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Parenteral Nutrition

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Introduction

Parenteral nutrition can be considered one of the 20th century's medical breakthroughs. Its discovery and first implementation in the 1960s greatly enhanced clinical medicine by providing a means for complete and safe feeding of patients with nonfunctional gastrointestinal (GI) tracts. Experimentation with intravenous feeding can be traced as far back as the 1600s, when sharpened quills were used to administer a mixture of milk and wine into the veins of dogs.[1] The 1800s brought the administration of saline, and by the 1930s 5% dextrose and protein hydrolysates were being infused intravenously.[2] Several factors limited the safe infusion of nutrients intravenously. One factor was the large volumes that were provided, usually more than 3 liters per day.[2] These volumes were generally not tolerated by patients for long periods of time, and often resulted in pulmonary edema. Another factor was the attempt to deliver hyperosmolar solutions peripherally, which was the common practice in the early years. Dextrose solutions greater than 10% concentration were not tolerated, and resulted in thrombosis. Lastly, volume and the osmolality restrictions resulted in caloric delivery limitations. This all led to experimentation with alternate fuel substrates, alcohol and fat, due to their increased caloric provision of 7 and 9 kcalories per gram, respectively. Research quickly revealed that alcohol was not going to be the answer, as it resulted in hepatoxicity and other side effects when delivered in large amounts.[1] Intravenous fat delivery was an enticing alternative due to its high caloric load and decreased osmolality. Initially, provision of intravenous fat was achieved with cottonseed oil in the 1950s. However, it was removed from the market, as it was associated with jaundice, fever, and bleeding.[3] Research continued in Europe, where emulsions made from soybean oil were successfully administered.[2]

Great advancement came in 1967, when cannulating the subclavian vein was introduced to administer intravenous nutrients. Wilmore and Dudrick[4] first reported successful provision of centrally administered nutrition to an infant with intestinal atresia. In the 1970s advancements continued with the use of crystalline amino acids rather than protein hydrolysates, recommendations for standard amounts of vitamins and minerals, and the reintroduction of lipids in the United States.[1] After the 1970s, the focus turned to fine-tuning the parenteral solutions with the development of specialized amino acid sources

TABLE 43.1

Development of Total Parenteral Nutrition (TPN) Guidelines

Organization	Year
American Society for Parenteral and Enteral Nutrition	1986, 1993
American College of Physicians	1987, 1989
American Gastroenterology Association	1989
U.S. Dept of Health and Human Services	1990

TABLE 43.2

Indications for TPN[5-8]

Clinical Situation	Consensus
Short bowel syndrome	Inability to absorb adequate nutrients orally <60 cm small bowel may require indefinite use
Severe pancreatitis	Recommended if enteral nutrition causes abdominal pain, ascites, or elevated amylase/lipase Increased fistula output with enteral feedings Intravenous lipids are considered safe if serum triglyceride levels are <400 mg/dl
Enterocutaneous fistula	Fistula that exhibits increased output with enteral nutrition
Intractable diarrhea or vomiting	Recommended for losses greater than 500-1000 ml/day with inability to maintain adequate nutritional status
Bowel obstruction, ileus	With obstruction and malnutrition awaiting surgery >7 days Prolonged ileus >5-7 days with poor nutritional status
Perioperative support	Preoperative support is indicated for severely malnourished patients with expected postoperative NPO status >10 days For those with postoperative complications rendering NPO >10 days
Inflammatory bowel	If enteral nutrition not tolerated or if precluded by GI fistulas
Critical care	Unable to gain enteral access, instability, abdominal distention with prolonged reflux of enteral feedings, expected to remain NPO >7 days
Eating disorders	Severe malnutrition and inability to tolerate enteral feeding for psychological reasons
Pregnancy	Safe in pregnancy; hyperemesis gravidarum

for disease states, approval of total nutrient admixtures by the Food and Drug Administration, and development of new access devices and delivery systems.[1]

Rationale for Use of Parenteral Nutrition

Parenteral nutrition was first developed to provide nutrition to those unable to take complete nutrition via the GI tract due to an inability to digest or absorb nutrients. A nonfunctioning GI tract and failure to tolerate enteral nutrition still remain the primary reasons for parenteral nutrition. Certain accompanying conditions also need consideration, such as a patient being nutritionally at risk, and projected inability to consume anything by mouth for at least 7 to 14 days.[5] Over the past two decades several organizations have developed practice guidelines to identify the appropriate use for parenteral nutrition (Table 43.1). Situations that indicate the need for parenteral nutrition include short bowel syndrome and malabsorption, bowel obstruction, severe pancreatitis, intractable diarrhea or vomiting, prolonged ileus, and high-output GI fistulas (Table 43.2).[5-8]

Comparison of Parenteral and Enteral Nutrition

While parenteral nutrition can be lifesaving when used appropriately, it may also potentiate adverse clinical outcomes. The GI tract not only functions to digest and absorb

TABLE 43.3

Factors that Contribute to Increased Gut Permeability

Absence of enteral stimulation
Broad spectrum antibiotics
H_2-receptor blockers
Decreased GI hormone secretion

nutrients, but also serves as a large immunologic organ in the body by acting as a protective barrier against intraluminal toxins and bacteria. Approximately 50% of the body's immunoglobulin-producing cells line the GI tract, with 80% of the body's manufactured immunoglobulin being secreted across the GI tract.[9] During severe physiologic stress gut ischemia can occur, leading to mucosal damage and disruption of the barrier function and ultimately passage of bacteria and toxins into the bloodstream.[10] In addition, common clinical practices as well as physiologic changes during acute stress can lend to bacterial overgrowth in the proximal GI tract and impact the gut's protective barrier (Table 43.3). Whether or not bacterial translocation occurring in animals and humans during acute stress is clinically significant remains debatable. Animal studies support the statement that enteral rather than parenteral nutrition maintains gut integrity and immune responsiveness, and prevents bacterial translocation.[11-15] However, there was no significant difference in overall outcome in an acute pancreatitis model,[11] but in animals with induced bacterial pneumonia, those that received total parenteral nutrition (TPN) had a higher mortality rate.[15] There is no hard evidence to support the statement that parenteral nutrition results in clinically significant bacterial translocation in humans.[16,17]

Despite this lack of evidence, other disadvantages of parenteral nutrition exist. The metabolic response to intravenous glucose differs from oral glucose. This may be due to the fact that the liver retains a large portion of glucose when provided orally, resulting in less systemic hyperglycemia and hyperinsulinemia.[18] A meta-analysis comparing enteral and parenteral nutrition also concluded that plasma glucose concentrations are lower during enteral than parenteral nutrition.[19] Plasma glucose and insulin concentrations, glucose oxidation, CO_2 production, and minute ventilation increase in proportion to the proportion of kcalories administered in TPN.[20] Prolonged infusion of high rates of glucose (>4 mg/kg/min) results in *de novo* lipogenesis in the majority of critically ill patients.[20] Furthermore, TPN is associated with increased septic morbidity[16,19,21,22] and increased cost[16, 23] when compared with enteral nutrition in trauma patients.

Vascular Access

Peripheral

Prior to initiating parenteral nutrition, vascular access is obtained. Determination of venous access is based upon the duration of therapy, patient limitations, and availability of equipment and facilities. Central or peripheral veins may be used for the provision of parenteral nutrition. Peripheral access with conventional needles uses the small veins of the extremities — typically the hands and forearms. These small veins are easily sclerosed by hypertonic parenteral solutions. Therefore, to minimize phlebitis and thrombosis of the veins, it is recommended that peripheral parenteral solutions (PPN) consist of osmolalities ≤900 mOsm/L.[5] Even with appropriate PPN, intravenous sites may need frequent changing to maintain venous patency.[1] The increased fluid requirement necessary to

TABLE 43.4

Typical PPN Order

Macronutrient	Usual Concentration in PPN Solution	gm/L or mEq/L	Kcal/L	mOsmol/L
Dextrose (6%)	5-10%	60*	240	150
Amino acids (3%)	3-5%	30*	120	300
Lipid (20%)	30-60% (of kcal)	20*	200	300
Sodium		35+	—	70
Potassium		30+	—	60
Magnesium		5+	—	5
Calcium			—	7
Total			560	892

* gm/L; + mEq/L

TABLE 43.5

Indications for Peripheral Parenteral Nutrition

Indication	Example
Patient expected to be NPO 5-7 days	Postoperative ileus
Inadequate GI function expected for 5-7 days	Hyperemesis gravidarum
Transitioning to an oral diet or tube feeding	Patient with Crohn's disease flare
Central venous access is contraindicated	Coagulopathy, sepsis, venous thrombosis
Malnourished patients expected to be NPO for several days	Preoperative small bowel obstruction
Patients with nutrient requirements that can be met with PPN	Obese patient with good venous access, small or elderly people

minimize the PPN solution's osmolality limits nutrient provision as well as the clinical utility of PPN (Table 43.4).

PPN solutions vary considerably among institutions. Some may only use dextrose with electrolytes, vitamins, and minerals while others may include lipids and amino acids to increase the kcalories and minimize catabolism. PPN formulations composed of carbohydrate, amino acids, and lipid generally provide 1000 to 1500 kcal/day . However, PPN may be useful when the long term plan for nutrition is uncertain and the patient requires interim nutrition intervention in which the GI tract is nonfunctional, such as with prolonged ileus or hyperemesis gravidarum (Table 43.5).

Central

Central venous access refers to the large veins in the trunk. The primary indications for central venous access include chemotherapy, antibiotic administration, risk of tissue necrosis with vesicant medications, and provision of TPN due to its pH and increased osmolality. Access is obtained with specialized catheters, with the distal tip placed into the vena cava or right atrial area. The most common venipuncture sites include the subclavian, jugular, femoral, cephalic, and basilic veins (Table 43.6). Several varieties of central venous catheters are available, the most common being polyurethane and silicone (Table 43.7). Most catheters are available in a variety of French sizes, lengths, and number of portals or lumens. Multilumen versions provide for simultaneous infusion of TPN with multiple or incompatible drugs.

Physiologic, functional, psychological, and social factors all need consideration prior to determining the type and location of catheter placement (Table 43.8). If the patient is in the acute care setting and unlikely to be discharged with TPN, the physiologic factors are

TABLE 43.6

Central Venous Catheter Placement[24,25]

Method	Vessels	Description
Percutaneous approach	Subclavian	a. Venipuncture and passage of a guidewire through the needle followed by removal of the needle and catheter placement over the guidewire
a. Modified Seldinger technique	Internal & external jugular Antecubital	
b. Peel-away introducer sheath and tissue dilator		b. Catheter passes through the introducer into the vein and introducer tears longitudinally, leaving the catheter in place
Cutdown	Cephalic External & internal jugular	Surgical dissection, isolation of the vessel, and catheter placement
Tunneled		6 cm catheter segment is tunneled through the subcutaneous tissues between the venipuncture site and the skin exit site
Implanted ports		A reservoir with a silicone disk and attached silicone tube is implanted under the clavicle in a subcutaneous pocket

TABLE 43.7

Central Venous Catheter Characteristics

Material	Description
Silicone elastomer	Known as Silastic (Dow Corning) Biomaterial for longterm indwelling devices Increased elasticity and flexibility for minimal damage to intima Resistant to hydrolytic enzymes; hydrophobic surface resists bacterial adherence Considered chemically inert in blood Guide wire or peel-away introducer needed for insertion due to soft texture
Polyurethane	Increased flexibility and strength; resistance to hydrolytic enzymes Decreased incidence of inflammatory changes and thrombophlebitis with short term use Anticoagulation required with long term use for thrombosis prevention
Polyvinyl chloride	Stiff material Increased rate of thrombogenicity Infrequently used
Polyethylene	High tensile strength Minimal irritation if used for short duration Associated with platelet adherance and fibrous capsule formation with long duration
Polytetrafluoroethylene	Known as Teflon; stable; demonstrates nonadhesive, antifriction properties; resistant to degradative enzymes Smooth and hydrophobic catheter surface Not suitable for long term use due to rigidity which causes irritation and thrombosis formation
Hydrogel	Hydrophilic polymers designed for biological use Absorbs water up to 90% of the catheter's dry weight without dissolving Most inert and nonthrombogenic of biomaterials Material lacks durability unless copolymerized with other monomers
Coated/bonded catheters	Antimicrobial impregnated catheters: catherters with the cationic surfactant tridodecylmethylammonium chloride facilitate bonding of anionic antibiotics to both the internal and external catheter surfaces Antiseptic-coated catheters: polyurethane catheters bonded with silver sulfadiazine and chlorhexidine to the external surface

From Krzywda, E.A. and Edmiston, C.E. *ASPEN Practice Manual,* 1998. With permission.

TABLE 43.8

Patient Factors for Vascular Access Device Selection

Patient Factor	Considerations
Physiologic	Vein physiology
	Hypercoagulable states
	Diabetes
	Clotting abnormalities
	Skin disorders and conditions
	Previous surgical procedures in the thorax or vascular system
	Morbid obesity
	Surgical risk
	Known allergies to vascular materials
Functional	Impaired vision, dexterity
	Developmental disabilities
	Frailty
Psychological	Needle phobia (not ideal candidates for implanted ports)
	Body image issues (implanted port less disturbing than tunneled)
	Previous experience with vascular access devices
Social	Support system for line and catheter care
	Financial implications

From Evans, M. *Nutr. Clin. Prac.* 14: 172; 1999. With permission.

of primary concern. However, if a patient is to receive parenteral nutrition in an alternate care setting, practitioners should consider the other listed factors for optimal patient compliance.[24]

Parenteral Nutrient Components

Parenteral nutrient solutions are complex formulations that usually contain the macronutrients, carbohydrate, protein, and fat for energy provision, as well as electrolytes, trace elements, vitamins, water, and occasionally medications. These components need to be individualized for patients based upon their primary diagnosis, chronic diseases, fluid and electrolyte balance, acid-base status, and specific nutrition goals.[26]

Carbohydrate

Carbohydrate serves as the primary energy source in parenteral solutions. The amount of carbohydrate provided is based upon the patient's individual nutrient requirements and glucose oxidation rate. Although the exact requirement is individualized, guidelines are available. A minimum of 100 gm per day is often used as the obligate need for the central nervous system, white blood cells, red blood cells, and renal medulla.[26] The maximum rate of glucose oxidation in adults is 4 to 7 mg/kg/min,[5] or 400 to 700 gm for a 70-kg person, with the lower range suggested for critically ill patients secondary to endogenous glucose production. Excessive carbohydrate provision is associated with hyperglycemia, excessive carbon dioxide production, and hepatic steatosis.[26]

Carbohydrate is provided almost exclusively as dextrose monohydrate in parenteral solutions. Each gram of hydrated dextrose provides 3.4 kcal/gram. Commercial dextrose preparations are available in concentrations from 5 to 70% (Table 43.9). Dextrose solutions have an acidic pH (3.5 to 5.5) and are stable after autoclave sterilization.[26] Sterilization

TABLE 43.9

Intravenous Dextrose Solutions

Dextrose Concentration %	Carbohydrate (gm/L)	Calories (kcal/L)	Osmolarity (mOsm/L)
5	50	170	250
10	100	340	500
20	200	680	1000
30	300	1020	1500
50	500	1700	2500
70	700	2380	3500

also increases the shelf life of dextrose solutions so that they can be stored for extended periods at room temperature.

Glycerol is a simple organic compound consisting of the elements carbon, hydrogen, and oxygen. Glycerol yields 4.3 kcal/gram when oxidized to carbon dioxide and water, and does not require insulin for cellular uptake. When provided in low concentrations (3%) with amino acids, it has been found to be protein sparing.[27] Because of these advantages, glycerol is used an alternative source of calories in some parenteral formulations, primarily in PPN.

Fat

Since its introduction in Europe in the mid-1960s, intravenous fat emulsions have been extensively used as a nutrient source in parenteral nutrition. The aqueous fat emulsions available in the U.S. as of 1999 consist of long-chain triacylglycerols (TAG) manufactured from soybean and safflower oil. Therefore, the lipid emulsions not only provide a source of kcalories but also essential fatty acids. These products contain egg yolk phospholipid as an emulsifying agent and glycerin, which make the products nearly isotonic. The glycerol raises the caloric concentration of the 10% emulsion to 1.1 kcal/mL and the 20% emulsion to 2.0 kcal/mL. The phospholipid may contribute to the phosphorus intake of patients who receive large amounts of lipids (>500 mL/day). Combinations of long-chain and medium-chain TAG emulsions have been available in Europe for several years.

Most patients tolerate daily infusion of lipids provided as an intermittent or continuous infusion, often as part of a total nutrient admixture (TNA). Continuous delivery with a moderate dose is favored over intermittent infusion due to decreased fluctuations in serum TAG levels and improved fat oxidation.[28] The requirement of a test dose is usually eliminated with continuous delivery, as the administration rate tends to be less than that with the test dose. Patients should still be monitored for fever, chills, headache, and back pain during the first dose of intravenous lipid. Absolute contraindications to intravenous fat emulsions include pathologic hyperlipidemia, lipoid nephrosis, severe egg allergy, and acute pancreatitis associated with severe hypertriglyceridemia.[26] Caution should be taken in delivery to patients with severe liver disease, adult respiratory distress syndrome, or severe metabolic stress. If serum TAG levels are greater than 500 mg/dL, lipids should be held with only the minimal requirements for essential fatty acids (EFA) provided to avoid further metabolic complications.

Lipid requirements are met by providing at least 4% of energy as EFA or approximately 10% of energy as a commercial lipid emulsion from safflower oil[1] to prevent EFA deficiency. Since lipid emulsions vary in their composition of EFA depending on the oil source, the minimum amount provided is based upon the EFA content rather than a percentage of

total energy. Recommendations for optimal lipid delivery have evolved over the years. It once was common practice to provide 50 to 70% of energy as lipid due to its concentrated energy source and decreased volume. However, over the years concerns that long-chain triglycerides impair neutraphil function, endotoxin clearance, and complement synthesis have resulted in the recommendation to limit lipid administration to 1 gm/kg per day[29] or 25 to 30% of total energy.[30]

Protein

The primary function of protein in parenteral nutrition is to provide nitrogen to maintain nitrogen balance to help minimize loss of lean body mass and protein degradation for gluconeogenesis. The protein utilized for parenteral nutrition is primarily in the form of crystalline amino acids. Parenteral amino acid products can be divided into standard and modified. Standard amino acid products are suitable for the majority of patients. They contain a balanced or physiologic mixture of essential and nonessential amino acids in which the ratios are based on FAO/WHO recommendations for optimal proportions of essential amino acids. Standard formulations are available in a range of concentrations from 3 to 15%. Most institutions stock 10 and 15% concentrations, since more dilute solutions can be made readily by adding sterile water with an automated compounder.

Modified amino acid solutions are designed for patients with disease- or age-specific amino acid requirements. Formulations are marketed for adults with hepatic failure, renal dysfunction, metabolic stress, and for neonates with special requirements for growth and development. These modified formulations are significantly more costly than the standard formulations and may not always prove as cost-effective; therefore, strict criteria should be established for their use.

Patients with hepatic failure develop multiple metabolic abnormalities including electrolyte disturbances and alterations in amino acid metabolism. In severe liver disease, hepatic encephalopathy can occur which is associated with decreased branched chain amino acid (BCAA) serum levels and elevated aromatic amino acid (AAA) and methionine serum levels. Patients with hepatic disease without encephalopathy may be provided with moderate levels of standard amino acids with close monitoring of their mental status. When hepatic encephalopathy is severe (≥Grade II), a modified hepatic protein formulation may be beneficial. These formulations have high concentrations of BCAA (~45% of protein) and low concentrations of AAA and methionine. Improvement in hepatic encephalopathy and lower mortality have been found in some patients who received this formulation.[31]

Modified formulations are marketed for patients with renal failure. These formulas contain mainly essential amino acids, and were designed on the premise that endogenous urea could be used to synthesize nonessential amino acids. This hypothesis has been challenged, thus questioning the usefulness of these formulas. Prospective, randomized, controlled studies have demonstrated that standard amino acids are as effective as modified amino acids in patients who have renal failure and who require parenteral nutrition.[32,33] Thus, patients with severe renal failure may be given standard amino acids as part of parenteral nutrition in most clinical situations.[24]

A parenteral formulation with an enhanced BCAA formulation is marketed for patients with metabolic stress such as that caused by trauma, burns, and sepsis. Metabolic stress causes an efflux of amino acids from skeletal muscle and the gut to the liver for gluconeogenesis and support of acute phase protein synthesis.[34] Metabolically stressed patients have also been shown to have increased serum levels of AAA and decreased BCAA levels. Therefore, the rationale of using a high BCAA formula in these patients is to provide the preferential fuel to the body and normalize the patient's amino acid patterns. Multiple

studies have evaluated the benefits of high BCAA formulations in metabolic stress. Some studies have shown positive benefits when using these formulations, such as nitrogen retention, improved visceral protein levels, and reversal of skin test anergy, but there were no differences in morbidity or mortality.[35-37] Other studies have failed to exhibit significant outcome advantages of BCAAs over standard amino acid formulas in metabolic stress.[38-40] Therefore, since the cost-effectiveness of high BCAA solutions has not been clearly demonstrated, initiation of nutrition support with a standard amino acid solution is recommended in patients with metabolic stress.[5]

Protein requirements are based upon the patient's clinical condition. For normal healthy adults the recommendation is for 0.8 gm/kg per day.[41] In the critically ill population, a range of 1.5 to 2.0 gm/kg/day is appropriate.[5] For patients with renal or hepatic disease, protein recommendations vary according to the disease stage and its intervention. For those with renal disease on peritoneal dialysis, 1.2 to 1.5 gm/kg/day of ideal body weight is recommended for maintenance or repletion. For hemodialysis, 1.1 to 1.4 gm/kg of ideal body weight per day is recommended for maintenance or repletion.[42] For patients with uncomplicated hepatic dysfunction, 0.8 to 1.5 gm/kg dry weight is suggested; for end-stage liver disease with encephalopathy, 0.5 to 0.7 gm/kg; if a high BCAA formula is used, then 0.8 to 1.2 gm/kg/day is suggested.[43]

Electrolytes

Electrolytes are essential nutrients that perform many critical physiologic functions. Electrolytes are added to parenteral solutions based upon individual need. The amount added daily varies based upon the patient's weight, disease state, renal and hepatic function, nutrition status, pharmacotherapy, acid-base status, and overall electrolyte balance. Extrarenal electrolyte losses may be a result of diarrhea, ostomy output, vomiting, fistulas, or nasogastric suctioning. As patients become anabolic during parenteral nutrient delivery they may experience increased requirements for the major intracellular electrolytes (potassium, phosphorus, and magnesium). During refeeding of undernourished patients, these electrolytes should be monitored frequently and replenished accordingly.

Small adjustments in electrolyte intake can affect patient morbidity and mortality and therefore need careful monitoring. General recommendations for electrolyte provision are provided in Table 43.10. Electrolyte products are commercially available (Table 43.11), and the composition of the parenteral solution is dependent upon the compatibility of each electrolyte with the other components of the admixture. For calcium provision, calcium gluconate is the preferred form for parenteral formulations due to its stability in solution and decreased chance of dissociating and forming a precipitate with phosphorus. Whether to provide an electrolyte as a chloride or an acetate salt depends on the patient's acid-base status. Generally, acid-base balance is maintained with providing chloride and acetate

TABLE 43.10

Parenteral Electrolyte Recommendations

Sodium	60-150 mEq/d
Potassium	70-150 mEq/d
Phosphorus	20-30 mmol/d
Magnesium	15-20 mEq/d
Calcium	10-20 mmol
Chloride	Equal to Na+ to prevent acid-base disturbances

From Skipper, A. In: *Contemporary Nutrition Support Practice.* W.B. Saunders, Philadelphia, 1998, p. 227. With permission.

TABLE 43.11

Commercially Available Electrolyte Formulations[25,26]

Sodium chloride	Magnesium sulfate
Sodium acetate	Magnesium chloride
Sodium phosphate	Calcium chloride
Sodium lactate	Calcium gluconate
Potassium chloride	
Potassium acetate	
Potassium phosphate	
Potassium lactate	

in a 1:1 ratio. If a patient has altered acid-base status with skewed electrolyte levels, then the chloride:acetate ratio can be adjusted to facilitate correction. Acetate and chloride are also present in the base amino acid solutions in various amounts, and should be considered when attempting electrolyte homeostasis.

Electrolytes increase the osmolarity of the parenteral solution; however, large amounts can be added to solutions with amino acids and dextrose without affecting the stability. When lipids are added to the parenteral solutions caution is needed when adding electrolytes, as there are limitations and hazards.[1] An insoluble precipitate can form when there are excess cations in the parenteral solutions, as with calcium and phosphate, which may not be visualized in total nutrient admixtures. Crystal formation in the lungs with subsequent death was reported in patients as a result of precipitate formation in TPN solutions.[44] The solubility of calcium and phosphorus varies with the volume of the solution, its pH, the type of calcium preparation, the temperature at which the solutions are stored, and the order of admixture.[1] Solutions can be prepared with a range of calcium and phosphorus contents as long as the product of calcium (in mEq) and phosphorus (in mmols) is less than 200.[45]

Vitamins and Trace Elements

Vitamins are typically added to every parenteral formulation in doses consistent with the American Medical Association Nutrition Advisory Group's recommendations.[46] Guidelines are established for the 12 essential vitamins (Table 43.12). Most institutions use a

TABLE 43.12

AMA Recommendations for Parenteral Vitamin Intake

Vitamin	Amount
Vitamin A	3,300 IU
Vitamin D	200 IU
Vitamin E	10 IU
Vitamin C (ascorbic acid)	100 mg
Folacin	400 µg
Niacin	40 mg
Riboflavin	3.6 mg
Thiamine	3 mg
Vitamin B_6 (pyridoxine)	4 mg
Vitamin B_{12} (cyanocobalamin)	5 µg
Pantothenic acid	15 mg
Biotin	60 µg

Adapted from Multivitamin preparations for parenteral use. A statement by the Nutrition Advisory Group. *J Parenter Enteral Nutr* 3: 258, 1979.

TABLE 43.13

AMA Recommendations for Parenteral Mineral Intake

Element	Amount
Zinc	2.5-4 mg/day
Copper	0.5-1.5 mg/day
Manganese	150-180 µg/day
Chromium	10-15 µg/day
Selenium*	40-80 µg/day

* Suggested intake.

Adapted from Guidelines for essential trace element preparations for parenteral use: A statement by the Nutrition Advisory Group. *J Parenter Enteral Nutr* 3: 263, 1979.

commercially available multiple-entity product which contains 12 essential vitamins for adults. The multivitamin preparations for adults do not contain vitamin K because it antagonizes the effects of warfarin in patients receiving this medication. In adults, vitamin K may be administered by adding 1 to 2 mg/day to the parenteral solution or by giving 5 to 10 mg/week intramuscularly or subcutaneously.[26] Individual vitamin preparations are also available and are used to supplement the multivitamin doses when a deficiency state exists, or with increased needs due to disease or medical condition.

Trace minerals are essential to normal metabolism and growth, and serve as metabolic cofactors essential for the proper functioning of several enzyme systems. Although the requirements are minute, deficiency states can develop rapidly secondary to increased metabolic demands or excessive losses. Most clinicians add these micronutrients daily; however, there are clinical conditions necessitating trace mineral restriction and therefore adjustments in the daily intakes.

The Nutrition Advisory Group of the American Medical Association has also published guidelines for four trace elements known to be important in human nutrition.[47] The suggested amounts of zinc, copper, manganese, and chromium for adults are listed in Table 43.13. Since the original recommendations, it has become more evident that selenium also is essential, and many clinicians add this element to the parenteral solution daily along with the other four.[26] Most institutions use a commercially available multiple-entity product, but there are also single-entity mineral solutions available for use during times of increased requirements or when certain minerals are contraindicated. Zinc requirements are increased during metabolic stress due to increased urinary losses, and with excessive GI losses as with diarrhea and increased ostomy output. Manganese and copper are excreted through the biliary tract, whereas zinc, chromium, and selenium are excreted via the kidney. Therefore, copper and manganese should be restricted or withheld from parenteral nutrition in patients with cholestatic liver disease.[26] Selenium depletion has been found in patients receiving long-term TPN, as well as with thermal injury, acquired immunodeficiency syndrome, liver failure, and critical illness.[26,47]

Other Additives

Many patients receiving TPN are also receiving multiple medications, leading to the desire to add the medications to the TPN solutions. Using TPN as a drug delivery vehicle is very tempting, as it may allow for continuous medication infusion in addition to minimizing fluid volume delivery by eliminating the need for a separate dilutent for each medication

TABLE 43.14

Medications Compatible with Parenteral Solutions

Albumin[a]	Cyanocobalamin	Hydromorphone	Nafcillin
Amikacin	Cyclophosphamide	Imipenem-cilastatin	Neostigmine
Aminophylline[a]	Cytarabine	Insulin, regular[a]	Netilmicin
Azlocillin	Digoxin[a]	Iron dextran	Oxacillin[a]
Caffeine	Dipyridamole	Isoproterenol[a]	Oxytocin
Carbenicillin[a,b]	Dobutamine	Kanamycin[a]	Penicillin G[a]
Cefamandole[a]	Dopamine[a]	Lidocaine[a]	Phenobarbital
Cefazolin[a]	Doxycycline	Meperidine[a]	Phytonadione[a]
Cefoperazone	Erythromycin[a]	Metaraminol	Piperacillin
Cefotaxime	Famotidine[a]	Methicillin[a]	Polymyxin B
Cefoxitin[a]	Fluorouracil[b]	Methotrexate	Ranitidine[a,b]
Ceftazidine	Folic Acid	Methyldopa	Tetracycline
Ceftriazone	Furosemide[a]	Methylprednisolone	Ticarcillin[a,b]
Cephalothin[a,b]	Ganciclovir	Metoclopramide[a]	Tobramycin[a]
Chloramphenicol[a]	Gentamicin[a]	Mezlocillin	Vancomycin
Chlorpromazine	Heparin[a]	Miconazole	
Cimetidine[a]	Hydralazine	Morphine	
Clindamycin[a]	Hydrochloric acid	Moxalactam	

[a] Compatible with total nutrient admixtures (TNA)

[b] Some data suggest incompatibility under certain conditions. Visual compatibility only; tested with parenteral nutrition solution without electrolytes; drug may chelate with divalent cations and cause precipitation.

From Strausburg, K. Parenteral nutrition admixture. *ASPEN Practice Manual,* 1998. With permission.

administered. However, scrutiny is needed prior to adding medications to the TPN solution, as there is potential for drug-drug and drug-nutrient interactions. Issues needing consideration include medication compatibility with TPN constituents, the effect of pH changes on TPN compatibility and drug effectiveness, whether the infusion schedule of the TPN is appropriate to achieve therapeutic levels of the drug, and the potential for interactions among the drugs if more than one is added.[1] The complexity of these issues usually leads to consultation with a pharmacist experienced in TPN compounding and compatibility, reference to the institution's policy and procedure manual, or contact with the drug manufacturers. Medications most frequently added to TPN include albumin, aminophylline, cimetidine, famotidine, ranitidine, heparin, hydrochloric acid, and regular insulin.[1] Table 43.14 list medications compatible with TPN solutions, and Table 43.15 lists those medications which are incompatible with TPN solutions.

Insulin

Even with care to avoid excess carbohydrate delivery, patients receiving TPN often become hyperglycemic. One method of achieving desired blood glucose control with continuous TPN infusions is by adding regular insulin to the TPN solution. A few studies have suggested that absorbance of insulin to glass bottles, polyvinyl chloride bags, and tubing occurs,[49,50] with the greatest loss occurring during the first hour of infusion.[51] So, when adding insulin to TPN solutions to optimize blood glucose control, it is important to remember that the patient may have an increased insulin requirement due to absorbance.

Histamine H_2-Receptor Blockers

Stress ulcer prophylaxis with the addition of H_2-receptor blockers to avoid stress ulcers is common practice with patients on TPN who are not receiving any gastric nutrients.

TABLE 43.15

Medications Incompatible with Parenteral Solutions

Amphotericin B	Methyldopa[a]
Amikacin[a]	Metronidazole (with $NaHCO_3$)
Ampicillin[b]	Phenytoin[a]
Cephradine	Tetracycline[a,c]
Iron dextran[a,d]	

[a] Incompatible with total nutrient admixtures (TNA)

[b] Some visual compatibility data suggest compatibility under certain conditions

[c] Compatible with lipid alone; however, may chelate with divalent cations of TNAs

[d] Visually incompatible with TNAs when reconstituted with 5% dextrose in water; visually compatible when reconstituted with normal saline solution

From Strausberg, K. Parenteral nutrition admixture. *ASPEN Practice Manual,* 1998. With permission.

This may be achieved by adding the H_2-receptor blockers to the TPN solution. Famotidine (20 and 40 mg/L) and ranitidine hydrochloride have been shown to be stable in parenteral nutrition solutions and three-in-one admixtures.[52-56]

Heparin

In order to reduce the complications of catheter occlusion related to fibrin formation around the catheter tip, heparin may be added to the TPN solution. Adding up to 1000 units of heparin per liter reduces the incidence of catheter occlusion without exhibiting anticoagulant effects on serum.[1] Larger amounts of heparin may be used for peripheral parenteral nutrition.

Methods of Administration

Serious complications with TPN may develop if careful initiation and monitoring are not followed. TPN solutions may be infused continuously over a 24-hour period, or cycled over shorter time intervals. If a patient is critically ill or just beginning to receive TPN, it is suggested to infuse it over a 24-hour period until patient tolerance is demonstrated. TPN should not be initiated at goal levels of nutrients, as many patients may not tolerate this prescription. Proportional increases in carbohydrate-dependent electrolytes such as magnesium and phosphorus, in protein-dependent electrolytes such as potassium, and in volume-dependent electrolytes such as sodium should be made as the macronutrients are increased.

For patients with diabetes mellitus, stress hyperglycemia, steroids, or risk for refeeding syndrome, dextrose should be restricted initially to approximately 100 to 150 gm/day. For other patients with normal glucose tolerance, dextrose may be initiated at 200 to 250 gm/day. If after 24 hours serum glucose levels are acceptable, then the dextrose may be advanced to goal over the next 24 to 48 hours as indicated. Capillary glucose measurements should be obtained three to four times daily until the values are normal for two consectutive days. Regular insulin may be administered according to a sliding scale.[1] A continuous intravenous insulin infusion may be substituted for sliding scale if serum glucose levels are consistently elevated beyond suggested levels. Insulin may also be added to the TPN solution; however, one needs to remember that providing insulin in this manner

confines the delivery over the time period of the TPN mixture, and if the hyperglycemia resolves then the TPN bag must be discontinued to avoid inadvertent hypoglycemia. For patients requiring insulin prior to TPN institution, approximately half of the established insulin requirement may be included as regular insulin in the initial bag of TPN formula.[1] If blood glucose levels are less than 200 mg/dL, approximately two-thirds of the previous day's subcutaneous insulin dose may be added to the TPN as regular insulin. Regardless of the method of insulin delivery, the goal is to consistently maintain blood glucose levels between 120 and 200 mg/dl.[5]

Lipids may be infused for up to 24 hours, and may reduce the effect of lipids on the reticuloendothelial system.[29] Lipids can be given with the first TPN infusion unless serum triacylglycerol levels are elevated. It is suggested to maintain triacylglycerol levels at ≤400 mg/dL while lipids are being infused.[1] If triacylglycerol levels exceed the recommended level, lipids should be held until levels normalize. As this occurs, patients may be provided with lipids in amounts to prevent essential fatty acid deficiency. For persistent or severe hypertriacylglycerolemia or for patients with egg allergy, oral or topical safflower oil can be administered to alleviate the symptoms of essential fatty acid deficiency.[58] Critically ill patients may also be receiving significant amounts of lipid from lipid-based medications, which may predispose them to hypertriacylglycerolemia prior to TPN infusion. The amount of lipid from medications should be considered in the final TPN formulation to avoid providing excess long-chain triacylglycerol.

Although parenteral nutrition is usually provided over a 24-hour continuous rate, it may also be delivered in a cyclic pattern. Cyclic TPN has been suggested for patients who are stable and receiving TPN for an extended duration. During TPN, circulating insulin levels remain elevated, reducing the amount of carbohydrate that enters the cell, thus favoring hepatic lipogenesis.[1] Cyclic TPN also allows for some time off of the TPN pump, allowing for patient mobility, and therefore it is usually utilized with ambulatory patients. For individuals with limited vascular access, cyclic infusion may be required in order to administer necessary medications or blood products. Conversion from 24-hour continuous infusion to cyclic infusion can be accomplished in two to three days. The largest concern is with the initiation and discontinuation of the carbohydrate infusion and potential for hyperglycemia and rebound hypoglycemia. Another concern is with the increased volume delivery over a shorter time frame. Most stable patients can tolerate cyclic TPN over 8 to 14 hours.

Parenteral Nutrition Discontinuation

Eventually in all patients, the goal is to transition from TPN to enteral nutrition — either tube feeding or oral intake. Prior to discontinuing TPN, assurance that the patient is consuming and absorbing adequate nutrients enterally is imperative. This is usually assessed by diet histories and kcalorie counts. TPN should be decreased as the enteral intake and tolerance improves to avoid overfeeding. TPN may be discontinued once the patient is tolerating approximately 65 to 75% of goal nutrients. For patients who are eating, TPN may be reduced and stopped over a 24- to 48-hour period. If TPN is inadvertently but abruptly discontinued in patients who are not eating, all insulin should be stopped and blood glucose levels should be monitored for 30 minutes after discontinuation of TPN. Based upon the blood glucose levels, appropriate therapy should be implemented.[1] Lastly, if the TPN was used as a vehicle for medication or electrolyte administration, an alternate plan should be made once it is discontinued. Attempting to switch medications to the enteral route is usually employed. Consultation with a pharmacist can help facilitate this transition.

Complications of Parenteral Nutrition

Complications of parenteral nutrition have been widely reported. However, TPN can be safe with minimal complications when it is managed and monitored by a multidisciplinary team of trained professionals. The type of complications that may arise are diverse and include mechanical, infectious, and metabolic.

Mechanical complications of catheter insertion (Table 43.16) include pneumothorax, hydrothorax, and great vessel injury. The catheter malposition may result in venous thrombosis, causing head, neck, or arm swelling, or possibly a pulmonary emobolus. To minimize morbidity, obtaining a chest radiograph before using a new central line for TPN

TABLE 43.16

Mechanical Complications of Parenteral Nutrition

Complication	Possible Cause	Symptoms	Treatment	Prevention
Pneumothorax	Catheter placement by inexperienced personnel	Tachycardia, dyspnea, persistent cough, diaphoresis	Large pneumothorax may require chest tube placement	Experienced personnel to place catheter
Catheter embolization	Pulling catheter back through needle used for insertion	Cardiac arrhythmias	Surgical removal of catheter tip	Avoid withdrawing catheter through insertion needle
Air embolism	Air is inspired while line is interrupted and uncapped	Cyanosis, tachypnea, hypotension, churning heart murmur	Immediately place patient on left side and lower head of bed to keep air in apex of the right ventricle until it is reabsorbed	Experienced personnel to place catheter
Venous thrombosis	Mechanical trauma to vein, hypotension, hyperosmolar solution, hypercoagulopathy, sepsis	Swelling or pain in one or both arms or shoulders or neck	Anticoagulation therapy with urokinase or streptokinase; catheter removal	Silicone catheter, adding heparin to TPN, low dose warfarin therapy
Catheter occlusion	Hypotension, failure to maintain line patency, formation of fibrin sheath outside the catheter, solution precipitates	Increasing need for greater pressure to maintain continuous infusion rate	Anticoagulation therapy with urokinase or streptokinase	Larger diameter catheter, routine catheter flushing, monitor solution for a precipitate
Phlebitis	Peripheral administration of hypertonic solution	Redness, swelling, pain at peripheral site	Change peripheral line site, begin central TPN if necessary	Maintain osmolarity of peripheral solution ≤ 900 mOsm/kg
Catheter-related sepsis	Inappropriate technique of line placement, poor catheter care, contaminated solution	Unexplained fever, chills, red, indurated area around catheter site	Remove catheter and replace at another site	Follow strict protocols for line placement and care

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is important to ensure correct line placement and absence of internal injuries that may have occurred during insertion.

Catheter-related infections can carry a high mortality rate and increased medical costs for a single event. A catheter infection rate of less than 3% is desirable.[5] Appropriate use of aseptic technique by trained personnel is essential to maintain an acceptable catheter infection rate. Nursing protocols should be established for dressing changes and line manipulation. Dressings should be changed every 48 hours and should include local sterilizing ointment and an occlusive dressing. Since gram-positive catheter-related sepsis may be treated with antibiotics, removal of the catheter is not always necessary. Catheter removal is usually necessary with gram-negative organisms.

With close monitoring of TPN, avoidance of metabolic complications (Table 43.17) is possible. Refeeding syndrome may be defined as a constellation of fluid, micronutrient, electrolyte, and vitamin imbalances that occur within the first few days after refeeding a starved patient. Refeeding syndrome may involve hemolytic anemia, respiratory distress, paresthesias, tetany, and cardiac arrythmias.[59] Typical biochemical findings include hypokalemia, hypophosphatemia, and hypomagnesemia. Proposed risk factors for refeeding include alcoholism, anorexia nervosa, marasmus, rapid refeeding, and excessive dextrose infusion. In order to prevent the syndrome from occurring it is suggested to replete serum potassium, phosphorus, and magnesium concentrations prior to beginning TPN; limit initial carbohydrate to 150 gm/day, fluid to 800 mL, and sodium intake to no more than 20 mEq/day in at-risk patients; include adequate amounts of potassium, magnesium, phosphorus, and vitamins in the TPN solution; and increase carbohydrate-dependent minerals in proportion to increases in carbohydrate when TPN is advanced.[59]

Hyperglycemia (nonfasting blood glucose >220 mg/dL) is a common metabolic complication of TPN. Risk factors include metabolic stress, medications, obesity, diabetes, and excess dextrose administration. Careful glucose monitoring, especially in the first few days of TPN administration, can help guide advancement of dextrose to goal. Administration of dextrose in amounts less than the maximum glucose oxidation rate (4 to 7 mg/kg/min) and initiating dextrose in reduced amounts (100 to 150 gm/day) in at-risk patients may help minimize the occurrence of hyperglycemia.[5]

Patients receiving TPN may also experience fluid and electrolyte abnormalities (Table 43.17). The etiology of the abnormalities may be related to several factors including the patient's medical condition and treatment, medications, or excessive or inadequate free water provision. Fluid balance and electrolyte status should be monitored closely (Table 43.18), with corrections in abnormalities made accordingly.

Summary

Parenteral nutrition has been a major medical advancement over the past several decades. Its institution has saved lives of many people who may have otherwise died of malnutrition. The next several decades will most likely bring more advances in the technology and science of parenteral nutrition. With careful selection, implementation, and monitoring, parenteral nutrition is a medical vehicle for nutritional supplementation of numerous diseases.

TABLE 43.17

Metabolic Complications of Parenteral Nutrition

Complication	Possible Cause	Treatment
Hypovolemia	Inadequate fluid provision, overdiuresis	Increase fluid delivery
Hypervolemia	Excess fluid delivery, renal dysfunction, congestive heart failure, hepatic failure	Fluid restriction, diruetics, dialysis
Hypokalemia	Refeeding syndrome, inadequate potassium provision, increased losses	Increase intravenous or parenteral potassium
Hyperkalemia	Renal dysfuntion, too much potassium provision, metabolic acidosis, potassium-sparing drugs	Decrease potassium intake, potassium binders, dialysis in extreme cases
Hyponatremia	Excessive fluid provision, nephritis, adrenal insufficiency, dilutional states	Restrict fluid intake, increase sodium intake as indicated clinically
Hypernatremia	Inadequate free water provision, excessive sodium intake, excessive water losses	Decrease sodium intake, replete free water deficit
Hypoglycemia	Abrupt discontinuation of parenteral nutrition, insulin overdose	Dextrose delivery
Hyperglycemia	Rapid infusion of large dextrose load, sepsis, pancreatitis, steroids, diabetes, elderly	Insulin, reduce dextrose delivery
Hypertriglyceridemia	Inability to clear lipid provision, sepsis, multisystem organ failure, medications altering fat absorption, history of hyperlipidemia	Decrease lipid volume provided, increase infusion time, hold lipids up to 14 days to normalize level
Hypocalcemia	Decrease vitamin D intake, hypoparathyroidism, citrate binding of calcium due to excessive blood transfusion, hypoalbuminemia	Calcium supplementation
Hypercalcemia	Renal failure, tumor lysis syndrome, bone cancer, excess vitamin D delivery, prolonged immobilization, stress hyperparathyroidism	Isotonic saline, inorganic phosphate supplementation, corticosteroids, mithramycin
Hypomagnesemia	Refeeding syndrome, alcoholism, diruetic use, increased losses, medications, diabetic ketoacidosis, chemotherapy	Magnesium supplementation
Hypermagnesemia	Excessive magnesium provision, renal insufficiency	Decrease magnesium provision
Hypophosphatemia	Refeeding syndrome, alcoholism, phophate-binding antacids, dextrose infusion, overfeeding, secondary hyperparathyroidism, insulin therapy	Phosphate supplementation, discontinue phosphate-binding antacids, avoid overfeeding, initiate dextrose delivery cautiously
Hyperphosphatemia	Renal dysfunction, excessive provision	Decrease phosphate delivery, phosphate binders
Prerenal azotemia	Dehydration, excessive protein provision, inadequate nonprotein calorie provision with mobilization of own protein stores	Increase fluid intake, decrease protein delivery, increase non-protein calories
Essential fatty acid deficiency	Inadequate polyunsaturated long-chain fatty acid provision	Lipid administration

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TABLE 43.18

Suggested Monitoring of TPN

Parameter	Baseline Level	Acute Patients	Stable Patients
Electrolytes, BUN, Cr	Yes	Daily	1-2 × week
Chemistry Panel Ca^{2+}, PO^{4-}, Mg^{2+}	Yes	Daily until stable, then 2-3 × week	Weekly
LFTs	Yes	2 × week	Weekly-monthly
Triacylglycerol	Yes	Weekly unless abnormal then 2 × week	Weekly-monthly
Capillary glucose	2-3 × day	3 × day until consistently < 200 mg/dl	2 × day until consistently < 200 mg/dl
Intake and output	Yes	Daily	Daily or by physical exam
Weight	If available	Daily	Monthly
CBC with differential	Yes	Weekly	Weekly
PT, PTT	Yes	Weekly	Weekly

BUN: blood urea nitrogen; PT: prothrombin time;
PTT: partial thromboplastin time; CBC: complete blood count;
LFT: liver function test; Cr: creatinine

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