Patients in the intensive care unit (ICU) are unable to nourish themselves orally. In addition, critical illness increases nutrient requirements as well as alters metabolism. Typically, ICU patients rapidly become malnourished unless they are provided with involuntary feeding either through a tube inserted into the GI tract, called enteral nutrition (EN), or directly into the bloodstream, called parenteral nutrition (PN). Between the 1960s and the 1980s, PN was the modality of choice and the premise was that if some is good, more is better, which led to overfeeding regimens called hyperalimentation. Later, the dangers of overfeeding, hyperglycemia, fatty liver, and increased sepsis associated with PN became recognized. In contrast, EN was not associated with these risks and it gradually became the modality of choice in the ICU. However, ICU patients in whom the gastrointestinal tract was nonfunctional (i.e., gut failure) required PN to avoid malnutrition. In addition, EN was shown, on average, to not meet nutrient requirements, and underfeeding was recognized to increase complications because of malnutrition. Hence, the balanced perspective has been reached of using EN when possible but avoiding underfeeding by supplementing with PN when required. This new role for PN is currently being debated and studied. In addition, the relative merits and needs for protein, carbohydrates, lipids, and micronutrients are areas of study.

INTRODUCTION

The groundwork for parenteral nutrition was laid in the 1940s and the 1950s by Arvid Wretlind, who developed lipid emulsion and amino acid mixtures, which are used to this day for parenteral nutrition. At that time, the increased mortality from energy deficit was recognized, and in 1965, Hadfield showed that PN resulted in successful esophagogastrectomy in 13 emaciated patients with a mortality rate of 14% and no major complications; this contrasted with a mortality rate of 37% and 29% major complications in a non-treated cohort. In 1968, Dudrick and Rhodes spearheaded the use of high-energy parenteral nutrition called hyperalimentation. Subsequently, PN became the major route of nutritional support on both sides of the Atlantic. Over the next two decades, a number of studies consisting of small controlled trials suggested that PN was harmful and promoted increased sepsis. Consequently, EN is now recommended as the preferred route of nutritional support in critically ill patients. The present review examines the current role of PN in the care of ICU patients.

EFFECT OF INTENSIVE CARE AND CLINICAL STATUS ON PATIENT NUTRITION

Intensive care is associated with complete bed rest and even immobility due to the use of sedatives and muscle relaxants. Prolonged immobility is known to cause progressive muscle loss. The patient who cannot eat, is ventilated, and is not force-fed will progressively starve. This starvation is intensified by increased energy requirements, insulin resistance, and increased protein catabolism. Furthermore, patients entering the ICU are often older and obese. The incidence of obesity has increased...
over the years in the general population, and in particular, in intensive care units. Increasing rates of obesity in the general population have had a profound effect on the incidence of insulin resistance among patients entering the ICU. Increased insulin resistance occurs in obese patients and causes hyperglycemia, which will significantly increase the risk of infection. PN, in which hypertonic solutions of glucose and lipids can be infused ad libitum, can result in significant hyperglycemia, which, in turn, promotes sepsis. When considering the use of PN in ICU patients, the age of the patient, the presence of obesity and insulin resistance, and the risk of hyperglycemia all need to be kept in mind.

**NUTRIENT REQUIREMENTS OF PATIENTS IN THE ICU**

**Energy requirements**

In the 1930s, surgeons observed that patients who were starved or who had low body weight did poorly as compared with those who were fed or were of normal weight. Over the next 30 years, the importance of feeding patients in the hospital and avoiding weight loss resulted in the development of intravenous nutrients in the form of amino acid mixtures, lipid emulsions, and glucose for total PN (TPN). Initial assessment of the outcome with TPN was very positive. Hadfield pointed out that the most rewarding result of using TPN was the ability to successfully perform an esophagectomy in 13 emaciated patients with minimal complications in comparison with an untreated group.

In North America, “hyperalimentation” later became the buzzword. Hyperalimentation referred to the practice of infusing energy well above the maintenance requirements with a view to stimulating high insulin levels, which would drive protein anabolism in muscle. The recommendations at that time were that if some was good, more was better; publications routinely recommended the administration of 3,000 kcal/d. It was believed that 30–40% of energy intake above the resting energy expenditure (REE) would be required to optimally meet the metabolic requirements of seriously ill patients. This practice continued into the 1990s without any controlled outcome data. At about that time, the rise of evidence-based medicine made it imperative to show benefit via controlled clinical trials. A controlled trial of preoperative TPN in 395 patients undergoing laparotomy or non-cardiac thoracotomy was consequently undertaken. The patients who were randomized to TPN were given 1,000 kcal/day above the REE for 7–15 days before surgery and for 3 days after surgery. The control groups received the standard diet. This aggressive feeding regimen resulted in more sepsis in the TPN patients than in the control group (14.1 versus 6.4%; \( P = 0.01 \); relative risk [RR], 2.20; 95% confidence interval [CI], 1.19–4.05). Subgroup analysis showed that the patients receiving TPN who were only mildly malnourished had a higher rate of sepsis than controls, but severely malnourished patients had no increase in sepsis and nonseptic complications were reduced.

This study indicated that the overfeeding of patients without malnutrition causes harm. In subsequent studies in the ICU setting, totaling 63 ventilated patients, it was observed that sedated and ventilated patients did not have significant hypermetabolism and that their REE was approximately 1,500 kcals/day. A recent prospective study of feeding called the Tight Calorie Control Study (TICACOS) showed that in patients in whom REE was measured, an average of 24.7/kcals/kg/day was required. Furthermore, in TICACOS, patients receiving energy intake slightly exceeding the measured metabolic rate had lower mortality than those receiving less. However, the ICU stay was prolonged in those receiving higher energy intakes. In contrast, other observational studies have suggested that patients with energy intakes below these levels, even as low as 9–18 kcal/kg/day, have a better outcome. This was particularly the case when PN was given to obese patients. These contradictory results are likely due to differences in the initial nutritional state of the individuals as well as the duration of their stay in the ICU. Conceptually, obese patients will have sufficient body fat to meet any energy defect due to hypocaloric feeding. Obese patients are also insulin resistant and prone to complications of feeding. The duration of ICU stay will determine the cumulative energy deficit, which can promote complications if it exceeds energy stores, a concept supported by the observational study of Alberda et al. in which patients with a body mass index (BMI) measured as body weight (kg)/height squared (m), of <25 and especially <20 benefited by increasing energy intake to meet their metabolic requirements. In contrast, those with a BMI >25 and <40 kg/m² did not benefit from additional feeding.

While the energy needs of patients in the ICU remain controversial, overfeeding in excess of metabolic requirements is undesirable. Feeding sufficient energy to meet measured energy expenditure is likely to be beneficial in malnourished patients and in those with prolonged ICU stays. In these patients, feeding sufficient protein-energy to meet requirements will avoid severe cumulative energy deficits.

**Lipid emulsions in parenteral nutrition**

Lipid emulsions are composed of triglycerides emulsified with egg phospholipid, and the emulsion is rendered isotonic by adding glycerol as an osmotically active nutrient.
The lipid emulsion currently available in North America is made of soy-based triglyceride, which is a long-chain triglyceride (LCT) and its major fatty acid component is linoleic acid. Linoleic acid, on the one hand, provides an essential omega-6 fatty acid; on the other, this fatty acid is a precursor for proinflammatory prostaglandins and thromboxanes. In Europe, there are other emulsions that contain a mixture of soy triglyceride and medium-chain triglycerides (LCT-MCT) or that contain fish oil, which is rich in omega-3 fatty acids that have an anti-inflammatory effect. Recently, an LCT emulsion made up of olive oil, which has less linoleic acid and is, therefore, less likely to produce proinflammatory end products, has become available.18

Metabolically, the patients with sepsis and trauma in the ICU and the patients fed hypocalorically use fat as an energy substrate. Hence, lipids should be an important energy source in patients with trauma. Use of lipids as an energy source reduces the amount of glucose infused, resulting in lower risk of hyperglycemia and reduced insulin requirements.11

**Criticisms about the use of lipid emulsions in PN**

There are two primary criticisms about the use of lipid emulsions in PN. 1) Slow clearance leading to hyperlipidemia and adverse effects by blocking macrophage action and reducing gas exchange in the lungs. However, adverse effects do not occur if lipid is infused constantly at rates not exceeding 110/mg/kg/h.19 2) Increased risk of infectious complications. Battistella et al.20 showed increased infectious complications when lipid added to a glucose-based PN was compared to a relatively hypocaloric glucose-based PN alone. In contrast, lipid-based PN compared to isocaloric glucose-based PN did not result in increased sepsis in ICU patients receiving a bone marrow transplant who were markedly immunosuppressed.21 Also, when compared in random order with a purely glucose-based PN, there was less negative protein balance and less CO₂ production.11

**Specific benefits of fish oil emulsions**

These emulsions contain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA is the precursor for prostaglandins and thromboxanes, which reduce inflammation and platelet aggregation. In clinical trials, the use of fish oil emulsions has been shown to reduce the inflammatory response in acute pancreatitis.22 In a systematic review, parenteral fish oil emulsions were not shown to conclusively improve outcome.23 However, there were only four randomized trials, of which three small trials showed some benefit and one large trial was negative. The trial in which fish oil did not show any benefit had 30% protocol violations, and several patients received fish oil for less than 4 days.24 While the design of this trial was good, the short duration of fish oil administration and the dose may have altered the outcome.

In summary, the use of lipid emulsion as a part of PN, when infused at controlled rates, has beneficial effects metabolically and does not cause complications.

**Protein requirements**

Protein or amino acids (AA) are not known to cause infectious complications and they promote nitrogen retention, provide Krebs cycle intermediates, antioxidants, and anabolic factors for muscle and bowel. Protein or AA will maintain nitrogen balance even in the absence of adequate energy intake in malnourished patients.25 In pediatric patients in the ICU, those given 3.1 g/kg/day had a positive protein balance, while those receiving 1.7 g/kg/day did not attain a positive balance.26 In adolescent patients, 1.5 g protein/kg/day did not result in protein balance even when exogenous insulin improved protein synthesis rates. In contrast, 3.0 g/kg/day resulted in positive balance and was not further improved by insulin.27 Although these studies were not performed in adults, the trend seen in non-ICU patients of better protein balance from higher intakes than those generally recommended can promote a positive balance. Furthermore, in a controlled trial of extensively burned pediatric patients, higher protein intake increased survival.28

In adults, nitrogen balance studies showed that, irrespective of the energy intake, increased protein intake promoted more nitrogen retention, and nitrogen balance was achieved by an intake of about 1.2–1.5 g/kg/day.29 It should, however, be recognized that a parenteral amino acid mixture has 17% less protein energy than assumed and it is recommended that to give the recommended ICU protein requirements, as much as 1.8 g/kg/day of an amino acid mixture may have to be given.30

**Electrolyte requirements**

Sodium and water are infused to provide hydration, but potassium, phosphorus, and magnesium need to be added to allow anabolism. The cellular contents consist of two cations, potassium and magnesium, and two anions, phosphorus and protein. During anabolism, these electrolytes accumulate in a fixed stoichiometric relationship as protein is accumulated. It was shown in metabolic balance studies that absence of any one of potassium, phosphorus, or magnesium results in negative nitrogen balance. Hence, it is important during PN to avoid deficiency of potassium, magnesium, and phosphorus.
Micronutrients

Micronutrients are composed of trace elements and vitamins. They are critical for optimal utilization of protein, carbohydrates, and fats, which are collectively referred to as macronutrients. The current recommendations for micronutrients are summarized in Table 1. However, in critical illness the requirements for zinc may be increased and zinc is considered to be an important pharmac nutri tient.33 This area of the effect of critical illness on micronutrient requirements needs further large-scale trials.

NUTRITIONAL SUPPORT IN THE ICU

Patients in the ICU are sedated, ventilated, and sufficiently disabled that volitional oral feeding is either impossible or unlikely to successfully meet nutrient requirements. Under these circumstances, there are two options. The first is tube feeding of a formulated nutrient mixture called EN, and the other is PN. The various national guidelines differ from an extreme of PN to be given only after a very extensive attempt to feed EN, as stated in the Canadian guidelines,34 to PN after 7 days of attempting EN unsuccessfully, according to the US-based ASPEN guidelines,35 to starting PN within 48 h of not meeting caloric goals, according to the European guidelines of ESPEN.36 The other main controversy is the recommendations regarding lipids, which vary from the Canadian guidelines’ recommendation to never give lipids in PN to ICU patients to the ASPEN and ESPEN guidelines on lipid use.

Comparison of enteral versus parenteral nutrition

In a meta-analysis of 12 controlled clinical trials32 comparing EN versus PN, encompassing a total of 748 patients in ICUs, there was no difference in mortality between the two forms of nutritional support, but the incidence of sepsis was statistically higher in the patients receiving PN. On careful review of the data, only 6 of the 12 trials included a comparison of the rates of sepsis; three of those six studies showed no difference in sepsis incidence and the other three found increased sepsis in patients receiving PN. A detailed analysis of the three studies showing increased sepsis in patients receiving PN showed there was significant hyperglycemia in those receiving PN compared with those receiving EN. Despite the difference in sepsis rates in two of the studies, there were no differences in antibiotic use, ventilation time, and use of dialysis.36,37; it is, therefore, not clear whether the difference in sepsis rates between patients receiving PN and those receiving EN in these two studies resulted in any clinical harm.

In summary, the adverse effects of PN were associated with hyperglycemia and, despite the increase in sepsis rate, there was, surprisingly, no difference in antibiotic use or in other complications related to sepsis, such as ventilation requirements and dialysis. In the third study38 with increased sepsis in patients receiving PN on an intent-to-treat basis, there was no difference in length of ICU stay or cost. However, an increase in sepsis in patients receiving PN is a recurring theme. In a larger meta-analysis encompassing patients both in the ICU and in those with other indications there was, again, an increased infection rate in patients receiving PN as compared with those receiving EN or standard care. Again, in the latter study, there was an 18% reduction of major complications in patients who had upper gastrointestinal disease that prevented food intake and often resulted in serious malnutrition.

FACTORS INFLUENCING THE EFFECT OF PARENTERAL NUTRITION IN THE ICU

If EN is the standard of current care in the ICU, is there a role for PN?

In order to answer the question of whether there is a role for PN in the ICU, one needs to first examine if EN alone can adequately provide protein and energy to ICU patients. If EN cannot do so, then can the administration of inadequate protein energy adversely influence outcome? It is also important to determine the reason that PN seems to increase septic complications. Each of these issues is addressed below.
Can EN alone adequately provide protein and energy to ICU patients?

A large observational multicenter study performed in 167 ICUs across 37 countries and encompassing 2,772 patients showed that the average intakes of protein and energy were only 47.1 g/day and 1,034 kcal/day, respectively, which amounted to 56% and 59.2% of the prescribed protein and energy intakes for these patients. Since 86% of the patients received EN alone, it was clear that EN, on average, provided only half of the protein and energy intakes prescribed. This finding is supported by other studies showing that EN failed to provide the prescribed amounts of protein and energy to ICU patients.

Does underfeeding with EN alter outcome?

In a study by Alberda et al., mortality among patients with a BMI of less than 25 was reduced by the addition of energy and protein, but patients with a BMI of between 25 and 35 did not benefit. Hence, the initial nutritional status alters the need for additional protein and energy. In a survey of 63,646 ICU patients in 2003, it was shown that more than 50% had a BMI of 25 or more. Hence, in at least 50% of patients, underfeeding by EN does not influence outcome over a short ICU stay. Even in patients with a BMI above 25, as the cumulative energy deficit increases (i.e., being on EN for a long time in the ICU) risk of sepsis increases. However, for the other 50%, it is clear that underfeeding using enteral nutrition alone may increase 60-day mortality.

Cause of increased sepsis with overfeeding through PN

Parenteral nutrition can provide the prescribed amount of nutrients without the impediments seen with gastrointestinal intolerance associated with EN. PN, therefore, carries the potential risk of overfeeding. Overfeeding has many deleterious consequences, especially in insulin-resistant patients who are metabolically diabetic. In a prospective observational study, 90% of patients became insulin resistant during their ICU stay. Overfeeding is associated with hyperglycemia, fatty liver, and bloodstream infections. In the study of Dissanaike et al., the number of patients who had bloodstream infections increased progressively along with increasing energy intake; correspondingly, in those without excess energy, sepsis rates decreased progressively. Furthermore, among those who received about 25 kcal/kg/day, which is the desired energy intake level, the infection rate was only 5%. In the Veterans Administration trial, in which patients were overfed by 1,000 kcal/day above resting requirements, increased sepsis was seen both in those who were nutritionally normal and in those who were mildly malnourished. In contrast, those who were severely malnourished did not show increased sepsis. This relationship between malnutrition and absence of complications with PN are supported by another meta-analysis performed by Braunschweig et al.

Patients on PN compared with those receiving no nutritional support

Applying the factors referred to above, it can first be asked whether nutrition given parenterally alters outcome. In a meta-analysis of 26 controlled clinical trials, encompassing 2,211 patients, there was no reduction in mortality or in the incidence of major complications among patients receiving PN. However, among malnourished patients, there was a significant reduction in complications. In the same study, it was concluded that the reduction in complications was especially seen in older studies of lower quality. The authors of the meta-analysis concluded that PN did not have any benefit for patients as compared with patients who did not receive nutritional support. However, a careful analysis of the data in this paper, when considered in relation to the recent increase in obesity rates among ICU patients, would suggest an alternative explanation. Older studies were more likely to include nonobese malnourished individuals who, therefore, would benefit from PN, whereas more recent studies would include patients who received PN, despite the fact that they were obese, and were, therefore, significantly overfed. In support of this possibility are the results of a controlled clinical trial of preoperative patients receiving PN. In that trial, the patients receiving PN, as a whole, had more sepsis, than controls, but in the subgroup of malnourished patients, the risk of sepsis was not increased and noninfectious complications fell from about 40% to 20%. It should be pointed out, however, that the patients receiving PN in that study received 1,000 calories above their metabolic requirements, resulting in overfeeding. As discussed above, such an excess of calories given to patients without malnutrition would increase the risk of sepsis, a finding that is consistent with the observed result.

In a study of thin Chinese patients undergoing hepatectomy, who weighed about 50 kg and had a triceps skinfold thickness of only 10 mm, PN significantly reduced complications, sepsis, and the use of diuretics. The findings in this study, together with the information from the meta-analysis referred to above, suggest that if PN is given to patients who are malnourished, significant benefits may be observed. On the other hand, excessive calorie intake given parenterally to nonmalnourished patients can increase sepsis.
In line with the relationship of nutritional status to the outcome of PN are the results of another meta-analysis, which indicated that in patients with a high degree of protein-energy malnutrition, standard care was associated with increased mortality and a trend toward increased sepsis as compared with PN.69

**SUPPLEMENTAL PARENTERAL FEEDING**

In ICU patients, both nutrient deficits and overfeeding are harmful. EN tends to underfeed and, in time, will result in undesirable protein-energy deficits.52 In this situation, supplemental PN may be beneficial, provided that overfeeding is avoided.53 Furthermore, the benefits of supplemental feeding will likely be observed in patients who are not overweight or obese at the outset. The greatest benefit may thus occur in those with a low BMI.

Three randomized trials have attempted to determine if supplemental PN used to avoid protein-energy deficit would alter outcome. Casaer et al.54 randomized 2,312 patients to receive PN within 48 h or after 8 days. The early PN group received 1,200 g of intravenous glucose over the first 48 h without protein and then received only 40 g of protein per day, which was 0.5 g/kg and a total of about 0.8 g/kg. On average, these patients stayed in the ICU for only 3.5 days and had a mortality rate of 6.2%; 51% of them had a BMI between 25 and 35. The results showed that delayed PN was associated with approximately 3% more patients being discharged alive from the ICU at 8 days and a 4% lower incidence of infection, but no difference in mortality. The main problem with this study was that the patients were not at risk for protein-energy deficit in the ICU, so the use of PN overfed the patients. In addition, the patients received 1,200 g of protein-free glucose to start, which created protein deficiency for the first 48 h of therapy. The second trial called TICACOS,13 involved 130 patients who were all given EN and randomized to either tight calorie administration by providing PN to make up energy deficit based on indirect calorimeter or given PN to make up a total of 25 kcal/kg/day. Since both groups received PN, the question was whether rigorous control to avoid calorie deficit would be beneficial. The tight calorie group was in positive energy balance but got 1.0 g/kg/day of protein. The control group received 0.8 g/kg/day and was in negative energy balance. The tight calorie group had more cases of infection and was overfed energy with a large fat stores will protect muscle by using fat as a source of energy under these circumstances, but the obese patient risks hyperglycemia, fatty liver, and hyperlipidemia with overfeeding.

The third trial, called SPN, resulted in reduced sepsis, reduced use of antibiotics, and fewer days on a ventilator. This study, in its complete form, has been accepted and is pending publication in the Lancet.

In summary, the foregoing data suggest the role of PN depends upon the following factors:

- **Function of the gastrointestinal tract.** PN is essential if the gastrointestinal tract cannot be used to feed. It may become necessary if the gastrointestinal tract cannot be used to provide the targeted protein-energy intake. Intolerance, small bowel injury, and ischemia are the three main impediments to enteral feeding.

- **Duration of feeding.** The longer the patient is in the ICU, the greater the cumulative risk of over- or underfeeding. PN, if not carefully matched to needs, overfeeds and EN underfeeds in the majority of patients. The occurrence of either situation causes complications.

- **Nutritional status of the patient.** The initial nutrient reserves of the patient determine how they respond to either over- or underfeeding. The malnourished patient with minimal body fat will rapidly catabolize protein to meet energy requirements if underfed. It was shown in Irish hunger strikes that death occurred when body fat was depleted and body protein was being catabolized to meet energy requirements.56 In contrast, persons with large fat stores will protect muscle by using fat as a source of energy under these circumstances, but the obese patient risks hyperglycemia, fatty liver, and hyperlipidemia with overfeeding.

- **Metabolic effect of the clinical condition.** Trauma, sepsis, preexisting diabetes, and renal and hepatic failure all influence the utilization and requirements for nutrients. Inflammation and inflammatory cytokines all induce insulin resistance and impair macronutrient utilization.

The quantity and type of nutrient fed (energy or protein). The feeding of excess carbohydrate and fat increases complications, but high protein intake is desirable in ICU patients.57

**ROLE OF PARENTERAL NUTRITION**

**Small bowel dysfunction**

Based on the above five considerations, PN becomes necessary if the gastrointestinal tract cannot be used. Alter-
natively, it may be used as a supplement if adequate protein and energy cannot be given enterally.

**Duration of feeding**

The inability to feed the prescribed amounts of protein and energy makes PN essential to avoid large deficits as the duration of ICU stay becomes prolonged.

**Nutritional status**

Patients with malnutrition will benefit from parenteral supplements if EN cannot provide requisite amounts of protein and energy.

**Metabolic status**

The presence of insulin resistance and the activation of proinflammatory cytokines result in the need to prevent hyperglycemia through insulin treatment. Increased inflammatory response leads to the use of fish oil emulsions that have eicosapentaenoic acid and docosahexaenoic acid, which are anti-inflammatory in their activity.

**Components of PN**

A recent editorial about controlled trials of PN in the ICU concluded the following: “Adequate protein delivery (1.3–2.0 g/kg per day), as prescribed by current ICU nutrition guidelines, is likely required to show any optimal benefit from early calorie delivery, this benefit of protein delivery may be independent of reaching energy goals alone.”

Hence, attention to meeting protein requirements may be very important when giving PN.

**CONCLUSION**

Malnutrition has to be avoided in the ICU and patients with established intestinal failure must be given PN to avoid malnutrition. However, if the gastrointestinal tract is functional, the role of PN is controversial.

When EN can be given, the current role of PN in the ICU is likely to be recognized as supplemental feeding to avoid underfeeding enterally, especially in patients who enter the ICU with malnutrition or in those with minimal reserves of fat. Overfeeding of especially well-nourished patients must be avoided. The benefits of PN are best seen when protein intake is maximized and excessive glucose infusion is avoided.

**REFERENCES**


629