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REVIEW ARTICLE

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Major clinical approaches to macro and micronutrients in enteral therapy according to international guidelines and clinical studies: a systematic review

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Abstract

Introduction: In the context of Nutritional Therapy (NT), critically ill patients are associated with a state of catabolic stress and a systemic inflammatory response. Patients admitted to intensive care units (ICU) have a prevalence of malnutrition greater than 35%. The main objective of parenteral nutrition (PN) is to provide a nutrient mix closely related to requirements safely and avoid complications. However, PN poses a considerable risk of overfeeding, which can be just as harmful as underfeeding. Long-term survival data (expressed as 6-month survival) will also be considered a relevant outcome measure. **Objective:** It was performed a systematic review to evaluate the main clinical approaches of macro and micronutrients in enteral therapy according to international guidelines and clinical studies. **Methods:** The present study followed a concise systematic review model, following the systematic review rules (PRISMA). The literary search process was carried out from August to October 2022 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, using scientific articles from 2011 to 2022. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** It was found 118 studies that underwent eligibility analysis, and then 20 of the 22 total studies were selected for this systematic review. According to the GRADE instrument, most studies showed homogeneity in their results, with I2 =97.7% >50%. Standard crystalline amino acid solutions, while devoid of side effects, remain incomplete regarding their composition (eg glutamine). Lipid emulsions have come a long way and are now included in bi- and tri-compartment feeding bags, allowing for true total PN as long as daily micronutrients are prescribed. The issue of exact individual needs for energy, macro, and micronutrients has not yet been resolved. Many complications attributed to total PN are the consequence of under or overfeeding. Total PN indications have evolved towards its use alone or in combination with enteral nutrition. The start time varies by country between admission (Australia and Israel), day 4 (Swiss), and day 7 (Belgium, USA). The most important issue may be an individualized and time-dependent prescription of the feeding pathway, energy, and substrates.

Keywords: Nutritional Therapy. Parenteral nutrition. Macronutrients. Micronutrients. Guidelines.

Introduction

In the context of Nutritional Therapy (NT), critically ill patients are associated with a state of catabolic stress and a systemic inflammatory response. Patients admitted to intensive care units (ICU) have a prevalence of malnutrition greater than 35% **[1]**. When analyzing only trauma patients, it is observed that, even if they are well nourished, after hospital admission, they tend to develop protein-calorie malnutrition quickly. Studies carried out with critically ill patients found that 40% of patients have a weight loss of more than 10 kg in a period immediately after ICU admission **[1-3]**.

The prevalence of childhood malnutrition has been decreasing in recent decades but remains high when compared to developed countries. Likewise, the percentage of deaths from severe malnutrition at the hospital level is well above the recommendation of the World Health Organization **[4]**. In the case of patients over 80 years of age, a Dutch study released at the 39th edition of the European Congress of Clinical Nutrition (ESPEN) in 2017 associated the percentage of muscle

mass with complications and in-hospital death. In the group with low muscle mass, 45% had complications and 23% died in the hospital, against 15% and 4%, respectively, in the group with normal muscle mass **[1]**.

Studies have shown that disease severity, body temperature, and certain drugs, such as muscle relaxants and sedatives, can elevate or reduce energy metabolism. Variations occur according to the population evaluated, in general, an increase in total energy expenditure (TEE) between 110- 120% is observed in patients undergoing elective surgery, and in clinicians, 135-150% in postoperative situations. - trauma, and 150-170% in sepsis **[3]**.

In this sense, the American Society for Parenteral and Enteral Nutrition (ASPEN) and ESPEN described the use of Parenteral Nutrition (PN). PN can be considered a third route to human nutrition after oral ingestion and enteral nutrition. The main objective of PN is to provide a nutrient mix closely related to requirements safely and avoid complications. However, PN poses a considerable risk of overfeeding, which can be just as harmful as underfeeding. Long-term survival data (expressed as 6-month survival) will also be considered a relevant outcome measure **[5]**.

The critically ill patient is a heterogeneous individual in terms of the phases of the underlying disease, such as the number and severity of organ dysfunction. Pathophysiological changes or therapeutic measures may vary considerably between individual critically ill patients. To be effective, therapy for a specific disease requires a correct indication, and the disease needs to be precisely defined. Furthermore, NT in a critically ill patient is an adjunct therapy, but never a substitute for the causal therapy of the underlying disease, eg as sepsis resulting from peritonitis or pneumonia, hemorrhagic shock, or severe trauma **[2]**.

In this way, macro and micronutrients stand out. Macronutrients are represented by carbohydrates, proteins, and fats or lipids, they are distributed in food and must be ingested daily to ensure a healthy diet. Although, as a general rule, a daily percentage of each macronutrient is established, it should be remembered that people perform different activities in different routines, and also, due to pathologies, they may require different food and supplement demands **[2,3]**.

Micronutrients are represented by vitamins and minerals and are present in a wide variety of foods. Each of these nutrients performs specific functions that are essential for the health of our cells and their harmonious functioning. Unlike macronutrients, vitamins and minerals are needed in small amounts. However, to reach the recommended consumption of these nutrients, their supply through food or supplements must be daily and from different sources, also depending on the clinical conditions of each individual **[2,5]**.

After performing several assessments, and considering various aspects of the patient, NT is started in critically ill patients. In this context, the guidelines, and practical clinical reviews published by nutrition societies for the nutritional management of the patient are consulted, such as the American Society of Parenteral Enteral Nutrition (ASPEN), the European Society of Clinical and Metabolic Nutrition (ESPEN) and the Brazilian Guidelines on Nutritional therapy (DITEN). In them, there are recommendations for energy and macronutrients, such as proteins, carbohydrates, and lipids, for different types of patients, including critical and critical ones.

Therefore, the present study aimed to carry out a systematic review to evaluate the main clinical approaches of macro and micronutrients in enteral therapy according to international guidelines and clinical studies.

Methods

Study Design

The rules of a systematic review of the PRISMA Platform (Transparent reporting of systematic review and meta-analysis-HTTP://www.prisma-statement.org/) were followed.

Data Sources and Research Strategy

The search strategies for this systematic review were based on the keywords (MeSH Terms): *Nutritional Therapy. Parenteral nutrition. Macronutrients. Micronutrients. Guidelines*. The research was carried out from August to October 2022 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. In addition, a combination of keywords with the Booleans "OR", "AND" and the "NOT" operator were used to target scientific articles of interest.

Study Quality and Risk of Bias

The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument.

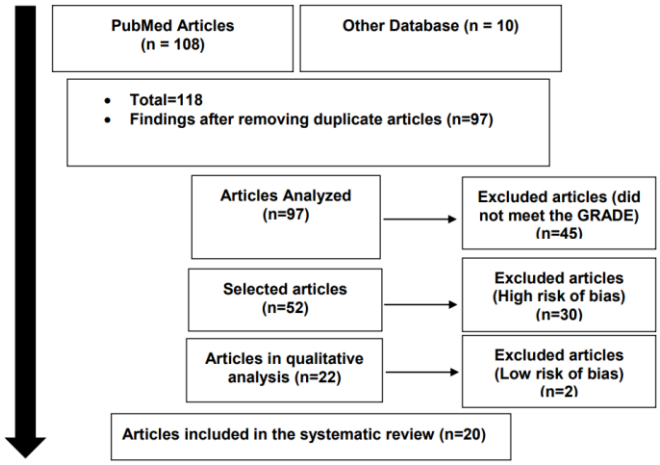
Results and discussion

Summary of Literary Findings

A total of 118 articles were found. Initially, article duplication was excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing articles that did not include the

topic of this article, resulting in 52 articles. A total of 22 articles were fully evaluated and 20 were included and developed in the present systematic review study (Figure 1). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 30 studies at high risk of bias and 45 studies that did not meet the GRADE.

Figure 1. Flowchart showing the article selection process.



Nutritional Recommendations - Macro and Micronutrients

In the context of patients at high nutritional risk and inability to use the digestive tract, PN should be started as early as possible. Supplemental PN should be considered in case of unsatisfactory enteral therapy <60% of protein caloric intake after five to seven days. Thus, the use of early PN significantly reduces the incidence of complications only in the group of malnourished patients **[1]**.

Furthermore, there is lower mortality and a lower tendency to risk infections in malnourished patients with PN compared to standard therapy. In a controlled clinical study, the use of PN in the preoperative period showed a higher incidence of sepsis, which did not occur in the subgroup of malnourished patients, who when using PN showed a significant reduction in non-infectious complications **[2]**.

Thus, it is suggested to consider the use of supplemental PN after 5 to 7 days in patients who were unable to reach a protein caloric intake >60% through the digestive tract. Given the available evidence, the use of supplemental PN should be considered on a case-by-case basis, after a period of 5 to 7 days within which enteral nutrition should be initiated whenever possible. This period seems to be sufficient for patients to be better classified into risk categories and for the intervention initiated more accurately and effectively **[3]**.

Lipid emulsions must appear as an integral part of PN, as a caloric source, and also to ensure the provision of essential fatty acids for patients with prolonged time in the ICU. More balanced lipid emulsions containing medium-chain triglycerides (MCT), olive oil (OO), and fish oil (FO) should be considered in critically ill patients, who indicate PN **[3-5]**.

Soybean oil-based lipid emulsions should be avoided in critically ill patients. The lipid formulations used in PN are composed of triglycerides, with phospholipids as emulsifiers. There are several types of lipid formulations available on the market for use in PN **[1,5]**. The addition of eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids to lipid emulsions has demonstrable effects on cell membranes and inflammatory processes. Lipid emulsions with fish oil probably reduce the length of stay of critically ill patients in the ICU. There is no evidence of clinical superiority between the use of ready-to-use PN and manipulated PN **[5]**.

In addition, it is recommended that the blood glucose target should be set between 140 and 180 mg/dL for clinical patients under intensive care. Although expert societies may disagree on the lower limit of the tolerance range (SCCM 150–180 mg/dL vs. ASPEN 140–180 mg/dL), there is consensus that strict glycemic control targets should not be used, at risk. of increased mortality. Glycemic levels above 180 mg/dL are increasingly associated with greater comorbidity. Randomized studies have also shown that measurements of blood glucose dispersion and minimum blood glucose are necessary **[5]**.

Furthermore, parenteral use of glutamine is contraindicated in patients with multiple organ dysfunction, renal dysfunction, hepatic dysfunction, or hemodynamic instability. In other situations, in association with well-indicated and elaborate PN, it can bring clinical benefits to critically ill patients, and can be considered on a case-by-case basis **[1]**.

In this sense, glutamine participates in many physiological, metabolic, immunological, antioxidant, synthetic, and structural processes. Due to its physicochemical characteristics, L-glutamine was completely omitted from the NP solutions. These solutions exclusively contain crystalline amino acids (AAs), with their specific solubility and thermal stability. Dipeptides with glutamine (alanyl-glutamine, or glycyl-glutamine, are more soluble and stable in aqueous solution) came to fill an important gap in the concentrations of AAs in solutions for PN, restoring or even increasing the content of AAs in these solutions **[1]**.

Also, serum phosphorus should be monitored in critically ill patients under enteral/parenteral nutrition, as frequent monitoring of serum phosphorus in critically ill patients and adequate replacement when appropriate. Hypophosphatemia is a frequent laboratory finding in critically ill patients and has been associated with sepsis, refeeding syndrome, use of diuretics, continuous dialysis methods, and alkalosis. Thus, by reducing the production of 2,3-diphosphoglycerate and ATP, negative effects on diaphragmatic contractility have already been documented, which may result in a delay in weaning from ventilation in critically ill patients **[1]**.

As proof of this, in a cohort study with 66 patients in which 123 weaning attempts were performed, it was observed that the success of weaning was correlated with the serum phosphorus level (1.18 ± 0.27 mmol/L x 1.06 ± 0.31 mmol/L (p=0.008) Those with a serum level < 0.8 mmol/L had a higher risk of failure than those with phosphorus within the laboratory reference value (RR=1.18; 95% CI, 1.06-1.32; p=0.01) In another retrospective study, including 67 patients with COPD on mechanical ventilation with an incidence of high hypophosphatemia (56.72%), a correlation was also observed (34.21 vs. 10.34%, p<0.05) between weaning failure and low phosphorus (< 0.87 mmol/L) **[3]**.

Besides, PN should be used in the early postoperative period in malnourished patients or patients at high nutritional risk who are unable to be fed orally or enterally. In well-nourished patients with contraindications to the use of the digestive route, 5-7 days should be waited to start PN. In this context, when it comes to the distribution of macronutrients, the highlight is the protein intake, which should correspond to values between 1.2–2.0 g/Kg/day (ASPEN) considering the current weight and the degree of stress of the organism, is that the proportions of carbohydrates and lipids should follow the traditional recommendations of the general public **[1]**.

According to ASPEN, it is important to emphasize that in the NT of critically ill patients, protein intake should be prioritized over energy intake because of its role in reducing mortality. For DITEN, it is important to observe whether there is a need to adjust the energy supply when deciding on the protein supply because if the energy supply is below the needs, the protein will be used as the main energy source **[1]**.

In Germany, a current guideline provides clinicians with consensus-updated recommendations for clinical nutrition in critically ill adult patients suffering from at least one acute organ dysfunction that requires specific drug therapy and/or a mechanical support device (e.g., mechanical ventilation) to maintain organ function. The validity period of the guideline is approximately fixed at five years (2018-2023) **[6]**.

A narrative review study presented the actual state of the art to provide the best quality PN, with special attention to pharmaceutical aspects such as instabilities, incompatibilities, and concomitant co-medication. PN is targeted as a single daily serving formulated as an oil-in-water emulsion, providing the necessary substrates for catabolic and anabolic metabolism, including macro and micronutrients and fluids. PN has a complex mixture of a pharmaceutical composition. However, after incorrect handling and administration, PN is associated with potentially serious or even fatal complications, mainly related to central venous access (eg, catheter-related sepsis) or a metabolic intolerance (eg, hyperglycemia, refeeding syndrome) due to improper administration. Therefore, compatibility and laboratory stability tests and pharmaceutical experience are a prerequisite to defining the composition of the PN, including nutrients or even mixed drugs to define the appropriate and individualized nutrition and medication regimen **[7]**.

In this sense, the metabolism of critically ill patients is characterized by a condition of catabolic stress, caused by a systemic inflammatory response and is associated with an increased rate of infection, the occurrence of multiple organ failure, and increased mortality. NT has been considered an "adjunctive therapy" for critically ill patients with the primary objective of providing energy to maintain muscle mass. Based on the scientific developments of recent years, it has become evident that adequate NT can favorably influence stress-related metabolic processes, reduce oxidative cell damage, and modulate the body's immune response **[8]**.

Another study presented a mnemonic derived from guidelines that provide a systematic monitoring process to increase pharmacists' confidence in PN monitoring, improving safety and efficacy. The American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines have been revised. Additional resources included a PubMed literature search (1980 to May 2016) using the search terms: total PN, mnemonic, indications, allergy, macronutrients, micronutrients, fluids, comorbidities, labs, peripheral line, and central line **[9]**.

Furthermore, the composition of personalized parenteral nutrition (PPN) mixtures for home parenteral nutrition offers the possibility to better satisfy the nutritional requirements of patients under selected clinical conditions. Thus, one study compared the composition of MPNPs with the composition of industrially manufactured common parental mixtures of

industrial nutrition (PMIN). Two hundred and ninety-eight patients (151 men, 147 women, aged between 17 and 87 years). The PPN formulation did not differ significantly from the PMIN in terms of total daily calories but was significantly different concerning nutrient composition ($p<0.01$). The analysis of the daily amount of nutrients per kg of body weight and by patient disease showed that 16/34 (47%) patients with benign chronic intestinal insufficiency, 47/233 (20%) patients with cancer, and 5/31 (16%) of patients grouped as 'carriers of other diseases' required personalized mixes. Therefore, despite the positive results of PPN and PMIN cannot be completely replaced due to special needs in macro and/or micronutrients of some patients **[10]**.

Regarding the pediatric context, hospitalized children are vulnerable to malnutrition during serious illness or recovery from injuries and are at subsequent risk of increased morbidity and growth retardation. In cases where enteral nutrition is not possible, PN can be used to ensure that patients at nutritional risk receive appropriate amounts of macro and micronutrients. Nutritional requirements cannot be met by 1 standard PN formulation in pediatric patients (18 years term) due to the wide range of requirements according to age, weight, maturity, and disease state. Individualized PN preparation is associated with several limitations, including prescribing errors, stability issues, and risk of infection. These risks can be avoided by the availability of a variety of pediatric PN formulations supplied as pre-mixed 3-chamber bags. Thus, a prospective study has previously demonstrated the practical handling and ease of use of 2 formulations of these bags, 1 designed for term infants up to 2 years of age and 1 for children and adolescents aged 2 to 18 years. Most pharmacists and nurses described the bag as easy to use and favored it over individual bottles. Therefore, these formulations offer a means of improving the quality of care in pediatric hospital units, especially in the absence of a nutritional support team **[11]**.

Yet another pediatric study reviewed the current literature evaluating the clinical outcomes of early and late-onset PN among critically ill children. The timing of PN onset varies among critically ill children and derives from an assessment of nutritional status, energy requirements, and physiological differences between adults and children, including higher nutritional requirements and lower body reserves. A recent randomized control study among critically ill children suggests better clinical outcomes by avoiding initiation of PN on the first day of admission to the ICU. Although there is no consensus on the optimal timing for the initiation of PN among critically ill children, recent literature does not support the prompt initiation of PN upon admission to a pediatric ICU **[12]**.

In addition, energy requirements change in critically ill patients and are influenced by the clinical situation, treatment, and process phase. Therefore, the most appropriate method for calculating caloric intake is indirect calorimetry. In the absence of this technique, fixed calorie intake (between 25 and 35 kcal/kg/day) or predictive equations such as the Penn State formula can be used to obtain a more accurate assessment of metabolic rate. Carbohydrate administration should be limited to a maximum of 4 g/kg/day and a minimum of 2 g/kg/day. Plasma blood glucose must be controlled to avoid hyperglycemia. Fat intake should be between 1 and 1.5 g/kg/day. Recommended protein intake is 1-1.5 g/kg/day, but may vary depending on the patient's clinical status. Special attention should be paid to micronutrient intake. There is a lack of consensus on micronutrient requirements. Some vitamins (A, B, C, E) are of great importance in critically ill patients, especially those undergoing continuous renal replacement techniques, patients with severe burns, and alcoholics, although the specific requirements of each of these types of patients have not yet been established. been attended **[13]**.

In this context, a retrospective study evaluated whether the withdrawal of a soybean oil-based lipid emulsion from the PN regimen in humans is associated with better concentrations of triglycerides and liver enzymes. Thus, 40 patients with hypertriglyceridemia (> 4.50 mmol/L) while receiving PN were analyzed from their medical records. Patients received 20% Intralipid as part of an all-in-one system containing all necessary macro and micronutrients, electrolytes, trace elements, and vitamins. Lipid emulsions were removed from the all-in-one mixture for a median of 5 (range, 1-23) days, after which triglyceride concentrations decreased significantly (mean difference -2.5 ± 0.30 mmol/L, $p<0.001$). Aspartate aminotransaminase and leukocyte counts decreased significantly (mean difference 35 ± 17 U/L, $p=0.049$, and 3.8±1.7*10E9 /L, $p=0.028$, respectively), while albumin level increased significantly (mean difference 2.1 ± 0.9 g/L, $p=0.027$). Alanine aminotransaminase showed a non-significant reduction (mean difference 30 ± 22 U/L, $p=0.194$). In 11 patients, the lipid emulsion was reintroduced, after which triglyceride levels showed a significant increase (mean difference 1.5±0.30 mmol/L, $p=0.001$). Short-term withdrawal of the lipid fraction in the NP mixture is associated with a significant reduction in plasma triglyceride concentration. Reintroduction was related to increased triglyceride concentration. In addition, liver enzyme abnormalities and leukocyte counts decreased,

while albumin levels increased, suggesting that even with the removal of the lipid emulsion, hepatocellular damage and systemic inflammation decreased **[14]**.

Furthermore, patients suffering from chronic liver failure are often malnourished and do not achieve an adequate intake of nutrients, in particular proteins. The main objective of the nutritional intervention is to provide sufficient protein (1.2-1.5 g/kg/day) and ensure adequate energy intake (total energy 30 kcal/kg/day). The livers of patients with IHC are depleted of glycogen and therefore prolonged periods of fasting (>12 h) should be avoided to avoid further breakdown of muscle protein in gluconeogenesis. Therefore, late-night snacks or even late-night oral nutritional supplements improve total body protein status and are therefore recommended. Nutritional intervention should be scaled up from nutritional counseling to oral nutritional supplements, enteral tube feeding, or parenteral nutrition, as appropriate. As in other malnourished patients, care should be taken to prevent refeeding syndrome or vitamin/trace element deficiency **[15]**.

Also, inflammatory bowel disease (IBD) is a chronic disease mediated by the immune system and characterized by inflammation of the gastrointestinal tract. This study is to understand how the use of PN may affect the adult population diagnosed with IBD. Thus, one study performed a systematic review, meta-analysis, and meta-regression. After a full-text review, only 15 studies were selected for qualitative synthesis and 10 for meta-analysis and meta-regression. The variables used were Crohn's Disease Activity Index (CDAI), albumin, body weight (BW), and postoperative complications (COM). NP has demonstrated efficacy in the treatment of IBD and is compatible with other drugs. CDAI and albumin improve, although the effect of NP is greater after some time. However, the effect on albumin may be less than the value observed in the meta-analysis due to possible publication bias. The PC does not change after the intervention. COM using NP was observed, although the proportion is low **[16]**.

In addition, long-chain n-3 polyunsaturated fatty acids modulate immune cell functions. In this sense, a study evaluated the impact of different lipid emulsions (LE) with supplemented doses of fish oil (FO) on the serum concentration of cytokines and in vitro production of cytokines in patients with intestinal failure in home PN. It was hypothesized that FO supplementation would decrease lipopolysaccharide (LPS)-stimulated cytokine production. Twelve patients receiving Smoflipid for at least 3 months received OP (Omegaven) for an additional 4 weeks. After this cycle, patients were randomized to subsequently receive 1 cycle of Lipoplus and 1 cycle of ClinOleic for 6 weeks or vice versa plus 4 weeks of Omegaven added after each cycle, in a cross-over study design. A comparison of baseline EL regimens showed lower LPS-stimulated IL-1β production in patients on Lipoplus than on the Smoflipid and ClinOleic regimens, as well as lower IL-8 compared to the Smoflipid regimen. Omegaven reduced serum IL-8 concentration under the Lipoplus regimen and decreased LPS-stimulated IL-1β production under Smoflipid and ClinOleic. IL-6 and TNF-α production was reduced only in those on Smoflipid. Regardless of the EL used, patients compared to healthy controls had higher concentrations of IL-6, IL-8, and TNF-α in serum and LPS-stimulated production of IL-6, as well as lower n-6/n-3 fatty acids. long-chain polyunsaturated fatty acids in erythrocyte phospholipids. LPS-stimulated IL-6 production correlated negatively with a parenteral dose of eicosapentaenoic acid + docosahexaenoic acid. In conclusion, OP-supplemented NP suppresses cytokine production in vitro **[17]**.

Another recent work, based on a special edition of Nutrients, contains 13 manuscripts (two reviews and 11 original publications) that reflect the broad spectrum of research currently being conducted in the field of dietary minerals. The manuscripts in this special edition collection include populations from several countries, including the US, Germany, Australia, Brazil, Poland, Japan, Colombia, Mexico, Saudi Arabia, Russia, Italy, South Korea, and Israel. The manuscripts presented cover a wide variety of topics in the field of minerals for NP, with an emphasis on the antimicrobial properties of magnesium and the potential to develop healthier foods, the link between Nrf2 and dietary selenium, iron, zinc and copper, the association between nicotianamine and deoxymuginic acid as improvers of iron bioavailability, investigation of dietary silicon and its impact on plasma concentrations of silicon in humans. Minerals make up only five percent of the typical human diet, but they are essential for normal health and function. Therefore, macro minerals are defined as minerals required by adults in amounts greater than 100 mg/day or that make up less than one percent of total body weight. Trace elements (or minerals) are generally defined as minerals needed in amounts from 1 to 100 mg/day by adults or less than 0.01% of total body weight. Ultra-trace minerals are generally defined as minerals that are needed in amounts less than 1 microgram/day. Selenium deficiency is uncommon but has been reported in parts of China where the local diet is lacking in selenium; this deficiency also occurs in individuals maintained on total PN without minerals. The clinical features of selenium deficiency are cardiomyopathy and skeletal muscle dysfunction **[18]**.

Finally, although mortality from critical illness has

declined over decades, the number of patients with long-term functional disabilities has increased, leading to decreased quality of life and significant healthcare costs. As an essential part of the multimodal interventions available to improve critical illness outcomes, optimal NT should be provided during critical illness, after ICU discharge, and after hospital discharge. Thus, a narrative review study summarized the latest scientific ideas and guidelines on NT in the ICU, especially PN. Based on recent literature and guidelines, gradual progression to caloric and protein goals is recommended during the initial phase of ICU stay. After this phase, a full caloric dose can be provided, preferably based on indirect calorimetry. Phosphate should be monitored for refeeding hypophosphatemia and, when it occurs, the caloric restriction should be instituted. For protein, at least 1.3 g protein/kg/day should be targeted after the initial phase. During the chronic phase of the ICU, and after discharge from the ICU, higher protein/calorie targets should be provided preferably in combination with exercise. Several pharmacological options are available to combine with NT to enhance the anabolic response and stimulate muscle protein synthesis. During and after ICU care, optimal NT is essential to improve long-term outcomes and reduce the likelihood that the patient will become a victim of a critical illness. Nutritional goals are not met at any stage of recovery. Personalized NT, respecting different targets during the phases of the patient's journey after a critical illness, should be prescribed and monitored **[19,20]**.

Conclusion

In the nutrition therapy scenario and after fifty years of the clinical introduction of total parenteral nutrition, several clinical studies have critically analyzed the evolution and changes that have marked its development and clinical use. Standard crystalline amino acid solutions, while devoid of side effects, remain incomplete regarding their composition (eg glutamine). Lipid emulsions have come a long way and are now included in bi- and tri-compartment feeding bags, allowing for true total parenteral nutrition as long as daily micronutrients are prescribed. The issue of exact individual needs for energy, macro, and micronutrients has not yet been resolved. Many complications attributed to total parenteral nutrition are the consequence of under or overfeeding. Total parenteral nutrition indications have evolved towards its use alone or in combination with enteral nutrition. The start time varies by country between admission (Australia and Israel), day 4 (Swiss), and day 7 (Belgium, USA). The most important issue may be an individualized and time-dependent prescription of the feeding pathway, energy, and substrates.

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Informed consent

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

It was applied by Ithenticate@.

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