, leading to the re-development of weight loss. Weight at the second paracetamol test remained below normal. PN was reintroduced for 30 days, which restored the patient's weight and enabled wound healing. During the second episode, EN was not counted as intake due to poor absorption, resulting in total energy delivery of 2800 kcal, while the EE was around 1550 kcal, with no sign of overfeeding.

Malabsorption syndromes

Malabsorption may result from functional or physical alterations.[34] Functional alterations consist of small bowel mucosa alterations and exocrine pancreas or bile production insufficiency, while physical alterations refer to anatomic abnormalities, such as upper GI resections or high output proximal GI fistula. Under these conditions, nutrients provided through the upper GI tract are either partially or totally unabsorbed. With exacerbation of clinical conditions, PN may be required.

Specific problems: fluid restriction

The solutions used for PN are generally less concentrated than enteral feeding products, which deliver up to 2.0 kcal/mL. Peripheral PN solutions contain more water for the same amount of energy than central PN solutions to promote better venous tolerance. In critically ill patients, fluid overload is a problem,[35] with the worst scenario being cases of renal failure. In chronic renal failure, renal replacement therapy (RRT) is a tool facilitating intradialytic PN.[36] Similarly, in the ICU, in the context of acute renal failure, RRT may reduce fluid volume and thus enable feeding.[36] The need to feed the patient particularly with PN generates additional fluid administration and may precipitate the decision to initiate RRT to control the fluid and metabolic balance.

Moreover, the perception of water delivery is more obvious with PN and may result in decisions to reduce feeding to avoid fluid overload, with consequential underfeeding.

Practical Aspects

Timing

PN or SPN should be introduced before the stage of malnutrition. Progression of enteral feeding should be monitored, and if not covering 60% of the goal by the end of day 3, SPN or PN should be considered. As indicated above, cumulative energy balance between −4000 kcal and −6000 kcal[13,14,28] or cumulative protein deficit exceeding −300 g or persistent delivery of <75% of the goal[16] should be signs for initiating PN or SPN between days 3 and 7 of the stay.[1] The intervention (completion of goal with SPN) should be repeated in case a recurrence of deficit occurs again during the ICU stay.

As with EN, progression of PN feeding is crucial, especially during the first 3–4 days in ICU, when endogenous glucose production covers close to 60% of EE. Full early PN feeding must be avoided since exogenous feeding is poorly tolerated, as reported in several large-scale studies, leading to higher infectious and respiratory complications.[37]

As PN solutions are micronutrient-free for stability reasons, initiation of treatment requires the mandatory administration of daily parenteral vitamins and trace elements. Vitamins, which are poorly tolerated by peripheral veins, may be mixed in the PN bag, but not trace elements.

Placing of peripheral PN

Peripheral PN requires the use of reduced concentrations of substrates, electrolytes, and micronutrients, along with large amounts of water to limit the osmolarity of the admixture up to a level tolerable by peripheral veins (i.e., <900 mOsmol/L).[38] Therefore, it is generally impossible to cover all needs using this route, as volumes up to 3 L may be required to deliver 1800 kcal. Peripheral PN remains a valuable but temporary nutrition support strategy whenever oral feeding or EN is transiently insufficient, but is expected to improve to optimal levels within 3–4 days, as typically after surgery. This time limitation must be considered, as prolonged peripheral PN generally results in phlebitis, and ultimately, underfeeding with the progressive build-up of a significant negative energy balance.

Specific PN monitoring

The use of PN and SPN exposes patients to the risk of overfeeding when predictive equations are applied to set the target, as these solutions are much easier to deliver than EN. Monitoring of the administered *vs.* prescribed amounts is therefore mandatory as for EN. PN monitoring includes indicators of energy and substrate overload.[39] Blood glucose monitoring is particularly important from the start, as critically ill patients often have a strong inflammatory response associated with insulin resistance. Prevention of acute glucose bolus is partly achieved by the progressive introduction of PN. An insulin protocol is required to maintain blood glucose within a limit of 6–8 mmol/L (6–10 mmol/L in diabetics).[40]

Thereafter blood triglyceride levels should be monitored ideally twice weekly (once weekly after stabilization). Weekly liver function tests (aspartate aminotransferase [ASAT], alanine aminotransferase [ALAT], and alkaline phosphatase) should be conducted as part of the follow-up. Acidosis is no longer observed.

Among the tools for detection of global energy and glucose overload, observation of hypercapnia with high VCO2 and weaning failure in persistent critically ill patients should initiate reconsideration of the energy target and glucose delivery.[41] In the absence of indirect calorimetry, a trial of energy delivery reduction by ~30% may be attempted for 48 h after ICU admission. If VCO2 does not decrease, energy overload is unlikely, and the initial goal should be re-established.

Refeeding Syndrome (RFS)

In malnourished patients, it is tempting to cover the full requirements from the start to prevent further underfeeding and clinical deterioration (note that this would be against recommendations e.g., in anorexia nervosa). This immediate full feeding is technically easy to achieve with PN but increases the risk of RFS. Monitoring of blood phosphate[39] and restricted progression of PN[42] are essential in these patients. A recent international point prevalence survey revealed hypophosphatemia in at least 15% of the ICU population.[43]

The precise incidence of RFS remains uncertain but numerous findings support its presence in 20–30% of the population.[44] The occurrence of hypophosphatemia upon initiation of feeding highlights the need for cautious progression of energy delivery.[42]

Conclusions

PN has been restricted for decades to patients unable to tolerate EN intake due to severe associated side-effects, such as acute hyperglycaemia and infectious complications. The optimization of substrate composition, particularly lipid emulsions, and availability of an all-in-one PN admixture has resulted in the broadening of its applicability. Recent studies have shown equivalent complication rates of nutrition therapy with EN and PN. Therefore, indications for PN have been extended beyond complete GI failure to include conditions such as insufficient EN, malabsorption, or specific needs that are impossible to cover with EN feeds.

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Conflicts of Interest

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