Nutrition in the Critically Ill Patient: Part II. Parenteral Nutrition

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ABSTRACT

Objective: *To review the human nutrition in the critically ill patient in a three-part presentation.*

Data sources: *Articles and published peer-review abstracts and a review of studies reported and identified through a MEDLINE search of the English language literature on parenteral nutrition.*

Summary of review: *Intravenous nutrition plays an important supportive role in the management of the critically ill patient who has prolonged gastrointestinal failure. Energy substrates consist of concentrated glucose and lipid solutions, although the former requires central venous access for its administration. The nitrogen requirement is supplied as L-amino acids which usually consist of a solution containing the essential amino acids which are supplemented by a few of the non-essential amino acids. While, amino acid mixtures of glutamine dipeptides, ornithine α-ketoglutarate, asparagine, oxaloacetate, arginine, aspartate and glutamate have been used in a variety of conditions, prospective randomised controlled trials have not consistently demonstrated improved survival with their use in the critically ill patient.*

The water soluble vitamins and vitamin K should supplement intravenous nutrition with amounts at least to meet the recommended daily allowance. Additional supplementation of thiamine, folic acid and ascorbic acid are often administered in the critically ill patient. Apart from zinc, the body stores of the essential trace elements of zinc, copper, iodine, iron, manganese, cobalt, selenium, chromium, fluoride and molybdenum are usually adequate to meet the needs of patients requiring parenteral nutrition for less than 3 months.

Conclusions: *In the critically ill patient with prolonged gastrointestinal failure, intravenous nutrition plays a supportive role in the management of a patient.* (**Critical Care and Resuscitation 2003; 5: 121-136**)

Key words: Nutrition, parenteral nutrition, enteral nutrition, critically ill

Intravenous nutrition, like renal dialysis, plays a supportive role in the patient's management. In general, it is indicated for patients who have prolonged gastrointestinal tract failure (usually greater than 7 - 10 days), who have lost more than 10% of their body weight because of inadequate nutrition, who are unable to take oral or enteral nutrition and who do not have a terminal illness (see Table 1).[1,2] However, in the critically ill patient (unless severe malnutrition or prolonged gastrointestinal failure exist),[3] intravenous nutrition has not been shown to be therapeutic, as it has no effect on mortality compared with standard intravenous fluid and an enteral diet.[4]

Functional gastrointestinal failure. Parenteral nutrition is often administered to patients following major abdominal surgery if there is severe malnutrition prior to surgery or there is a prolonged period of gastrointestinal failure (e.g. ileus, fistula, short-bowel syndrome, enteritis). Resection of 70 - 80% of the small bowel (i.e. remaining bowel length between 60 - 80 cm) may take 2 - 3 years before full gastrointestinal adaptation occurs to maintain nutritional status. When greater than 80 - 90% of the small bowel is resected, the adaptive ability of the small intestine is usually insufficient to

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maintain the patient's nutritional status, and parenteral nutrition will often be required for the remainder of the patient's life. Routine perioperative parenteral nutrition even in the malnourished patient has no beneficial effect.[5]

Parenteral nutrition may also be administered to patients with life threatening hyperemesis gravidarum or anorexia nervosa.

Table 1. Indications for total parenteral nutrition

Prolonged ileus
Intestinal fistula
Short-bowel syndrome
Pancreatitis
Ruptured thoracic duct with chylothorax or chylous ascites
Radiation enteritis
Chronic intestinal pseudo-obstruction

Malignancy. In cancer patients, the effects of tumour, surgery, chemotherapy or irradiation can lead to anorexia, vomiting and cachexia. While parenteral nutrition may be indicated for patients who are unable to take oral nutrition for a prolonged period,[6] it has not been associated with a uniform increase in survival in cancer patients,[7,8] and in one study of patients given chemotherapy for metastatic colon cancer, the parenteral nutrition group fared worse than the controls.[7] Currently, it is believed that, unless the patient is severely malnourished, routine use of parenteral nutrition in patients undergoing chemotherapy is not indicated.[9]

Bowel 'rest'. Parenteral nutrition is often used in patients who have inflammatory bowel disease to give the bowel a 'rest'. However, nutritional repletion (rather than bowel 'rest') is the major therapeutic effect.[10] Clinical improvement of the colitis may occur but is unpredictable.[11,12]

Intravenous energy substrates

Glucose and lipid solutions are the standard intravenous energy substrates. By comparison, intravenous fructose, xylitol, ethanol, glycerol and sorbitol have no added advantages and in critically ill patients may have adverse effects and are not recommended for routine use.

Dextrose. In the normal individual, a daily dextrose infusion of 4 mg/kg/min (5.8 g/kg/24 hr), suppresses gluconeogenesis maximally, with 40% of the infused dextrose undergoing immediate oxidation and the remaining 60% stored as glycogen and lipid.[13,14] Increasing the infusion rate increases the amount of glycogen and lipid stored which increases oxygen utilisation and carbon dioxide production.[15] Excessive glucose administration stimulates lipogenesis which generates excessive carbon dioxide and has been associated with failure to wean from ventilation.[16-18] However, when appropriate rather than excessive calories are administered, altering the proportion of glucose and fat in the diet has not been shown to alter $\dot{V}CO_2$[19] or increase the ability to wean patients who have acute[20] or chronic[21,22] respiratory failure. Other effects of excessive glucose administration include hepatic steatosis, resulting in hyperbilirubinaemia and an elevated plasma alkaline phosphatase.[23]

The gas exchange for 1 kcal of carbohydrate is 199 mL of oxygen and 198 mL of carbon dioxide (STPD), whereas the gas exchange for 1 kcal of fat is 225 mL of oxygen and 158 mL of carbon dioxide (STPD).[24] When comparing fat with glucose, for similar quantities of energy more oxygen is required for fat oxidation, a finding which has been observed clinically.[25] The respiratory exchange per kilocalorie (i.e. 4.1855 kJ) of substrate, and the energetics of the fuel metabolism, are shown in Tables 2 and 3, respectively.

In summary: Glucose should be used as the major caloric source in patients requiring parenteral nutrition and should be infused at a rate of no greater than 8 g/kg/day (i.e. 550 g of dextrose or 2000 kcal (8400 kJ)/day in a 70 kg subject). Unlike lipid, glucose can be monitored easily from plasma levels.

Lipid. Commercial parenteral fat solutions contain artificial chylomicrons and liposomes which consist of a bilayer of phospholipid surrounding an aqueous phase (consisting of water and glycerol) and represents excess emulsifier.[26] It is generally accepted that the

Table 2. Respiratory exchange per kilocalorie of substrate

Substrate	*Reaction*	*Products*	*O_2 consumed (mL STPD)*	*CO_2 produced (mL STPD)*	*RQ*
Glucose	Oxidation	$CO_2 + H_2O$	199	198	1.0
Intralipid®	Oxidation	$CO_2 + H_2O$	225	158	0.7
Glucose	Lipogenesis	PSOG	12	67	5.6

*PSOG = palmitylstearyloleyl triglyceride

Table 3. Energetics of fuel metabolism

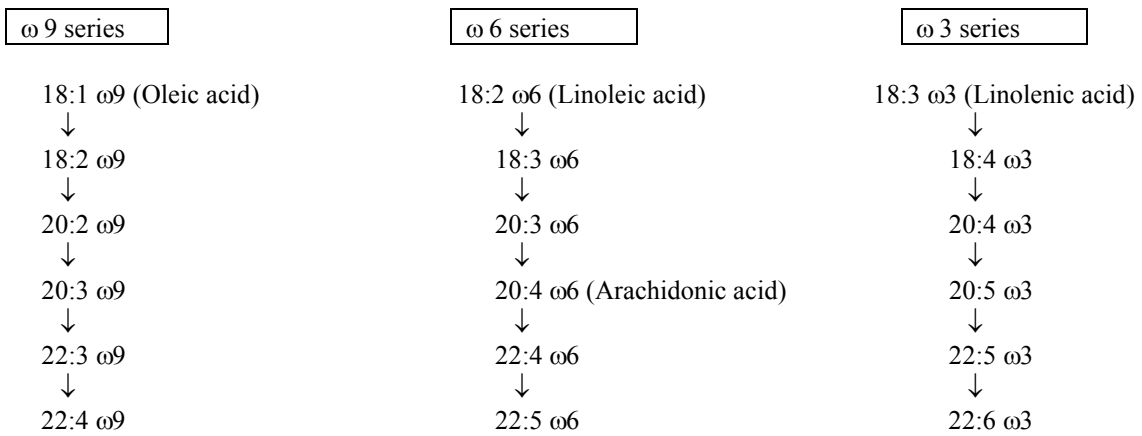
Substrate	Products	kcal/g	ATP/mol	ATP/kcal	ATP/CO_2	ATP/O_2
Glucose	$H_2O + CO_2$	3.75	38	0.057	6.3	6.3
Intralipid®	$H_2O + CO_2$	9.0	138	0.057	7.9	5.5

intravascular metabolism of the artificial chylomicrons in parenteral fat emulsions (e.g. Intralipid®), closely resembles that of chylomicrons[27] (with a rapid transfer of plasma apolipoproteins from HDL to the emulsion particles and back to the HDL with metabolism of the emulsion),[28] although the metabolic fate of the lipid (i.e. how much of the free fatty acid and glycerol liberated by the endothelial lipoprotein lipase is oxidised immediately and how much is stored as lipid) is not known. The liposomes are metabolised to an abnormal lipoprotein (lipoprotein-x) which is subsequently taken up by the reticuloendothelial system (RES). In the absence of sufficient amounts of apolipoprotein donated by the HDL (e.g. during rapid infusion of Intralipid®) the emulsion is not hydrolysed by lipoprotein lipase and may be taken up instead by the RES. The maximum clearance rate of chylomicrons in health is 0.12 $\pm$ 0.02 g/kg/hr (2.9 g/kg/24 hr),[29] although this is decreased with sepsis due to a reduction in lipoprotein lipase activity.[30] For each gram of a typical fat oxidised (e.g. palmitoyl-stearoyl-oleoyl-glycerol), 2028 mL (STPD) of oxygen are utilised, 1421 mL (STPD) of carbon dioxide are produced and 9 kcal of energy are generated (i.e. RQ 0.70).[24] As well as fat, 1 litre of 20% Intralipid® contains 15 mmol of organic phosphate, 20 - 36 IU α-tocopherol (vitamin E), 7 - 11 IU vitamin K_1 and 22.5 g of glycerol.

Lipid solutions are necessary only for the provision of essential fatty acids (i.e. linoleic acid and linolenic acid) and have no advantages as an energy source when compared with dextrose.[31-34] In the absence of essential fatty acids, a syndrome of diffuse scaly dermatitis initially confined to face arms and legs which then becomes generalised, alopecia,[35] delayed wound healing, increased susceptibility to infection, platelet dysfunction and fatty liver[36] may develop. Linoleic acid is required for the formation of arachidonic acid and the FFAs of the ω6 series (Figure 1). The ω9 polyunsaturated fatty acids only become quantitatively significant when linoleic and linolenic acids are withheld from the diet, because each series competes for the same enzyme systems, and affinities decrease from the ω3 to ω9 series. In the absence of linoleic acid and linolenic acids the same enzyme sequence for the ω6 series will convert oleic acid to FFAs of the ω9 series, increasing the ratio of 20:3 ω9 (eicosatrienoic acid) to 20:4 ω6 (arachidonic acid).[37] This ratio is known as the triene:tetraene ratio. A ratio of greater than 0.4 is usually taken as biochemical evidence of an essential fatty acid deficiency and is often found in patients who are receiving parenteral nutrition without fat for longer than 4 weeks.[38] The skin changes usually appear within 2 months following fat-free parenteral nutrition.[38] In an adult, the amount of linoleic acid sufficient to prevent an essential fatty acid deficiency from occurring, corresponds to the amount contained in 500 mL of 20% Intralipid® per week (i.e. greater than 4 g of linoleic acid per day).[39] Linolenic acid converts to fatty acids of the ω3 series (Figure 1).[40]

Some of the adverse inflammatory responses associated with multiple organ failure are thought to be due to the high content of linoleic acid present in lipid

Figure 2. Biosynthesis of the ω9, ω6 and ω3 series of polyunsaturated fats



solutions that use cottonseed oil or safflower oil compared with those that use soybean oil (e.g. Intralipid®, Table 4), which may promote the production of FFAs of the ω6 series.[41] It is proposed that by infusing solutions which have a high linolenic acid content, an increase in production of the ω3 fatty acid series may blunt the adverse inflammatory response in patients with multiple organ failure and, in theory, would be a preferable lipid substrate in these patients.[42] While an enteral solution enriched with ω3 fatty acids (and arginine and ribonucleic acids) used in critically ill patients did not reduce mortality, it appeared to reduce the length of stay and the number of acquired infections.[43,44] Nevertheless, even when solutions contain an identical lipid substrate (e.g. both Intralipid® and Ivelip® use soybean oil) other elements may be responsible for adverse lipid reactions. For example, Ivelip® (which has the addition of sodium oleate, a smaller particle size and different purification process for lecithin compared with Intralipid®) has been reported to cause jaundice in four long-term TPN patients that reversed with reinstitution of Intralipid®[45] (although others have challenged this finding).[46]

Table 4. Percentage of fatty acids in lipid emulsions

	Fatty acid	Soy-bean	Cotton-seed	Saf-flower
Saturated				
non essential				
Palmitic	16:0	9.2	25	7
Stearic	18:0	2.9	2.8	2.5
Unsaturated				
Palmitoleic	16:1	0.03	0	0
Oleic	18:1	26.4	17.1	13.0
essential				
Linoleic	18:2	54.3	52.7	77.0
Linolenic	18:3	7.8	0	0

Mixtures of medium- and long-chain triacylglycerols have also been infused in critically ill patients in an attempt to augment utilisation of fatty acids as energy substrates via a carnitine-independent mechanism.[42,47] These substances have a mild ketogenic effect but have no additional benefits in comparison with standard lipid solutions.[47] Medium-chain triglycerides do not contain essential fatty acids.[48]

Intralipid® may be mixed with dextrose, amino acids and electrolytes and, at room temperature, remains stable for 48 hr,[49] although with a low pH or high concentrations of the divalent ions of calcium and magnesium, rapid flocculation of the lipid may occur.[50] On the other hand, if stored at 4ºC, parenteral nutrition mixtures of dextrose, amino acids, Intralipid® and electrolytes, may remain stable for up to 3 months.[51] Heparin does not enhance clearance of Intralipid® in critically ill patients.[52]

The side-effects of Intralipid® include those listed in Table 5,[53-60] and is contraindicated in hyperlipidaemic states. If a severe fat overload syndrome occurs (e.g. hyperchylomicronaemia, fever, hepatosplenomegaly, coagulopathy, pancreatitis), plasmapheresis may be required to remove the excess plasma lipid.[61]

Table 5. Complications associated with intravenous lipid

Hepatomegaly
Clotting abnormalities
- Thrombocytopenia
- Prolonged prothrombin time

Immunological depression
- Reduced neutrophil chemotaxis and phagocytosis
- Impaired reticuloendothelial system function
- Enhanced bacterial virulence

Hypersensitivity
- Diarrhoea
- Urticaria

Pancreatitis
Cardiovascular
- Sinus bradycardia
- Hypoxia
- CVP catheter occlusion
- Warfarin resistance

Amino acids. Commercial formulations of amino acid solutions have been based on the pattern of amino acids in high class protein (e.g. egg protein or human milk)[62] or the safe recommended amounts of the essential amino acids, which are then supplemented with large amounts of a few non-essential amino acids.[63] With the latter solutions it has been assumed that, provided sufficient total nitrogen is administered, the other non essential amino acids are readily synthesised in vivo. However, there is not a ready exchange of nitrogen between all of the nonessential amino acids,[64] particularly in acutely ill patients and it is now believed that amino acid solutions should be formulated on their ability to maintain normal fasting plasma amino acid concentrations.[65] Ideally, the amino acid mixture should reflect the amino acid profile of protein ingested in a normal diet.[66] To reduce the oxidation of amino acids (i.e. their use as an energy substrate), a source of energy should be administered simultaneously with the amino

acids in a ratio of approximately 150 kcal (630 kJ) for each 1 g of nitrogen.

Because of poor solubility (e.g. cystine/cysteine, tyrosine) or instability (e.g. glutamine) cystine/cysteine, tyrosine and glutamine may not be included in commercial amino acid solutions. However, these amino acids may be required in acutely ill patients and have been delivered as synthetic dipeptides (e.g. glycyl-tyrosine, alanyl-cystine, glycyl-glutamine, alanyl-glutamine), as they are water soluble, stable and are rapidly hydrolysed within the body to release their constituent amino acids.[67]

Standard balanced amino acid solutions are effective in all diseases. Prospective randomised trials have shown no difference between BCAA enriched amino acid solutions and standard amino acid solutions in normal, injured[68,69] or septic patients.[69,70] Also, administration of essential amino acids (or their alpha-keto analogues) to patients who have acute renal failure, or BCAA solutions (or their alpha-keto analogues) to patients who have hepatic failure, have largely been discredited, as has been the practice of perioperative peripheral amino acid infusions.[31,71] Glutamine supplementation to parenteral nutrition solutions for home TPN patients may also be associated with elevation in liver enzymes, and is currently not recommended,[72] and while parenteral glutamine supplementation to parenteral and enteral feeding regimens has been shown in some studies to have advantages (e.g. critically ill patients,[73,74] surgical patients,[75] burns patients,[76] haematological malignancy[77]), one prospective randomised trial failed to show any reduction in infective complications or mortality in hospital patients requiring parenteral nutrition[78] which was confirmed by other studies using glutamine dipeptide-enriched total parenteral nutrition.[79,80] A meta-analysis of studies using glutamine enriched nutrients found that there was no significant reduction in mortality, although there may be a reduction in hospital stay and infectious complications (particularly in surgical patients).[81] Currently it is believed that glutamine enriched solutions should be used in critically ill patients only in the context of a prospective randomised and controlled clinical trial.[82,83]

In summary: While, amino acid mixtures of glutamine dipeptides, ornithine α-ketoglutarate and asparagine (glutamine homologues and derivatives[84]) and oxaloacetate, and arginine, aspartate and glutamate[85] have been used in a variety of conditions there are no prospective randomised controlled trials demonstrating improved survival with their use. As standard balanced amino acid solutions are just as effective in all diseases they should be used in patients with critical illness.

Protein solutions. Albumin solutions have been used to supplement parenteral nutrition in the belief that correction of hypoalbuminaemia will reduce the incidence of pulmonary oedema, gastrointestinal oedema (with intolerance to enteral nutrition), peripheral oedema (with poor wound healing and decubitus ulcers) and mortality.[86] In critically ill patients with albumin levels less than 25 g/L, albumin supplementation does not reduce the mortality rate, complication rate or length of hospital stay and the use of albumin to treat hypoalbuminaemia is not justified in this group of patients.[87,88]

Vitamins and trace elements

Vitamins are dietary compounds which act as cofactors for intermediary metabolism (Table 6). Because patients may develop a deficiency of the water soluble vitamins and vitamin K within 4 weeks without intake, these vitamins should be administered routinely to all patients receiving intravenous nutrition, in amounts to at least to meet the recommended daily allowance[89,90] (e.g. MVI-12® or Cernevit® with additional vitamin K; Table 7). In the acutely ill patient, the daily requirement for thiamine may increase up to 250 mg/day[91,92] and for folic acid up to 5 mg/day.[93] As an increase in the recommended daily allowance (RDA) for ascorbic acid from 60 mg to 200 mg has been suggested,[94] vitamin C intake may also need to be increased (e.g. up to 500 mg/day but less than 1 g daily)[95] during critical illness. The body stores of Vitamins A, D and E are usually sufficient for at least 3 months, and are only required in patients who require parenteral nutrition for periods longer than this. Other nutritional cofactors (e.g. carnitine 40 - 250 mg/day, coenzyme Q_{10} 60 -90 mg/day) are only required during rare deficient states.[96-98]

Vitamin toxicities (particularly with fat soluble vitamins) have also been described when excessive doses are administered (Table 8).[99,100]

Apart from zinc, the body stores of the essential trace elements of zinc, copper, iodine, iron, manganese, cobalt, selenium, chromium, fluoride and molybdenum are usually adequate to meet the needs of patients requiring parenteral nutrition for less than 3 months.[101] Normally, 2.5 mg/day of zinc will maintain its balance although, in patients who have excessive small-bowel losses, up to five times this amount may be required (e.g. an additional 12 mg/L of small bowel fluid loss).[102] Large exudative losses of zinc and copper have also been described in burns patients,[103,104] and an improved copper, zinc and selenium status has been described in a group of patients with 30% - 50% burns after a 12 hour infusion of 26.5 mg zinc, 2.4 mg copper and 82 μg selenium.[105] When patient's require parenteral nutrition for longer than 3 months, trace elements should be administered.

Table 6. Vitamins, cofactor function and clinical effects of deficiencies

Vitamin	Cofactor function	Clinical effects of deficiency
A	Formation of carotenoid proteins (vision) and glycoproteins (epithelial cell function)	Blindness (initially night blindness), xerosis, keratomalacia, hyperkeratotic dry skin
D	Calcium metabolism	Osteomalacia, bone pain, myopathy
E	Antioxidant	Peripheral neuropathy, ataxia, areflexia ophthalmoplegia, proximal myopathy.
K	Coagulation factors (II, VIII, IX, X), bone formation	Bleeding, osteoporosis
B1(thiamine)	Oxidative decarboxylation of pyruvate, α-KG and keto analogues ofthe BCAA, and the transketolase reaction	Beriberi wet beriberi (congestive cardiomyopathy), dry beriberi (peripheral neuropathy) sho shin beriberi (shock, lactic acidosis) Wernicke's encephalopathy (ophthalmoplegia, ataxia, confusion)
B_2 (riboflavin)	Oxidation reduction reactions (FAD)	Angular stomatitis, cheilosis, glossitis, dermatitis, pruritus, anaemia
B_6 (pyridoxine)	Amino acid metabolism	Peripheral neuropathy, paraesthesias, anaemia, glossitis
Niacin	Oxidation reduction reactions (NAD, NADH)	Pellagra (dermatitis, diarrhoea, dementia) glossitis, stomatitis, abdominal pain, depression, dysphagia, photosensitivity
Folic acid	Protein and DNA synthesis	Megaloblastic anaemia, thrombocytopaenia, neutropaenia, glossitis, diarrhoea
B_{12}	Protein and DNA synthesis	Megaloblastic anaemia, thrombocytopaenia, neutropaenia, glossitis, diarrhoea, peripheral neuropathy, subacute combined degeneration, depression
Biotin	Carboxylase reaction	Dermatitis, conjunctivitis, alopecia, ataxia, myalgias
Pantothenic acid	Incorporated in coenzyme A	Fatigue, headache, nausea, vomiting paraesthesias
Ascorbic acid	Acts as a redox ion in many oxidation reactions	Petechial haemorrhages, gum hyperplasia, perifollicular hyperkeratosis, purpura, poor wound healing, joint haemorrhages, Sjögren's syndrome, anaemia

The oral and intravenous recommendations for trace elements differ as the adsorption of trace elements by the gut varies from 0.5% to 2% of the oral intake for chromium to 75% or more for iodine, selenium and fluoride. The intravenous recommendations for chromium, manganese, molybdenum and iron are approximately 10% of the oral recommended dietary allowance (RDA), the intravenous recommendations for zinc and copper are approximately 50% of the oral RDA and the intravenous recommendations for selenium, fluoride and iodine are approximately 100% of the oral RDA. (see Table 9).[101,106-113] In children (and perhaps in adults)[114] manganese should be restricted to 0.018 umol/kg/day (0.001mg/kg/day).[115]

Special clinical problems

Hepatic failure. The BCAA-enriched mixtures have not yet been shown conclusively to reduce encephalopathy, or mortality, in patients with acute or chronic hepatic failure.[116-118]

Renal failure. During a 6 hour haemodialysis (Kolff dialyser), 18 - 25 g of albumin and 2.5 g of amino acids are lost, and during a peritoneal dialysis exchange of 36 - 64 L, between 18 - 60 g of albumin and 3 - 12 g of amino acids are lost.[119] However, with

Table 7. Recommended dietary allowance (RDA) and intravenous (IV) requirements of vitamins for adults in 24 hr and MVI-12® and Cernevit® contents.

Vitamin	*RDA (mg)*		*MVI-12®*	*Cernevit®*
	oral	*IV*	*(mg)*	*(mg)*
A	1	1	1	1.05
D	0.01	0.005	0.005	0.0055
E	15	10	10	10.2
K	0.12	1	-	-
B_1 (thiamine)	1.5	3	3	3.51
B_2 (riboflavin)	1.7	3.6	3.6	4.14
B_6 (pyridoxine)	2.2	4	4	4.53
Niacin	18	40	40	46
Folic acid	0.4	0.4	0.4	0.414
B_{12}	0.003	0.005	0.005	0.006
Biotin	0.03	0.06	0.06	0.069
Pantothenic acid	6	15	15	17.25
Ascorbic acid	90	100	100	125

Vitamin A, 1 IU = 0.3 μg; Vitamin E, 1 IU = 1 mg; Vitamin D_3, 1 IU = 0.025 μg.

current continuous veno-venous haemodiafiltration (CVVHDF) techniques, only small amounts of low molecular weight plasma proteins (e.g. $beta_2$ microglobulin) are found in the effluent, although the daily loss of 10 - 20 g of amino acids still occur.[120,121] While special amino acid formulations consisting of the eight essential amino acids, histidine and arginine have reduced the mortality[122] and duration of acute renal failure,[123] they have not been shown to be any more effective than the conventional amino acid mixtures.[119,124,125] As there may not be a free nitrogen exchange between the non essential amino acids,[64] conventional amino acid mixtures are often preferred in patients who have acute renal failure.[124]

Respiratory failure. Specially designed formulas with low carbohydrate and high fat content have not been shown to improve morbidity or reduce mortality in patients who have acute or chronic respiratory failure. Standard parenteral nutrition solutions are used and hypercaloric diets are avoided.[126]

Critically ill or hypermetabolic 'stress' states. Specially designed formulas with increased BCAA and glutamine have not been shown to improve morbidity or reduce mortality in patients who have multiple organ failure, although glutamine supplementation may maintain normal intestinal function in these patients.[127] Currently, standard parenteral nutrition solutions are used in critically ill patients and hypercaloric intakes are avoided.[126]

In one prospective randomised controlled study of 84 critically ill patients unable to receive enteral nutrition, glutamine enriched parenteral nutrition (i.e. 25g/day) significantly improved survival at six months (24 out of 42 survived) compared with the control group (12 out of 42 survived) who received an isonitrogenous equivalent parenteral nutrition.[73] However, in another prospective randomised, double blind, controlled trial in 168 patients requiring parenteral nutrition, where standard feeds were compared with feeds in which 3.8 g of the total nitrogen was replaced with the equivalent 20 g glutamine, no significant difference in infection rates or mortality were found,[78] although some have argued that glutamine may not have been given early enough or long enough.[128]

Bone marrow transplantation. Glutamine supplemented parenteral nutrition (e.g. 0.57 g/kg/day or 40 g/70 kg/day, associated with a reduction in aspartate, glutamate, alanine, glycine, serine, and proline) was shown in one study to improve nitrogen balance, decrease the incidence of infection and shorten hospital stay in bone marrow transplanted patients.[77] Glutamine (which may be unstable in solution unless it is stored at 4°C[129] or mixed in solution immediately before use, or given as a dipeptide) may cause this effect by serving as a skeletal muscle fuel, as alpha-ketoglutarate (which has the same carbon skeleton as glutamine and is stable in solution) has a similar effect and may be the agent of choice.[130]

However, in another prospective randomised controlled study of 40 patients with haematological and solid cancer who received high-dose chemotherapy and autologous peripheral stem cell transplantation, parenteral glutamine (alanyl- glutamine) supplementation (30 g/day) was associated with a more severe oral mucositis, a later hospital discharge and a

Table 8. Vitamin toxicity and rare clinical disorders that may require an excess vitamin dose

Vitamin	*Clinical effects of excess*	*Conditions for which a higher than normal dose of vitamins are justified*
A	Raised intracranial pressure ('pseudotumor cerebri') causing headache, anorexia nausea, vomiting, fatigue, somnolence, papilloedema Desquamation of skin and mucous membranes cheilitis, hair loss Oedema, haemorrhage, epistaxis, petechiae, elevated INR Long bone tenderness Hepatomegaly, splenomegaly Hypercalcaemia, elevated liver enzymes	Fat malabsorption
D	Hypercalcaemia (nephrolithiasis, renal failure, metastatic calcification Polydipsia, polyuria, hypertension Abdominal pain, nausea, vomiting, constipation Psychosis, polyneuropathy	Fat malabsorption
E	Increased anticoagulant effect of warfarin	Fat malabsorption
K	Neonatal jaundice, kernicterus, Haemolytic anaemia	Fat malabsorption (obstructive liver disease)
B_1		Critical illness
B_6	Peripheral neuropathy, ataxia, seizures Decreased effect of L-dopa Dependency	Pyridoxine dependency Sideroblastic anaemia Homocystinuria INH poisoning
Niacin	Peptic ulcer, alopecia, dry skin Hyperkeratosis (resembling acanthosis nigricans) Elevated liver enzymes	
Folic acid		Congenital megaloblastic anaemia Homocystinuria Malabsorption Pregnancy Critical illness
B_{12}		Juvenile pernicious anaemia Transcobalamin II deficiency Homocystinuria
C	Oxalate stones Haemolytic anaemia (in G-6-PD deficiency)	Critical illness

greater relapse rate compared with patients who received glutamine-free TPN.[131]

Administration

To infuse the required calories and amino acids without administering excessive quantities of fluid, parenteral nutrition solutions need to be hypertonic and thus venotoxic, therefore central venous cannulation is essential for their administration. The subclavian route is often chosen for central venous access as this site makes the catheter easy to secure and is comfortable for the patient. Jugular (internal or external) antecubital, femoral and cephalic veins are other routes which may be used.

Monitoring

The standard 4-hourly vital signs of temperature, pulse, respiration and blood pressure are performed. Plasma glucose is measured 1-6 hourly. Plasma sodium, potassium, glucose, creatinine, phosphate, calcium, magnesium, albumin and liver function tests are measured daily to twice weekly and haemoglobin, white cell count, INR and body weight may be measured weekly. Urinary biochemistry measurements are performed when indicated.

Table 9. Estimated trace-element needs in adult patients receiving total enteral nutrition (EN) or total parenteral nutrition (TPN)

	mg/24 hr (μmol/24 hr)		Clinical effects of deficiency
	EN	**TPN**	
Chromium	0.05 - 0.1 (1 - 2)	0.01 - 0.02 (0.2 - 0.4)	Glucose intolerance, peripheral neuropathy
Cobalt	(given as B_{12})	(given as B_{12})	B_{12} deficiency
Copper	1 - 2 (16 - 32)	0.5 - 1.0 (8 - 16)	Anaemia, leucopaenia
Fluoride	1 - 4 (0.05 - 0.16)	1 - 2 (0.05 - 0.08)	Dental caries
Iodine	0.07 - 0.15 (0.6 - 1.2)	0.07 - 0.15 (0.6 - 1.2)	Goitre
Iron	10 - 15 (180 - 270)	1 - 2.5 (18 - 45)	Anaemia
Manganese	1.5 - 5 (27 - 94)	0.07 - 0.15 (1.3 - 2.7)	Vitamin K resistant prolongation in prothrombin time, change in hair colour.
Molybdenum	0.1 - 0.2 (1 - 2)	0.01 - 0.02 (0.1 - 0.2)	Intolerance to i.v. sulphur amino acids with irritability, coma, tachycardia, tachypnoea
Selenium	0.04 - 0.08 (0.5 - 1.0)	0.04 - 0.08 (0.5 - 1.0)	Cardiomyopathy, proximal muscle weakness, myalgia
Zinc	4 - 12 (62-184)	2 - 6 (31 - 92)	Dermatitis, diarrhoea, alopecia. alteration in taste and smell

Complications

Complications associated with parenteral nutrition include the immediate and late complications associated with catheter insertion, and those associated with the infused solution (Table 10). Catheter infection is usually diagnosed if an episode of sepsis for which no other septic focus can be identified resolves with removal of the catheter. It occurs in 2 - 5% of patients with central venous catheters, 50% of which are due to *Staphylococcus epidermidis*. Treatment consists of removing the catheter and administering isotonic fluids through a peripheral intravenous line for 24 - 48 hr, before reinserting another central venous catheter and recommencing parenteral nutrition. Empirical therapy with intravenous vancomycin 1 gm has been recommended with subsequent antibiotic administration depending on the culture results.

Complications relating to the infused solutions (e.g. hyperglycaemia) or deficiencies (i.e. 'refeeding syndrome' with hypophosphataemia, hypokalaemia and hypomagnesaemia)[132] may also occur (Table 10). Hepatic dysfunction associated with parenteral nutrition is often multifactorial[133] and due to steatosis (caused by excess glucose administration, manganese toxicity, or deficiency of essential fatty acids, amino acids, choline or carnitine - presenting with a conjugated hyperbilirubinaemia, raised plasma ALP and gamma glutamyl transpeptidase) or hepatitis with periportal inflammation

Table 10. Complications with parenteral nutrition

Catheter complications
Immediate
- Trauma (arterial, venous, pleural, mediastinal, cardiac or neural damage)
- Failure of insertion, catheter malposition
- Catheter or guide wire, embolus or knotting
- Arrhythmias, air embolism

Delayed
- Infection (septicaemia, endocarditis)
- Venous thrombosis, thrombophlebitis
- Pulmonary embolism
- Catheter occlusion

Solution complications
- Polymyopathy, osteomalacia
- Pulmonary oedema
- Hepatic dysfunction (steatosis, hepatitis)
- Acalculous cholecystitis
- Metabolic
  - hyperglycaemia, hyponatraemia, hypokalaemia, hypoglycaemia (20 - 40 min after ceasing glucose)
  - hypophosphataemia, hypocalcaemia, hypomagnesaemia
  - metabolic acidosis (lactate, RTA)
  - vitamin, essential fatty acid and trace metal deficiencies

(due to toxicity from altered bile salts, tryptophan metabolites, endotoxin, or sodium bisulphite).[134-136] The hepatic disorder may also be due to disease or disorders which require the patient to receive parenteral nutrition (e.g. inflammatory bowel disease, short bowel syndrome, sepsis, malignancy).[137] In one study, metronidazole 500 mg twice daily prevented the development of cholestasis associated with parenteral nutrition;[138] in another study, cyclic parenteral nutrition (i.e. administered only during an 8 - 12 hr period throughout the day) reduced the cholestasis.[139] Acalculous cholecystitis may be caused by biliary 'sludge' associated with parenteral nutrition,[140] which may be reduced by daily intravenous cholecystokinin (50 ng/kg).[141] The cholestasis associated with parenteral nutrition has also been treated successfully with 10 mg/kg/day (in 6-hourly doses) of ursodeoxycholic acid.[142]

Osteomalacia with back pain, periarticular bone pain and spontaneous fractures can occur in patients receiving prolonged parenteral nutrition, due to vitamin D deficiency,[143] vitamin D excess,[144,145] hypophosphataemia,[146] hypercalcuria with calcium deficiency (due to high levels of amino acids,[147] low phosphate intake[148] and prolonged natriuresis),[149] D-lactate accumulation,[150] or aluminium toxicity.[151] Disodium pamidronate (20 - 40 mg i.v.) 1 to 3-monthly (monitoring plasma calcium and bone mass), is often useful in reducing chronic urinary calcium loss and bone pain in patients resistant to other therapy (e.g. vitamin D, transdermal oestradiol).

Hypouricaemia associated with parenteral nutrition is due to an increase in renal urate excretion.[152] Lactic acidosis associated with parenteral nutrition may be caused by thiamine deficiency which is provoked by the infused glucose[153] (which may also be associated with shock, i.e. 'sho shin' or acute pernicious beriberi)[154] or fructose, sorbitol or xylitol toxicity, and hyperchloraemic acidosis may be caused by excess arginine or lysine hydrochloride.[155]

Parenteral nutrition in practice

Parenteral nutrition solutions are prescribed daily in association with the patient's fluid and electrolyte requirements, both of which are considered when the daily plasma biochemical results are available. The temperature and pulse chart are viewed, to assess whether the patient may be developing catheter sepsis, and the fluid balance chart and daily urinalysis are also reviewed.[156] As the majority of patients will require between 1000 - 2000 kcal (4200 - 8400 kJ) and 40 - 80 g of protein, one may begin with 650 - 1300, 'non-nitrogen' kcal (2730 - 5460 kJ) per day (i.e. 20 - 40 mL/hr of an amino acid dextrose mixture that consists 5% amino acid and 35% dextrose, increasing by 10 - 20 mL/hr per day until the patient receives 30 - 80 mL/hr, depending upon the age and sex of the patient and degree of malnutrition).[156]

However, severely malnourished patients should be fed slowly, increasing to the assessed caloric and nitrogen requirements over 7 - 14 days to avoid the 'refeeding' syndrome.[132,157,158] On average, most patients receive 1 - 1.5 L of the amino acid dextrose solution daily, administering 50 - 75 g protein and 1300 - 2000 kcal, respectively (Table 11). An electrolyte solution (usually 0.9% saline) is added to the second line of the central venous catheter and is used for the patient's daily fluid and electrolyte requirements (adding extra saline, potassium, phosphate and magnesium to this infusion as needed). This infusion is also used as a vehicle for intravenous drugs and central venous pressure measurements.

Table 11. Daily protein and energy equivalent using a 1:1 mixture of Synthamin 17® and 70% dextrose

Dose (mL/hr)	Protein equivalent (g/24 hr)	Non-nitrogen (kcals/24 hr)	kJ/24 hr
10	12	325	1370
20	24	650	2730
30	37	970	4070
40	49	1300	5460
50	61	1620	6800
60	74	1940	8150
70	86	2260	9490
80	98	2590	10900

Soluble insulin is added to the amino acid dextrose mixture in patients who have been previously insulin dependent. There is approximately 50% loss of insulin from parenteral nutrition solutions due to non-specific binding to infusion material,[159] although recent changes to the material have reduced the insulin binding in some instances to 10%.[160] In non-insulin dependent diabetics, or in patients who have become glucose intolerant, insulin is only added to the mixture if the plasma glucose is consistently greater than 6 - 8 mmol/L. In one single-centre study of mechanically ventilated critically ill patients admitted to a surgical intensive care unit who received 200 - 300 g of glucose intravenously for the first day and 20 - 30 non nitrogen calories/kg per day (20% - 40% as lipid) and 0.13 - 0.26 g of nitrogen /kg/day either parenterally, enterally or mixed thereafter (until discharge from the intensive care unit); an insulin infusion (up to 50 U/hr) to maintain the blood glucose between 4.4 - 6.1 mmol/L (with hourly blood sugar measurements until stable and then 2 - 4 hourly) was associated with a reduction in morbidity (e.g. renal failure, infection, polyneuropathy) and mortality

(particularly in patients who remained in the intensive care unit for > 5 days) when compared with an insulin infusion to maintain the blood glucose between 10 - 11.1 mmol/L.[161]

The two 5 mL vials of MVI-12® or 5 mL of one reconstituted Cernevit® vial are infused over 5 min daily, and either 1 mg of vitamin K_1 is administered daily or 10 mg of vitamin K_1 is administered once a week. The multivitamin preparations are not added to the parenteral nutrition solution as up to 80% of vitamin A and up to 50% of riboflavine and pyridoxine are degraded by sunlight.[67] Thiamine is also altered (up to 10% in 12 hr)[162] and vitamin C is oxidised by the antioxidant agent sodium bisulphite,[163] which is present in some amino acid solutions.[67] Vitamin B_{12} and K are also reported to be sensitive to the TPN solution pH and/or oxidative conditions.[162]

For the purpose of administering essential fatty acids, 500 mL of 20% Intralipid® is infused once a week. For patients who are ambulant, the intravenous nutrition may be infused over 12 - 14 hr during the night and the central venous line is 'heparin locked' at the completion of the infusion to allow the patient to leave the hospital for extended periods throughout the day.

Anabolic steroids do not promote visceral protein synthesis and are not indicated in patients receiving parenteral nutrition.[164] Growth hormone will promote positive nitrogen balance (which may be due to stimulation of endogenous insulin-like growth factor),[165,166] although its place (and the place of insulin-like growth factor) in parenteral nutrition therapy is at best not yet clear.[167-169] Recently, two large prospective randomised, placebo-controlled trials in critically ill patients, revealed that growth hormone (somatotropin) was associated with an increased mortality, and so currently it is not recommended for the treatment of acute catabolism in critically ill patients.[170]

Somatostatin has been used successfully in combination with parenteral nutrition in patients who have large fistula losses, to suppress enteric secretions, reduce the fistula losses (often by greater than 50%)[157] and allow the fistula to heal. A continuous infusion of 6 mg/day for 2 days followed by 3 mg/day until the fistula closes,[157] or the longer acting somatostatin analogue, octreotide 100 μg subcutaneously two or three times a day,[171] may be used.

Acute discontinuation of parenteral nutrition will not cause symptomatic hypoglycaemia in the majority of patients.[172] However, to reduce the risk of a reactive hypoglycaemia, particularly in patients with hepatic failure, decreasing the infusion rate by half in the first hour and to one quarter in the second hour before discontinuing the parenteral nutrition, may be desirable.

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REFERENCES

1. Sitzmann JV, Pitt HA, and the Patient Care Committee of the American Gastroenterological Association. Statement on guidelines for total parenteral nutrition. Dig Dis Sci 1989;34:489-496.
2. ASPEN Board of Directors. Guidelines for use of parenteral and enteral nutrition in adult and pediatric patients. J Parenter Enteral Nutr 2002;26(1 Suppl):1SA-138SA.
3. Klein S, Kinney J, Jeejeebhoy K, et al. Nutrition support in clinical practice: review of published data and recommendations for future research directions. Summary of a conference sponsored by the National Institutes of Health, American Society for Parenteral and Enteral Nutrition, and American Society for Clinical Nutrition.Am J Clin Nutr 1997;66:683-706.
4. Heyland DJ, MacDonald S, Keefe L, et al. Total parenteral nutrition in the critically ill patient: a meta-analysis. JAMA 1998;280:2013-2019.
5. The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. Perioperative total parenteral nutrition in surgical patients. N Engl J Med 1991;325:525-532.
6. Drasin H, Rosenbaum EH, Stitt C. The importance of nutrition in patients with cancer. Arch Intern Med 1978;138:1335-1336.
7. Brennan MF. Total parenteral nutrition in the cancer patient. N Engl J Med 1981;305:375-382.
8. Chlebowski RT. Effect of nutritional support on the outcome of antineoplastic therapy. Clin Oncol 1986;5:365-379.
9. The American College of Physicians. Parenteral nutrition in patients receiving cancer chemotherapy. Ann Intern Med 1989;110:734-736.
10. Christie PM, Hill GL. Effect of intravenous nutrition on nutrition and function in acute attacks of inflammatory bowel disease. Gastroenterology 1990;99:730-736.
11. Elson CO, Layden TJ, Nemchausky BA, Rosenberg JL, Rosenberg IH. An evaluation of total parenteral nutrition in the management of inflammatory bowel disease. Dig Dis Sci 1980;25:42-48.
12. Dickinson RJ, Ashton MG, Axon ATR, Smith RC, Yeung CK, Hill GL. Controlled trial of intravenous hyperalimentation and total bowel rest as an adjunct to the routine therapy of acute colitis. Gastroenterology 1980;79:1199-1204.
13. Wolfe RR, Allsop JR, Burke JF. Glucose metabolism in man: responses to intravenous glucose infusion. Metabolism 1979;28:210-220.
14. Wolfe RR, O'Donnell TF Jr, Stone MD, Richmand DA, Burke JF. Investigation of factors determining the optimal glucose infusion rate in total parenteral nutrition. Metabolism 1980;29:892-900.

15. Silberman H, Silberman AW. Parenteral nutrition, biochemistry and respiratory gas exchange. J Parenter Enteral Nutr 1986;10:151-154.
16. Larca L, Greenbaum DM. Effectiveness of intensive nutritional regimens in patients who fail to wean from mechanical ventilation. Crit Care Med 1982;10:297-300.
17. Bassili HR, Deitel M. Effect of nutritional support on weaning patients off mechanical ventilators. J Parenter Enteral Nutr 1981;5:161-163.
18. Amene PC, Sladen RN, Feeley TW, Fisher R. Hypercapnia during total parenteral nutrition with hypertonic dextrose. Crit Care Med 1987;15:171-172.
19. Talpers SS, Romberger DJ, Bunce SB, Pingleton SK. Nutritionally associated increased carbon dioxide production. Excess total calories vs proportion of carbohydrate calories. Chest 1992;102:551-555.
20. Talpers SS, Romberger D, Bunce S, Pingleton S. High carbohydrate concentrations do not increase carbon dioxide production in mechanically ventilated patients. Am Rev Resp Dis 1988;137:61.
21. Wilson DO, Rogers RM, Hoffman RM. Nutrition and chronic lung disease. Am Rev Respir Dis 1985;132:1347-1365.
22. Sue DY, Chung MM, Grosvenor M, Wasserman K. Effect of altering the proportion of dietary fat and carbohydrate on exercise gas exchange in normal subjects. Am Rev Resp Dis 1989;139:1430-1434.
23. Lowry SF, Brennan MF. Abnormal liver function during parenteral nutrition: relation to infusion excess. J Surg Res 1979;26:300-304.
24. Frayn KN. Calculation of substrate oxidation rates in vivo from gaseous exchange. J Appl Physiol 1983;55:628-634.
25. Mondejar EF, Lombardo MD, de la Cruz AJP, Morales AM, Ruiz JMT, Orihuela JAF. Variations in oxygen consumption and carbon dioxide production during parenteral nutrition. Intensive Care Med 1982;8:169-172.
26. Ferezou J, Bach AC. Struture and metabolic fate of triacylglycerol- and phospholipid-rich particles of commercial parenteral fat emulsions. Nutrition 1999;15:44-50.
27. Hallberg D. Elimination of exogenous lipids from the bloodstream. An experimental methodological and clinical study in dogs and man. Acta Physiol Scand 1965;254(suppl):1-24.
28. Asami H, Iriyama K. In vitro transfer of apolipoproteins from plasma lipoproteins to artificial lipid particles. Nutrition 1990;6:143-149.
29. Iriyama K. Lipid for a parenteral use: development and future perspectives. Nutrition 1994;10(suppl):521-522.
30. Spitzer JJ. Lipid metabolism in endotoxic shock. Circ Shock 1979;1(Suppl):69-79.
31. Moore FD. Energy and the maintenance of body cell mass. J Parenter Enteral Nutr 1980;4:228-260.
32. Clouse RE, Alpers DH. Energy sources for total parenteral nutrition patients: would sugar suffice. Gastroenterology 1984;87:226-227.
33. Long CL. Fuel preferences in the septic patient: Glucose or lipid? J Parenter Enteral Nutr 1987;11:333-335.
34. Tracey KJ, Legaspi A, Albert JD, et al. Protein and substrate metabolism during starvation and parenteral refeeding. Clin Sci 1988;74:123-132.
35. Riella MC, Broviac JW, Wells M, Scribner BH. Essential fatty acid deficiency in human adults during total parenteral nutrition. Ann Intern Med 1975;83:786-789.
36. McCarthy MC, Cottam GL, Turner WW Jr. Essential fatty acid deficiency in critically ill surgical patients. Am J Surg 1981;142:747-751.
37. Goodgame JT, Lowry SF, Brennan MF. Essential fatty acid deficiency in total parenteral nutrition: time course of development and suggestions for therapy. Surgery 1978:84:271-277.
38. Fleming CR, Smith LM, Hodges RE. Essential fatty acid deficiency in adults receiving total parenteral nutrition. Am J Clin Nut 1976;29:976-983.
39. Ladefoged K, Jarnum S. Metabolic complications to total parenteral nutrition. Acta Anaesthol Scand 1985;29:89-94.
40. Holman RT, Johnson SB, Hatch TF. A case of human linolenic acid deficiency involving neurological abnormalities. Am J Clin Nutr 1982;35:617-623.
41. Cerra FB. How nutrition intervention changes what getting sick means. J Parenter Enteral Nutr 1990;14(suppl):164S-169S.
42. Ball MJ, Sear JW. Intravenous feeding with medium chain triglycerides. Effect on blood gases and the complement system in critically ill patients. Anaesthesia 1986;41:423-426.
43. Bower RH, Cerra FB, Bershadsky B, et al. Early enteral administration of a formula (Impact®) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: results of a multicenter, prospective, randomised, clinical trial. Crit Care Med 1995;23:436-449.
44. Braga M, Gianotti L, Vignali A, Cestari A, Bisagni P, Di Carlo V. Artificial nutrition after major abdominal surgery: impact of route of administration and composition of the diet. Crit Care Med 1998;26:24-30.
45. Gerard-Boncompain M, Claudel JP, Gaussorgues P, et al. Hepatic cytolytic and cholestatic changes related to a change of lipid emulsions in four long-term parenteral nutrition patients with short bowel. JPEN J Parenter Enteral Nutr 1992;16:78-83.
46. Giudicelli A, Dobbie R, Tucker HN. Hepatic cytologic and cholestatic changes in long-term parenteral nutrition. JPEN J Parenter Enteral Nutr 1992;16:494-495.
47. Ball MJ, White K. Metabolic effects of intravenous medium-and long-chain triacylglycerols in critically ill patients. Clin Sci 1989;76:165-170.
48. Nehra V, Mascioli EA. Medium-chain triglycerides: a new frontier. Nutrition 1995;11:309-310.
49. Lawrence RI, Flukes WK, Braithwate PA. Total parenteral nutrition using a combined nutrient solution. Aust J Hosp Pharm 1981;11:40-42.

50. Black CD, Popovich NG. Stability of intravenous fat emulsions. Arch Surg 1980;115:891.
51. Campos ACL, Paluzzi M, Meguid MM. Clinical use of total nutritional admixtures. Nutrition 1990;6:347-356.
52. D'Angio R, Quercia R, Orlando R, Nitingale C, Drezner D. The effect of heparin on the clearance of intravenous lipid emulsion in critically ill surgical patients. J Parenter Enteral Nutr 1987;11(suppl 1):19S.
53. Wan JM-F, Teo TC, Babayan VK, Blackburn GL. Invited comment: lipids and the development of immune dysfunction and infection. J Parenter Enteral Nutr 1988;12(suppl):43S-48S.
54. Hiyama DT, Griggs B, Mittman RJ, Lacy JA, Benson DW, Bower RH. Hypersensitivity following lipid emulsion infusion in an adult patient. J Parenter Enteral Nutr 1989;13:318-320.
55. Lashner BA, Kirsner JB, Hanauer SB. Acute pancreatitis associated with high concentration lipid emulsion during total patenteral nutrition therapy for Crohn's disease. Gastroenterology 1986;90:1039-1041.
56. Traub SL, Sheffield AD, Meeran MK. Sinus bradycardia associated with peripheral lipids and total parenteral nutrition. J Parenter Enteral Nutr 1985;9:358-360.
57. Venus B, Smith RA, Patel C, Sandoval E. Hemodynamic and gas exchange alterations during Intralipid infusion in patients with adult respiratory distress syndrome. Chest 1989;95:1278-1281.
58. Main J, Pennington CR, Richards JM. Administration of fat emulsions with nutritional mixtures from the 3-liter delivery system in total parenteral nutrition. J Parenter Enteral Nutr 1986;10:247-248.
59. Lutomski DM, Palascak JE, Bower RH. Warfarin resistance associated with intravenous lipid administration. J Parenter Enteral Nutr 1987;11:316-318.
60. Connon JJ. Diarrhoea possibly caused by total parenteral nutrition. N Engl J Med 1979;301:273-274.
61. Kollef MH, McCormack MT, Caras WE, Reddy VVB, Bacon D. The fat overload syndrome: successful treatment with plasma exchange. Ann Intern Med 1990;112:545-546.
62. Weller LA, Calloway DH, Margen S. Nitrogen balance of men fed amino acid mixtures based on Rose's requirements, egg white protein and serum free amino acid patterns. J Nutr 1971;101:1499-1508.
63. Irwin ME, Hegsted DM. A conspectus of research on amino acid requirements in man. J Nutr 1971;101:539-545.
64. Jackson AA, Golden MHN. (^{15}N) glycine metabolism in normal man: the metabolic alpha amino acid pool. Clin Sci 1980;58:517-522.
65. Worthley LIG, Dollman WB, Wiltshire SL, Philcox JC, Hartley TF. Fasting and non-fasting serum amino-acid concentrations in three patients receiving home parenteral nutrition. Aust J Hosp Pharm 1984;14:2-5.
66. Worthley LIG, Philcox JC, Hartley TF. Fasting and non-fasting amino acid values in three home parenteral nutrition patients. A comparison between Synthamin 17® and Vamin N7%®. Anaesth Intens Care 1984;12:46-51.
67. Elia M. Changing concepts of nutritional requirements in disease: implications for artificial nutritional support. Lancet 1995;345:1279-1284.
68. Kuhl DA, Brown RO, Vehe KL, Boucher BA, Luther W, Kudsk KA. Use of selected visceral protein measurements in the comparison of branched-chain amino acids with standard amino acids in parenteral nutrition support of injured patients. Surgery 1990;107:503-510.
69. Vente JP, Soeters PB, von Meyenfeldt MF, Rouflart MMJ, van der Linden CJ, Gouma DJ. Prospective randomised double-blind trial of branched chain amino acid enriched versus standard parenteral nutrition solutions in traumatized and septic patients. World J Surg 1991;15:128-133.
70. Bower RH, Vallgren S, LaFrance R, et al. Branched chain amino acid-enriched solutions in the septic patient. a randomized, prospective trial. Ann Surg 1986;203:13-20.
71. Health and Public Policy Committee, American College of Physicians. Perioperative parenteral nutrition. Ann Intern Med 1987;107:252-253.
72. Hornsby-Lewis. L, Shike M, Brown P, Klang M, Pearlstone D, Brennan MF. L-Glutamine supplementation in home total parenteral nutrition patients: stability, safety, and effects on intestinal absorption. J Parenter Enteral Nutr 1994;18:268-273.
73. Griffiths RD, Jones C, Palmer TEA. Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. Nutrition 1997;13:295-302.
74. Goeters C, Wenn A, Mertes N, et al. Parenteral L-alanyl-L-glutamine improves 6-month outcome in critically ill patients. Crit Care Med 2002;30:2032-2037.
75. Morlion BJ, Stehle P, Wachtler P, et al. Total parenteral nutrition with glutamine dipeptide after major abdominal surgery: a randomized, double-blind, controlled study. Ann Surg 1998;227:302-308.
76. Wischmeyer PE, Lynch J, Liedel J, et al. Glutamine administration reduces Gram-negative bacteremia in severely burned patients: a prospective, randomised, double-blind trial versus isonitrogenous control. Crit Care Med 2001;29:2075-2080.
77. Ziegler TR, Young LS, Benfell K, et al. Clinical and metabolic efficacy of glutamine-supplemented parenteral nutrition after bone marrow transplantation. A randomized, double-blind, controlled study. Ann Intern Med 1992;116:821-828.
78. Powell-Tuck J, Jamieson CP, Bettany GE, et al. A double blind, randomised, controlled trial of glutamine supplementation in parenteral nutrition. Gut 1999;45:82-88.
79. Morlion BJ, Stehle P, Wachtler P, et al. Total parenteral nutrition with glutamine dipeptide after major abdominal surgery: a randomized, double-blind, controlled study. Ann Surg 1998;227:302-308.
80. Jian ZM, Cao JD, Zhu XG, et al. The impact of alanyl-glutamine on clinical safety, nitrogen balance, intestinal permeability, and clinical outcome in postoperative patients: a randomized, double-blind, controlled study of

120 patients. J Parenter Enteral Nutr 1999;23(5 Suppl):S62-66.
81. Novak F, Heyland DK, Avenell A, Drover JW, Su X. Glutamine supplementation in serious illness: a systematic review of the evidence. Crit Care Med 2002;30:2022-2029.
82. Miskovitz P. Glutamine supplementation in critically ill and elective surgical patients: does the evidence warrant its use? Crit Care Med 2002;30:2152-2153.
83. Buchman AL. Glutamine: commercially essential or conditionally essential? A critical appraisal of the human data. Am J Clin Nutr 2001;74:25-32.
84. Pesty FH, Sultan F. Glutamine homologues and derivatives: a limiting factor in current artificial nutrition? Nutrition 1997;13:575-577.
85. Berard MP, Zazzo JF, Condat P, Vasson MP, Cynober L. Total parenteral nutrition enriched with arginine and glutamate generates glutamine and limits protein catabolism in surgical patients hospitalized in intensive care units. Crit Care Med 2000;28:3637-3644.
86. Kaminski MV, Williams SD. Review of the rapid normalization of serum albumin with modified total parenteral nutrition solutions. Crit Care Med 1990;18:327-335.
87. Foley EF, Borlase BC, Dzik WH, Bistrian BR, Benotti PN. Albumin supplementation in the critically ill. A prospective, randomized trial. Arch Surg 1990;125:739-742.
88. Rubin H, Carlson S, DeMeo M, Granger D, Craig RM. Randomized, double-blind study of intravenous human albumin in hypoalbuminemic patients receiving total parenteral nutrition. Crit Care Med 1997;25:249-252.
89. Committee on Dietary Allowances, Food and Nutritional Board, National Research Council. Recommended daily allowances. 9th ed. Washington, DC: National Academy of Sciences, 1980:39-164.
90. Willett WC, Stampfer MJ. What vitamins should I be taking, doctor? N Engl J Med 2001;345:1819-1824.
91. Velez RJ, Myers B, Guber MS. Severe acute metabolic acidosis (acute beriberi): an avoidable complication of total parenteral nutrition. J Parenter Enteral Nutr 1985;9:216-219.
92. McConachie I, Haskew A. Thiamine status after major trauma. Intensive Care Med 1988;14:628-631.
93. Campillo B, Zittoun J, de Gialluly E. Prophylaxis of folate deficiency in acutely ill patients: results of a randomized clinical trial. Intensive Care Med 1988;14:640-645.
94. Bendich A. New data on vitamin C intake. Nutrition 1997;13;154-155.
95. Levine M, Rumsey SC, Daruwala R, Park JB, Wang Y. Criteria and recommendations for vitamin C intake. JAMA 1999;281:1415-1423.
96. Worthley LIG, Fishlock RC, Snoswell AM. Carnitine deficiency with hyperbilirubinaemia, generalized skeletal muscle weakness and reactive hypoglycaemia in a patient on long term total parenteral nutrition: Treatment with intravenous L-carnitine. J Parenter Enteral Nutr 1983;7:176-180.
97. Worthley LIG, Fishlock RC, Snoswell AM. Carnitine balance and effects of intravenous carnitine in two patients receiving long-term total parenteral nutrition. J Parenter Enteral Nutr 1984;8:717-719.
98. Ihara Y, Namba R, Kuroda S, Sato T, Shirabe T. Mitochondrial encephalomyopathy (MELAS): pathological study and successful therapy with coenzyme Q10 and idebenone. J Neurol Sci 1989;90:263-271.
99. Evans CDH, Lacey JH. Toxicity of vitamins: complications of a health movement. BMJ 1986;292:509-510.
100. Woolliscroft JO. Megavitamins: fact and fancy. Dis Mon 1983;29:1-56.
101. Phillips GD, Garnys VP. Parenteral administration of trace elements to critically ill patients. Anaesth Intens Care 1981;9:221-225.
102. Wolman SL, Anderson GH, Marliss EB, Jeejeebhoy KN. Zinc in total parenteral nutrition: requirements and metabolic effects. Gastroenterology 1979;76:458-467.
103. Berger MM, Cavadini C, Bart A, et al. Cutaneous zinc and copper losses in burns. Burns 1992;18:373-379.
104. Berger MM, Cavadini C, Bart A, et al. Selenium losses in 10 burned patients. Clin Nutr 1992;11:75-81.
105. Berger MM, Cavadini C, Chiolero R, Guninchard S, Krupp S, Dirren H. Influence of large intakes of trace elements on recovery after major burns. Nutrition 1994;10:327-334.
106. Doisey EA. Micronutrient controls on biosynthesis of clotting proteins and cholesterol. In Hemphill DD (ed) Trace Substances in Environmental Health VI, Columbia: University of Missouri. 1978:p193.
107. Flemming CR. Trace element metabolism in adult patients requiring total parenteral nutrition. Am J Clin Nutr 1989;49:573-579.
108. Abumrad NN, Schneider AJ, Steel D, Rogers LS. Amino acid intolerance during prolonged total parenteral nutrition reversed by molybdate therapy. Am J Clin Nutr 1981;34:2551-2559.
109. Jeejeebhoy KN, Chu RC, Marliss EB, Greenberg GR, Bruce-Robertson A. Chromium deficiency, glucose intolerance, and neuropathy reversed by chromium supplementation, in a patient receiving long-term total parenteral nutrition. Am J Clin Nutr 1977;30:531-538.
110. Fleming CR, Lie JT, McCall JT, O'Brien JF, Baillie EE, Thistle JL. Selenium deficiency and fatal cardiomyopathy in a patient on home parenteral nutrition. Gastroenterology 1982;83:689-693.
111. Rayman MP. The importance of selenium to human health. Lancet 2000;356:233-241.
112. Thompson CD, Robinson MF. Selenium in health and disease with emphasis on those aspects peculiar to New Zealand. Am J Clin Nutr 1980;33:303-323.
113. Shwenkin A. Trace elements and inflammatory response: implications for nutritional support. Nutrition 1995;11:100-105.
114. Forbes A, Jawhari A. Manganese toxicity and parenteral nutrition. Lancet 1996;347:1774.

115. Fell JME, Reynolds AP, Meadows N, et al. Manganese toxicity in children receiving long-term parenteral nutrition. Lancet 1996;347:1218-1221.
116. Erriksson LS, Persson A, Wahren J. Branched-chain amino acids in the treatment of chronic hepatic encephalopathy. Gut 1982;23:801-806.
117. Wharen J, Denis J, Desurmont P, et al. Is intravenous administration of branched chain amino acids effective in the treatment of hepatic encephalopathy? A multicenter study. Hepatology 1983;3:475-480.
118. Kanematsu T, Koyanagi N, Matsumata T, Kitano S, Takenaka K, Sugimachi K. Lack of preventive effect of branched-chain amino acid solution on postoperative hepatic encephalopathy in patients with cirrhosis: a randomized, prospective trial. Surgery 1988;104:482-488.
119. Mackenzie JD. Nutrition in dialysis. In: Bourne GH. (Ed) World review of nutrition and dietetics 1971;13:194-276.
120. Bellomo R, Dastalakis M, Martin H, et al. Nutritional and biochemical consequences of continuous arteriovenous haemodiafiltration (CAVHD). Anaesth Intens Care 1991;19:463.
121. Frankenfield DC, Reynolds HN. Nutritional effect of continuous hemodiafiltration. Nutrition 1995;11:388-393.
122. Abel RM, Beck CH, Abbott WM, Ryan JA, Barnett GO, Fischer JE. Improved survival from acute renal failure after treatment with intravenous essential amino acids and glucose. N Engl J Med 1973;288:695-699.
123. Abel RM, Shih VE, Abbott WM, Beck CH, Fischer JE. Amino acid metabolism in acute renal failure. Ann Surg 1974;180:350-355.
124. Feinstein EI, Blumenkrantz MJ, Healey M, et al. Clinical and metabolic response to parenteral nutrition in acute renal failure: controlled double-blind study. Medicine 1981;60:124-137.
125. Mirtallo JM, Schneider PJ, Mavko K, Ruberg RL, Fabri PJ. A comparison of essential and general amino acid infusions in the nutritional support of patients with compromised renal function. J Parenter Enteral Nutr 1982;6:109-113.
126. Talbot JM. Guidelines for the scientific review of enteral food products for special medical purposes. J Parenter Enteral Nutr 1991;15 (suppl):99S-173S.
127. Wilmore DW. Glutamine and the gut. Gastroenterology 1994;107:1885-1901.
128. Griffiths RD, Andrews F. Glutamine: a life threatening deficiency in the critically ill? Intensive Care Med 2001;27:12-15.
129. Hardy G, Bevan SJ, McElroy B, Palmer TEA, Griffiths RD, Braidwood C. Stability of glutamine in parenteral feeding solutions. Lancet 1993;342:186.
130. Wernerman J, Hammarqvist F, Vinnars E. α-ketoglutarate and postoperative muscle catabolism. Lancet 1990;335:701-703.
131. Pytlik R, Benes P, Patorkova M, et al. Standardized parenteral alanyl-glutamine dipeptide supplementation is not beneficial in autologous transplant patients: a randomized, double-blind, placebo controlled study. Bone Marrow Transplant 2002;30:953-961.
132. Solomon SM, Kirby DF. The refeeding syndrome: a review. J Parenter Enteral Nutr 1990;14:90-97.
133. Freund HR. Abnormalities of liver function and hepatic damage associated with total parenteral nutrition. Nutrition 1991;7:1-5.
134. Baker AL, Rosenberg IH. Hepatic complications of total parenteral nutrition. Am J Med 1987;82:489-497.
135. Sax HC, Bower RH. Hepatic complications of total parenteral nutrition. J Parenter Enteral Nutr 1988;12:615-618.
136. Craig RM, Neumann T, Jeejeebhoy KN, Yokoo H. Severe hepatocellular reaction resembling alcoholic hepatitis with cirrhosis after massive small bowel resection and prolonged total parenteral nutrition. Gastroenterology 1980;79:131-137.
137. Jeejeebhoy KN. Hepatic manifestations of total parenteral nutrition: need for prospective investigation. Hepatology 1988;8:428-428.
138. Capron J-P, Gineston J-L, Herve M-A, Braillon A. Metronidazole in prevention of cholestasis associated with total parenteral nutrition. Lancet 1983;i:446-447.
139. Matuchansky C, Morichau-Beauchant M, Druart F, et al. Cyclic (nocturnal) total parenteral nutrition in hospitalized adult patients with severe digestive diseases. Gastroenterology 1981;81:433-437.
140. Messing B, Bories C, Kunstlinger F, Bernier J-J. Does total parenteral nutrition induce gallbladder sludge formation and lithiasis? Gastroenterology 1983;84:1012-1019.
141. Sitzmann JV, Pitt HA, Steinborn PA, Pasha ZR, Sanders RC. Cholecystokinin prevents parenteral nutrition induced biliary sludge in humans. Surg Gynecol Obstet 1990;170:25-31.
142. Beau P, Labat-Labourdette J, Ingrand P, Beauchant M. Is ursodeoxycholic acid an effective therapy for total parenteral nutrition liver disease? J Hepatol 1994;20:240-244.
143. Klein GL, Horst RL, Norman AW, Ament ME, Slatopolsky E, Coburn JW. Reduced serum levels of 1 alpha,25-dihydroxyvitamin D during long-term total parenteral nutrition. Ann Intern Med 1981;94:638-643.
144. Seligman JV, Basi SS, Deitel M, Bayley TA, Khanna RK. Metabolic bone disease in a patient on long-term total parenteral nutrition: a case report with review of literature. J Parenter Enteral Nutr 1984;8:722-727.
145. Shike M, Harrison JE, Sturtridge WC, et al. Metabolic bone disease in patients receiving long-term total parenteral nutrition. Ann Intern Med 1980;92:343-350.
146. Klein GL, Targoff CM, Ament ME, et al. Bone disease associated with total parenteral nutrition. Lancet 1980;ii:1041-1044.
147. Bengoa JM, Sitrin MD, Wood RJ, Rosenberg IH. Amino acid-induced hypercalciuria in patients on total parenteral nutrition. Am J Clin Nutr 1983;38:264-269.
148. Wood RJ, Sitrin MD, Cusson GJ, Rosenberg IH. Reduction of total parenteral nutrition-induced urinary calcium loss by increasing the phosphorous in the total

parenteral nutrition prescription. J Parenter Enteral Nutr 1986;10:188-190.
149. Koo WWK. Parenteral nutrition-related bone disease. J Parenter Enteral Nutr 1992;16:386-394.
150. Karton MA, Rettmer R, Lipkin EW, Ott SM, Chait A. D-lactate and metabolic bone disease in patients receiving long-term parenteral nutrition. J Parenter Enteral Nutr 1989;13:132-135.
151. Ott SM, Maloney NA, Klein GL, et al. Aluminium is associated with low bone formation in patients receiving chronic parenteral nutrition. Ann Intern Med 1983;98:910-914.
152. Al-Jurf A, Steiger E. Hypouricemia in total parenteral nutrition. Am J Clin Nutr 1980;33:2630-2634.
153. Nakasaki H, Ohta M, Soeda J, et al. Clinical and biochemical aspects of thiamine treatment for metabolic acidosis during total parenteral nutrition. Nutrition 1997;13:110-117.
154. Valez RJ, Myers B, Guber MS. Severe acute metabolic acidosis (acute beriberi): an avoidable complication of TPN. J Parenter Enteral Nutr 1985;9:216-219.
155. Kushner RF. Total parenteral nutrition - asociated metabolic acidosis. J Parenter Enteral Nutr 1986;10:306-310.
156. Worthley LIG. Parenteral nutrition. Intens Crit Care Digest 1989;8:22-25.
157. di Costanzo J, Martin CJ, Mercier RR, Lafille C, Lepeuch D. Treatment of external gastrointestinal fistulas by a combination of total parenteral nutrition and somatostatin. J Parenter Enteral Nutr 1987;11:465-470.
158. Apovian CM, McMahon MM, Bistran BR. Guidelines for refeeding the marasmic patient. Crit Care Med 1990;18:1030-1033.
159. Mascioli EA, Bistran BR. TPN in the patient with diabetes. Nutr Support Service 1983;7:12-16.
160. Marcuard SP, Dunham B, Hobbs A, Caro JF. Availability of insulin from total parenteral nutrition solutions. J Parenter Enteral Nutr 1990;14:262-264.
161. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359-1367.
162. Baumgartner TG, Henderson GN, Fox J, Gondi U. Stability of ranitidine and thiamine in parenteral nutrition solutions. Nutrition 1997;13:547-553.
163. Smith JL, Canham JE, Wells PA. Effect of phototherapy light, sodium bisulfite, and pH on vitamin stability in total parenteral nutrition mixtures. J Parenter Enteral Nutr 1988;12:394-402.
164. Young GA, Yule AG, Hill GL. Effects of an anabolic steroid on plasma amino acids, proteins, and body composition in patients receiving intravenous hyperalimentation. J Parenter Enteral Nutr 1983;7:221-225.
165. Wilmore DW. Catabolic illness. Strategies for enhancing recovery. N Engl J Med 1991;325:695-702.
166. Ross RJM, Miell JP, Buchanan CR. Avoiding autocannibalism. Consider growth hormone and insulin-like growth factor 1. BMJ 1991;303:11471148.
167. Ponting GA, Halliday D, Teale JD, Sim AJW. Postoperative positive nitrogen balance with intravenous hyponutrition and growth hormone. Lancet 1988;i:438-440.
168. Manson JMcK, Smith RJ, Wilmore DW. Growth hormone stimulates protein synthesis during hypocaloric parenteral nutrition. Ann Surg 1988;208:136-142.
169. Ross RJM, Rodriguez-Arnao J, Bentham J, Coakley JH. The role of insulin, growth hormone and IGF-I as anabolic agents in the critically ill. Intens Care Med 1993;19:S54-S57.
170. Takala J, Ruokonen E, Webster NR, et al. Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med 1999;341:785-792.
171. Nubiola-Calonge P, Badia JM, Sancho J, Gil MJ, Segura M, Sitges-Serra A. Blind evaluation of the effect of octreotide (SMS 201-995) a somatostatin analogue on small-bowel fistula output. Lancet 1987;ii:672.
172. Wagman LD, Miller KB, Thomas RB, Newsome HH, Weir GC. The effect of acute discontinuation of total parenteral nutrition. Ann Surg 1986;204:524-529.