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Parenteral Nutrition: Macronutrient Composition and Requirements

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Abstract

Parenteral nutrition (PN) is a complex formulation designed to deliver fluid and nutrients in the absence of a functional gastrointestinal (GI) tract. The determination of whether a patient should receive PN rests on a thorough assessment of his or her clinical and nutritional status, with consideration given to the potential risks and benefits of PN. PN solutions can be classified by either route of infusion or by macronutrient content reflected in the inclusion or exclusion of intravenous fat emulsion. The preparation of a stable and safe PN formulation requires a series of careful calculations. This article addresses the appropriate use of PN, with a focus on macronutrient composition and requirements.

Introduction

Parenteral nutrition allows for the provision of energy, vitamins, minerals, electrolytes, fluid, and various medications via a peripheral or central vein. Since the introduction of PN in United States hospitals in the late 1960s, there has been a substantial increase in the demand for such specialized solutions. This has resulted in the diversification of health-care professionals prescribing PN, including physicians, pharmacists, nurse practitioners, and dietitians.

Today, more registered dietitians are faced with the task of not only recommending macronutrient provisions, but also prescribing the entire PN solution based on each patient's unique needs. Several publications provide evidence-based guidelines for the administration of PN (1–3). This article summarizes the standard practice guidelines and provides an overview of when to use PN, macronutrient composition and requirements, types of PN solutions, and calculations for designing the PN regimen.

Patient Selection

The determination of whether a patient should receive PN rests on a thorough assessment of his or her clinical condition and nutritional status. In cases of a nonfunctional GI tract, PN should be started within 7 to 14 days. However, severely malnourished or highly catabolic patients with GI dysfunction need PN within 1 to 3 days of hospital admission (2–4).

Before initiating PN, the clinician should consider the risks and weigh them against the potential benefits of PN. The routine use of PN in the acute setting places the patient at higher risk for fluid, nutrient, and electrolyte abnormalities as well as infectious and noninfectious catheter-related complications. Additional complications of PN extending to the long-term PN patient include metabolic bone disease and hepatobiliary dysfunction (5). The primary benefit of PN is the bypass of a nonfunctional GI tract via delivery of nutrients directly into the bloodstream. Of note, PN has not been shown to be superior to enteral nutrition (EN), and with careful administration, EN is safer, less expensive, and better tolerated than PN (6).

Indications for the use of PN are listed in Table 1. Perioperative PN is generally of most benefit in patients with moderate-to-severe malnutrition and high levels of metabolic stress (7). Very limited benefit has been shown with the use of PN in end-stage, metastatic cancer (8–10). Patients with anorexia or the inability to ingest enough nutrients orally should not receive PN unless enteral access is refused or impossible to obtain (11).

Macronutrient Composition

Dextrose

The primary energy source for the human body is carbohydrate. Brain and neural tissue, erythrocytes, leukocytes, the lens of the eye, and the renal medulla exclusively require glucose or use glucose preferentially. Therefore, carbohydrates form the basis of all PN solutions. The most commonly used carbohydrate source in PN formulas is dextrose monohydrate. Dextrose provides 3.4 kcal/g in its hydrated form and is available in a wide range of concentrations from 5% to 70% (Table 2). Percent concentration refers to the grams of solute per 100 mL of solution. A 5% dextrose solution contains 5 g of dextrose per 100 mL of solution or 50 g/L. Higher dextrose concentrations are used to decrease total volume for patients requiring fluid restriction.

Amino Acids

Protein is provided in PN for the maintenance of cell structure, tissue repair, immune defense, and skeletal muscle mass. Crystalline amino acids are used as the protein source for PN. These solutions are commonly available in concentrations ranging from 8.5% to 20% and provide 4 kcal/g (Table 2). Standard amino acid solutions are a physiologic mixture of both essential

Table 1. Indications for the Use of Parenteral Nutrition

- Intractable vomiting or diarrhea
- Prolonged paralytic ileus
- Lower gastrointestinal tract perforation or leak
- High-output enterocutaneous fistula
- Bowel ischemia
- Short bowel syndrome with severe malabsorption
- Complete lower intestinal obstruction
- Diffuse peritonitis
- Persistent gastrointestinal bleeding
- Repeated failure of enteral feeding or inability to maintain enteral access

and nonessential amino acids and vary in composition among manufacturers. A 15% or 20% standard amino acid solution may be used to concentrate the PN formula for patients with marked fluid overload.

Several disease-specific amino acid solutions are also available, primarily for use in renal or hepatic disease exacerbated by severe stress or critical illness (Table 3). Patients with declining renal function who are not undergoing dialysis may experience accumulation of urea nitrogen in the blood stream upon infusion of nonessential amino acids. In light of this, parenteral amino acid solutions containing only essential amino acids have been developed for this population. However, clinical trials have failed to show definitive improvement in renal function with these specialized solutions, and nonessential amino acids may become conditionally essential during periods of severe stress (12–14). See Table 4 for the categorization of amino acids.

Patients with hepatic encephalopathy refractory to medical management may be candidates for the use of branched-chain amino acid (BCAA) parenteral solutions (Table 4). BCAAs are oxidized primarily in the muscle instead of the liver, which preserves appropriate metabolic pathways in cases of liver failure. This area of clinical therapy has been studied extensively, but few controlled trials have demonstrated a benefit over standard amino acid solutions (15,16). In general, disease-specific amino acid solutions should not be used for more than 2 weeks because they provide an incomplete amino acid profile (17). Additionally, routine use is not recommended due to lack of supporting research and substantial expense associated with these specialized amino acid solutions.

Lipids

Lipids are a concentrated, isotonic source of energy providing 9 kcal/g and are available for intravenous (IV) use as oil-in-water emulsions ranging in concentration from 10% to 30% (Table 2). Lipid emulsions currently available in the United States contain long-chain triglycerides (LCT) in the form of soybean oil or safflower oil, egg phospholipids as an emulsifier, and water. Glycerol is added to create an isotonic solution.

The primary role of IV lipid emulsion is to prevent essential fatty acid (EFA) deficiency. Daily EFA requirements can be met with 4% of total calories as linoleic acid or 10% of total calories as a safflower oil-based lipid emulsion. Patients with a documented egg

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Table 2. Macronutrient Solutions

Nutrient	Concentration	Grams per Liter	Calories per Liter
Dextrose	5%	50	170
	10%	100	340
	20%	200	680
	50%	500	1,700
	70%	700	2,380
Amino Acids	8.5%	85	340
	10%	100	400
	15%	150	600
	20%	200	800
	Concentration	**Calories per Milliliter**	**Calories per Liter**
Lipid Emulsions	10%	1.1	1,100
	20%	2	2,000
	30%	3	3,000

Table 3. Disease-specific Amino Acid Solutions

Renal Failure	NephrAmine® 5.4% (B. Braun) RenAmin® 6.5% (Baxter) Aminosyn®-RF 5.2% (Hospira)	Essential amino acid solutions
Liver Disease	HepatAmine® 8% (B. Braun) BranchAmin® 4% (Baxter) Aminosyn®-HBC 7% (Hospira) FreAmine® HBC 6.9% (B. Braun)	Solutions high in branched-chain amino acids

B. Braun: Bethlehem, Pa.
Baxter: Deerfield, Ill.
Hospira: Lake Forest, Ill.

Table 4. Amino Acid Categorization

Essential	Nonessential	Conditionally Essential	Branched-chain
Isoleucine	Alanine	Arginine	Leucine
Leucine	Asparagine	Cysteine*	Isoleucine
Lysine	Aspartate	Glutamine*	Valine
Methionine	Glutamate	Histidine	
Phenylalanine	Glycine	Taurine	
Threonine	Hydroxyproline*	Tyrosine	
Tryptophan	Ornithine*		
Valine	Serine		

*Not routinely contained in parenteral nutrition amino acid formulations.

allergy should not receive IV lipids because of the egg phospholipid content. Patients with egg allergy who require PN as the sole source of nutrition for more than 3 weeks should be closely monitored for clinical and biochemical evidence of EFA deficiency. A triene: tetraene ratio of more than 0.2, in addition to excessive hair loss; poor wound healing; dry, scaly skin unresponsive to water-miscible creams; and/or alterations in platelet function can signify EFA deficiency (18).

In rare instances, cutaneous oil application may become necessary and is best used as a preventive measure in patients at risk for EFA deficiency. Miller and associates (18) reported successful prevention of EFA deficiency with 3 mg/kg/d safflower oil applied cutaneously over 4–6 weeks; Press and colleagues (19) reported correction of EFA deficiency with application of 2 to 3 mg/kg/d sunflower seed oil for 12 weeks.

In addition to providing a source of EFA, lipids are also useful for replacing excessive dextrose calories manifested by uncontrolled blood glucose levels or hypercapnia with delayed weaning from mechanical ventilation. Lipid emulsions containing medium-chain triglycerides (MCT), fish oil, and olive oil have been used in Europe since 1984, but are currently available in the United States for research purposes only. When compared with pure LCT emulsions, mixed MCT-LCT lipid emulsions have been shown to exert less stress on the liver, improve plasma antioxidant capacity, reduce generation of proinflammatory cytokines, improve neutrophil function, and enhance oxygenation in stressed patients (20–22).

Types of Solutions

PN solutions can be broadly classified as either total or peripheral PN based on route of administration and more specifically as "2-in-1" or "3-in-1" solutions based on macronutrient composition. A patient's clinical and nutrition status, estimated duration of therapy, and type of IV access are important considerations when determining the most appropriate form of PN.

Total Parenteral Nutrition

Total parenteral nutrition (TPN) refers to the administration of PN through a large-diameter central vein. Central access allows for the use of a highly concentrated, hypertonic solution, which can be tailored to meet the macronutrient and fluid requirements of individual patients. Patients requiring PN for longer than 2 weeks generally are candidates for PN via a central vein, using either a temporary central venous catheter (CVC) or a long-term CVC such as a tunneled catheter, an implanted port, or a peripherally inserted central catheter (PICC). Although TPN does offer greater freedom in formula preparation, CVCs can increase the risk of catheter-related blood stream infections, particularly when used for PN (23).

Peripheral Parenteral Nutrition

Peripheral parenteral nutrition (PPN) avoids the use of a central vein and associated complications. Because PPN is administered into a peripheral vein, the osmolarity of a PPN solution should not exceed 900 mOsm/L (Table 5). Patients receiving PPN are at risk for vein damage and thrombophlebitis if this osmolarity level is exceeded (24). Generally, PPN solutions are lipid-based because lipids are a concentrated calorie source and contribute fewer mOsm/g. Due to the lower dextrose concentration of PPN, there is less risk of hyperglycemia. However, PPN solutions provide fewer total calories, protein, and electrolytes per liter than hypertonic TPN solutions. PPN is an acceptable form of parenteral support when a patient is not hypermetabolic,

Table 5. Calculating the Osmolarity of PN Solutions

A. Total grams of amino acids **per liter** of solution	×	10	=	_____ mOsm
B. Total grams of dextrose **per liter** of solution	×	5	=	_____ mOsm
C. Total grams of fat (using 30% emulsion) **per liter** of solution	×	0.67	=	_____ mOsm
D. Total mEq of calcium, magnesium, potassium, and sodium **per liter** of solution	×	2	=	_____ mOsm
Add A, B, C, and D to derive total osmolarity of the PN solution			=	_____ mOsm

(For peripheral vein tolerance, total osmolarity **per liter** should be 900 mOsm/kg or less.)

Example: PPN solution containing 1,800 kcal, 80 g amino acids (AA), 130 g dextrose, and 115 g lipid in 2,400 mL volume plus 200 total mEq of calcium, magnesium, potassium, and sodium.

A. 80 g AA ÷ 2.4 L =	33 g AA/L	×	10	=	330 mOsm
B. 130 g dextrose ÷ 2.4 L =	55 g dextrose/L	×	5	=	275 mOsm
C. 115 g lipid ÷ 2.4 L =	48 g lipid/L	×	0.67	=	32 mOsm
D. 200 mEq electrolytes ÷ 2.4 L =	83 mEq/L	×	2	=	167 mOsm
Total Osmolarity				=	804 mOsm

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Table 6. Compatibility Ranges for Total Nutrient Admixtures

Macronutrient	Acceptable Range per Liter
Standard amino acids	20 to 60 g
Dextrose	35 to 253 g (119 to 860 kcal)
Fat	13 to 67 g (130 to 670 kcal)

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requires therapy for fewer than 2 weeks, has and can maintain adequate peripheral venous access, and does not require fluid restriction.

"2-in-1" Versus "3-in-1" Solutions

PN solutions are routinely comprised of carbohydrate, protein, electrolytes, vitamins, minerals, trace elements, medications, and sterile water. Such solutions are referred to as "2-in-1" solutions. Lipids can be infused separately or added to the PN solution to form a total nutrient admixture (TNA) or "3-in-1" solution. A 2-in-1 solution is favorable when patients have high protein or minimal fluid needs and can maintain euglycemia with the addition of a modest insulin dose.

TNAs that include lipids are convenient and require less nursing time for administration. A TNA may be especially advantageous in patients who have increased energy needs or who would benefit from reduced carbohydrate provisions due to persistent hyperglycemia or hypercapnia (2). The phospholipid outer layer imparts stability to intravenous lipids when provided in a 3-in-1 admixture. However, macronutrient components must fall within acceptable ranges per liter for the 3-in-1 solution to remain stable (Table 6). If one component falls outside of the acceptable range, the stability of the solution cannot be guaranteed for 24 hours. Disruption of stability can present as either distinctive creaming or "oiling out" in which the lipid portion separates from the aqueous phase of the solution containing dextrose and protein. In this case, the TNA cannot be infused due to risk of fat embolus with unemulsified lipid.

Macronutrient Requirements

Daily macronutrient requirements are individualized based on age, sex, anthropometrics, body composition, activity level, medical diagnoses, degree of metabolic stress, and clinical circumstances. Several techniques are available for the estimation and measurement of energy expenditure. The accuracy of predictive equations in hospitalized patients remains an area of debate due to physiologic differences among patients and the multitude of factors affecting the ability to obtain a valid body weight.

A retrospective review by Barak and colleagues (25) used indirect calorimetry measurements to uncover disease-specific stress factors useful in estimating calorie needs for hospitalized patients. When multiplied by the Harris-Benedict equation, estimated energy expenditure using these stress factors closely approximated established literature values. The authors recommended using actual weight of normal and underweight patients and an adjusted body weight equal to ideal body weight plus 50% of excess body weight for estimating energy expenditure of obese patients requiring nutrition support.

Indirect calorimetry is used to derive energy expenditure through measurements of O_2 consumption, substrate oxidation, and CO_2 production. Substrate utilization is reflected in the ratio of CO_2 produced to O_2 consumed or the respiratory quotient (RQ) (Table 7). In general, an RQ greater than 1.0 suggests administration of excess carbohydrate or total calories with ensuing lipogenesis. An ideal RQ is between 0.85 and 0.95, indicating protein sparing and mixed utilization of carbohydrate and fat (26). Despite the need to use protein for wound healing and maintenance of muscle mass, when estimating total daily energy requirements and prescribing PN, calories from all three substrates should be included (27).

Carbohydrate

The average adult requires approximately 100 g/d carbohydrate or 1 mg/kg/min to meet minimum daily requirements for central nervous system function. Without this daily requirement, protein is broken down to obtain the necessary fuel through gluconeogenesis. A minimum of 130 g/d carbohydrate is recommended for healthy adults and children as part of the Dietary Reference Intakes (DRI) (28). Prolonged underfeeding of carbohydrate and total calories via the enteral or parenteral route has been associated with poor wound healing, increased risk of infection, respiratory dysfunction, and an overall poor prognosis (29).

In cases of chronic underfeeding, the body adapts by decreasing reliance on carbohydrate and gluconeogenesis pathways and increasing utilization of ketones and fatty acids for energy. An increase in ketone body formation puts the patient at risk for ketoacidosis, a disruption of acid-base balance within the body (30). The reintroduction of carbohydrate loads causes a rapid shift to glucose as the primary fuel, thereby increasing the demand for insulin, which may not be available in adequate amounts to meet the demand. Hyperglycemia, hypophosphatemia, hypokalemia, hypomagnesemia, hypotension, dehydration, fluid retention, and

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Table 7. Respiratory Quotients for Various Substrates

Substrate	Respiratory Quotient
Alcohol	0.67
Fat	0.71
Protein	0.82
Mixed substrate	0.85
Carbohydrate	1.00
Lipogenesis	1.01 to 1.20

metabolic acidosis can occur with rapid refeeding of carbohydrate after prolonged starvation, known as the refeeding syndrome. Any existing electrolyte deficiencies should be corrected before initiating PN at 50% of caloric requirements or approximately 15 to 20 kcal/kg. PN can then be advanced over the next few days while closely monitoring electrolytes, blood glucose, and body weight.

Overfeeding is also of concern because excess carbohydrate administration has been associated with hyperglycemia, hepatic steatosis, and increased CO_2 production, which may preclude weaning of the ventilator-dependent patient (31). Continuous dextrose infusion rates greater than 4 mg/kg/min led to an increased incidence of hyperglycemia in a study of 37 nondiabetic PN patients (32). Intravenous carbohydrate administration, therefore, should not exceed 4 mg/kg/min in critically ill patients and 7 mg/kg/min in stable hospitalized patients, unless they are undergoing cycling of PN with careful monitoring of blood glucose levels (33). Replacement of excess carbohydrate with lipid calories may aid in the maintenance of euglycemia, the prevention of excess CO_2 production, and the reduction of lipogenesis.

Protein

Daily protein needs are based on the patient's age, weight, and nutritional and clinical status. Inadequate protein intake can result in negative nitrogen balance, depleted hepatic proteins, and delayed wound healing. The Recommended Dietary Allowance (RDA) for protein for healthy adults is 0.8 g/kg/d. In periods of acute illness, muscle breakdown is accelerated and exceeds protein synthesis, which results in a net negative nitrogen balance.

Hospitalized patients requiring PN generally need 1.5 to 2.0 g/kg/d protein, with adjustments made according to tolerance, clinical course, nitrogen balance, and monitoring of hepatic protein status (34). Critically ill patients receiving continuous venovenous hemodialysis may require up to 2.5 g protein per kilogram of dry body weight daily to promote nitrogen balance (17). Prerenal azotemia may develop as a result of dehydration or excess protein intake, although a mild increase in blood urea nitrogen (BUN) values can be expected with moderate-to-high amounts of protein infusion via PN. IV protein provisions should be decreased when BUN levels exceed 100 mg/dL (35).

Fat

Daily lipid requirements are met by providing adequate EFA in the form of linoleic acid. For healthy adults, the DRI for linoleic acid is 17 g/d for men and 12 g/d for women (28). This equates to about 10% of total calories as a commercial IV lipid emulsion of soybean or safflower oil. Lipid emulsions currently available in the United States are composed principally of LCT, which may have an immunosuppressive effect when administered in large amounts over short periods of time. Rapid infusion of IV lipids has been associated with the impairment of neutrophil production and the reduction of endotoxin clearance (36,37). An attempt should be made to limit IV lipid administration to 1 g/kg/d or 25% to 30% of total calories to avoid adverse reactions such as respiratory insufficiency, fever, chills, headache, back or chest pain, nausea, and vomiting.

PPN solutions are commonly lipid-based because of the low contribution of IV lipid to the osmolarity of the solution. Because PPN solutions have osmolarity restrictions and generally cannot meet total calorie requirements, patients receiving such solutions may be fed up to 50% of total calories as lipid safely. However, care must be taken to attempt to limit lipid administration to 1 g/kg/d. The overfeeding of lipids can also result in hypertriglyceridemia or reduced lipid clearance. In cases of suspected altered lipid metabolism, as in pancreatitis, sepsis, and moderate-to-severe liver disease, serum triglyceride levels should be monitored before and 6 hours after PN infusion (5). Lipid administration should be held when serum triglyceride levels exceed 400 mg/dL (2).

Designing the PN Solution

The route and nutrient composition of a PN solution governs the calculations needed for preparation of a safe PN formula. Most institutions have a standardized order protocol used by all clinicians prescribing PN. In addition, an expert panel representing the American Society for Parenteral and Enteral Nutrition recently published updated guidelines on safe practices for PN formulations (3). The panel recommends standardized ordering

Table 8. Guidelines for Dosing Macronutrients and Fluid in PN

	Normal Range	Minimum Dose	Maximum Dose
Total Calories (kcal/kg/d)	25 to 35	10 (for morbid obesity)	45 to 55 (for severe malnutrition)
Protein (g/kg/d)	0.8 to 1.5	0.8	2.5
Dextrose (mg/kg/min)	2 to 3.5	1	4 to 7
Fat (% total calories)	25 to 30	10% as commercial IV fat emulsion (4% as linoleic acid)	30
Fluid (mL/kg/d)	30 to 40	As per compatibility/ osmolarity guidelines	Variable, depending on fluid losses and need for repletion

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