Incompatibility in Parenteral Nutrition

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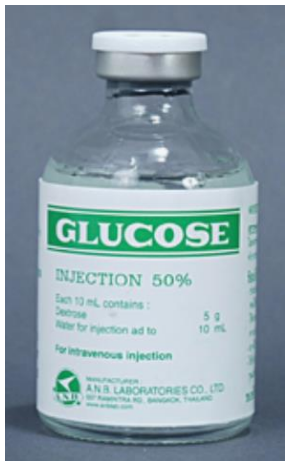
Outline

- List components typically incorporated into a parenteral nutrition (PN) formulation
- The major differences in commercially available crystalline amino acid formulations
- Compare and contrast the dextrose-amino acids (2-in-1) system for PN versus the total nutrient admixture system in terms of stability and compatibility and potential to support microbial growth if contaminated
- Factors that influence the stability of PN formulations
- List of guidelines for “hang times” of various PN components

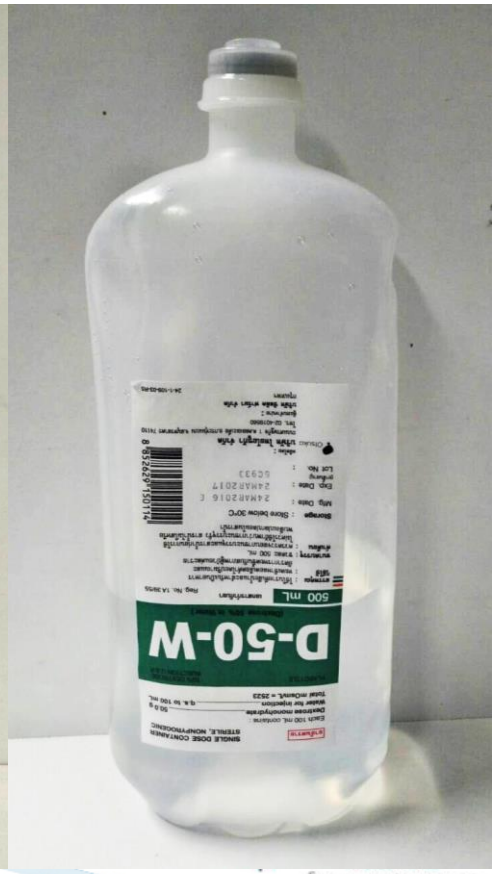
Formulation Components:

- Energy Substrates
  - Carbohydrates
  - Protein
  - Lipids or Intravenous Fat Emulsion (IVFEs)
- Electrolytes
- Vitamins
- Trace elements
- Sterile water for injection

Energy Substrates: Carbohydrate



- Dextrose
  - Hydrated form
  - 3.4 kCal per gram
  - 20%, 25%, 50% (GHP, Atlantic®, New York Chemical®, ANB Laboratory, Thai Otsuka, T.P Laboratories, P.P. Laboratories, etc)
  - pH 5.27 (3.2-6.5)

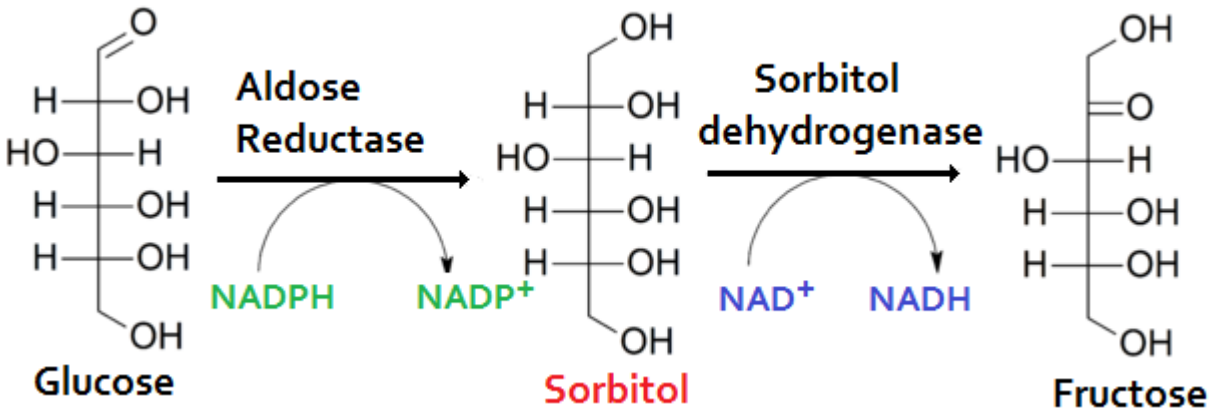


Energy Substrates: Carbohydrate

- Glycerol or Glycerin
  - A sugar alcohol
  - 4.3 kcal per gram
  - Intravenous Fat Emulsions (IVFEs) contain glycerol or glycerin to render the formulation isotonic
  - Glycerol in IVFEs add calories each mL of fat 10% IVFEs = 11 kCal, 20% IVFEs = 10 kCal

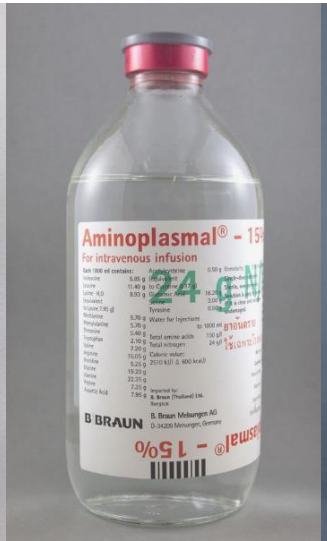
Energy Substrates: Carbohydrate

- Sorbitol or glucitol
  - A polyol (sugar alcohol)
  - 2.6 kCal per gram
  - Made from corn syrup
  - Convert to **fructose** by sorbitol-6-phosphate 2-dehydrogenase



Energy Substrates: Protein

- Protein
  - Crystalline amino acid
  - 4 kCal per gram (6.25 gram protein = 1 gram Nitrogen)
  - 3%, 5%, 7.2%, 8%, 10%, 15%
  - Mixtures of essential and nonessential amino acid, may also contains electrolytes



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Composition of some amino acid solutions

Product	Aminosol		Amiparen	Aminoplasmal	Aminoven infant	Aminoleban	Kidmin	Nephrosteril	Dipeptiven
Volume (mL)	500		500	500	100	500	200	250	100
Concentration (%w/v)	5	10	10	15	10	8	7.2	7	20
Amino acid (g)	25	50	50	75	10	40	14.4	17.5	20
% Essential amino acid	39.2		59	34	51	51.6	72	60	0
E/N Ratio	0.64		1.44	0.52	1.04	1.09	2.6	1.5	0
% Branch chain amino acid	18.8		30	16.4	30	35.5	45.8	30.8	0
Isoleucine **(g/100 mL)**	0.255	0.51	0.8	0.585	0.8	0.9	0.9	0.51	0
Leucine**(g/100 mL)**	0.445	0.89	1.4	1.14	0.13	1.1	1.4	1.03	0
Valine **(g/100 mL)**	0.24	0.48	0.8	0.72	0.9	0.84	1	0.62	0
% Aromatic amino acid	8.16		9.5	5.5	0.1	2.13	11.1	8.14	0
Phenylalanine **(g/100 mL)**	0.255	0.51	0.7	0.51	0.375	0.1	0.5	0.38	0
Tyrosine **(g/100 mL)**	0.065	0.126	0.05	0.05	0.42	-	0.05	-	0
Tryptophan **(g/100 mL)**	0.09	0.18	0.2	0.21	0.201	0.07	0.25	0.19	0
Electrolyte (mEq/Bot)									
Na^+	24		1	-	-	6	0.4	-	-
K^+	12.5		-	-	-	-	-	-	-
Cl^-	15.5		-	-	-	47	-	-	-
$H_2PO_4^{2-}$ (mMol)	2.25		-	-	-	-	-	-	-
Mg^{2+}	2.5		-	-	-	-	-	-	-
Acetate	29.5		60	-	-	-	9	-	-
Nitrogen (g/Bot)	4		8	12	1.49	6.4	2	2.7	3.2
Non protein calories (Kcal/Bot)	200 (from sorbitol)		-	-	-	-	-	-	-
Total energy (Kcal/Bot)	300		200	300	40	160	57.6	70	80
Osmolarity (mOsm/L)	1,540		960	1,290	885	900	580	645	921
pH				5.7 - 6.3	5.5-6	5.5-6.5			

Composition of some amino acid solutions

Product	Aminosol		Amiparen	Aminoplasmal	Aminoven infant	Aminoleban	Kidmin	Nephrosteril	Dipeptiven
Volume (mL)	500		500	500	100	500	200	250	100
Concentration (%w/v)	5	10	10	15	10	8	7.2	7	20
Amino acid (g/Bottle)	25	50	50	75	10	40	14.4	17.5	20
Essential Amino Acid (g/100 mL)									
Isoleucine	0.255	0.51	0.8	0.585	0.8	0.9	0.9	0.51	-
Leucine	0.445	0.89	1.4	1.14	0.13	1.1	1.4	1.03	-
Valine	0.24	0.48	0.8	0.72	0.9	0.84	1	0.62	-
Methionine	0.19	0.38	0.39	0.57	0.312	0.1	0.3	0.28	-
Threonine	0.205	0.41	0.57	0.54	0.44	0.45	0.35	0.48	-
Lysine	0.35	0.7	1.05	0.795	0.851*	0.61	0.5**	0.71	-
Phenylalanine	0.255	0.51	0.7	0.57	0.375	0.1	0.5	0.38	-
Tryptophan	0.09	0.18	0.2	0.21	0.201	0.07	0.25	0.19	-
Histidine	0.26	0.52	0.5	0.525	0.476	0.24	0.35	0.43	-
Conditionally essential Amino Acid (g/ 100 mL)									
Arginine	0.46	0.92	1.05	1.605	0.75	0.6	0.45	0.49	-
Cysteine	0.036	0.072	0.1	0.037	0.052	0.3	0.1	0.037	-
Glycine (Aminoacetic acid)	0.395	0.79	0.59	1.92	0.415	0.9	-	0.32	-
Glutamine	-	-	-	-	-	-	-	-	13.46
Proline	0.445	0.89	0.5	0.735	0.971	0.8	0.3	0.43	-
Tyrosine	0.065	0.126	0.05	0.05	0.42	-	0.05	-	-
Dispensable Amino Acid (g/100 mL)									
Alanine	0.685	1.37	0.8	2.235	0.93	0.75	0.25	0.63	8.2
Aspartic acid	0.065	0.13	0.1	0.795	-	-	0.1	-	-
Asparagine	0.186	0.372	-	-	-	-	-	-	-
Glutamic acid	0.23	0.46	0.1	1.62	-	-	0.1	-	-
Serine	0.12	0.24	0.3	0.3	0.767	0.5	0.3	0.45	-
Others (g/100 mL)									
Taurine	-		-	-	0.04	-	-	-	-
Ornithine	0.16	0.32	-	-	-	-	-	-	-
Malic acid	-		-	-	0.262	-	-	0.15	-

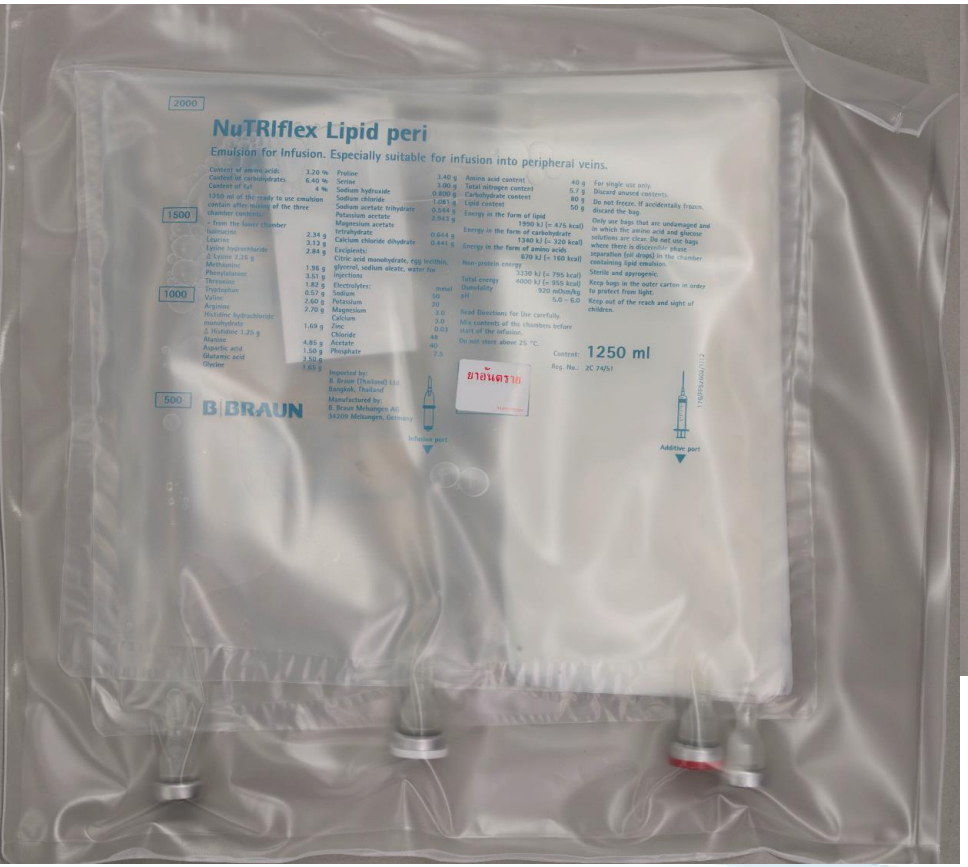
*l-Lysine acetate 1.2 g, **l-Lysine acetate 0.71 g

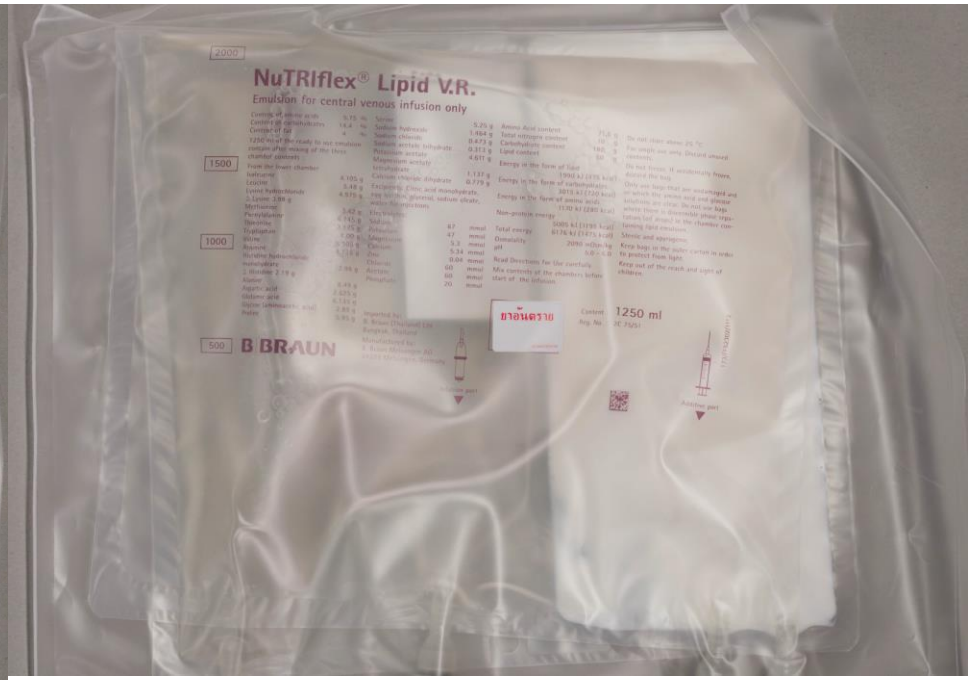
Neutral Acidic Basic

Composition of amino acid in 3-in-1 Formulations

Product	Bfluid	Nutriflex Lipid		Kabiven		Smofkabiven		Oliclinomel	
		Peripheral	VR Central	Peripheral	Central	Peripheral	Central	N4-500E	N7-1000E
Dextrose	75 gm (7.5%)	80 gm (6.4%)	180 gm (14.4%)	97 gm/1.44 L (6.7%)	100 gm/1.026 L (9.75%)	103 gm/1.448 L (7.1%)	125 gm/0.986 L (12.7%)	80 gm/L (8%)	160 gm/L (16%)
Amino acid (g/bag)	30 (3%)	40 (3.2%)	71.8 (5.75%)	34 (2.36%)	34 (3.31%)	46 (3.2%)	50 (5.1%)	22 (2.2%)	40 (4%)
Essential Amino Acid (g/100 mL)									
Isoleucine	0.24	0.187	0.328	0.118	0.165	0.16	0.25	0.132	0.24
Leucine	0.42	0.25	0.438	0.166	0.234	0.23	0.38	0.161	0.292
Valine	0.24	0.2	0.36	0.152	0.214	0.2	0.31	0.128	0.232
Methionine	0.117	0.156	0.273	0.118	0.165	0.13	0.22	0.088	0.16
Threonine	0.171	0.145	0.254	0.118	0.165	0.14	0.22	0.092	0.168
Lysine	0.3146	0.18	0.318	0.187	0.263	0.21	0.34	0.128	0.232
Phenylalanine	0.21	0.28	0.492	0.166	0.234	0.16	0.26	0.123	0.224
Tryptophan	0.06	0.045	0.08	0.039	0.055	0.063	0.1	0.04	0.072
Histidine	0.15	0.1	0.175	0.139	0.195	0.093	0.15	0.106	0.192
Conditionally essential Amino Acid (g/ 100 mL)									
Arginine	0.315	0.216	0.378	0.236	0.331	0.38	0.61	0.253	0.46
Cysteine	0.03	-	-	-	-	-	-	-	-
Glycine (Aminoacetic acid)	0.177	0.132	0.231	0.166	0.234	0.35	0.56	0.227	0.412
Glutamine	-	-	-	-	-	-	-	-	-
Proline	0.15	0.272	0.476	0.139	0.195	0.35	0.57	0.15	0.272
Tyrosine	0.015	-	-	0.0048	0.006	0.012	0.02	0.009	0.016
Dispensable Amino Acid (g/100 mL)									
Alanine	0.24	0.388	0.679	0.333	0.467	0.44	0.71	0.456	0.828
Aspartic acid	0.03	0.12	0.21	0.069	0.097	-	-	-	-
Asparagine	-	-	-	-	-	-	-	-	-
Glutamic acid	0.03	0.28	0.49	0.118	0.165	-	-	-	-
Serine	0.09	0.24	0.42	0.097	0.136	0.21	0.33	0.11	0.2
Others (g/100 mL)									
Taurine	-		-	-		0.032	0.05	-	
Electrolytes									
Phosphate (mMol)	10	7.5 (+20)	20 (+20)	11 (+11)	10 (+5)	11.9 (+10.6)	12 (+3)	8.6 (+6)	10 (+12)
Calcium (mEq)	5	6 (+14)	10.6 (+ 9.4)	4 (+10.4)	4 (+6)	4.6 (+10.4)	5 (+5)	4 (+6)	4 (+6)
Magnesium (mEq)	5	6 (+14)	10.6 (+9.4)	8 (+6.4)	8 (+2)	9.2 (+5.8)	10	4.4 (+6.8)	4.4 (+6.8)

Neutral Acidic Basic


2000
NuTRIflex Lipid peri
Emulsion for Infusion. Especially suitable for infusion into peripheral veins.
1500
1000
500
B BRAUN
1250 ml
ยาอันตราย


2000
NuTRIflex® Lipid V.R.
Emulsion for central venous infusion only
1500
1000
500
B BRAUN
1250 ml
ยาอันตราย

Energy Substrates: Intravenous Fat Emulsion (IVFE)

- Concentrated source of calories & essential fatty acids.
- Differ in triglyceride source (soybean oil or combination of soybean oil & safflower oil), fatty acid content, & commercially available concentrations (10%, 20%)
- These products also contain **egg phospholipids as emulsifying agent & glycerol** to make emulsion isotonic.
- Caloric content:
  - **10% emulsion = 1.1 kcal/mL**
  - **20% emulsion = 2 kcal/mL**

Comparison of Parenteral Lipid Emulsions

Product	Lipofundin MCT/LCT			Intralipid			ClinOleic	SMOF lipid	
Concentration (%)	10	20		10	20		20	20	
Volume (mL/Bot)	500	250	500	500	250	500	250	100	250
Lipid (g/Bot)	50	50	100	50	50	100	50	20	50
Soybean oil (%)	50	50	50	100	100	100	20	30	30
Safflower oil (%)	-	-	-	-	-	-	-	-	-
Coconut (MCT) oil (%)	50	50	50	-	-	-	-	30	30
Olive oil (%)	-	-	-	-	-	-	80	25	25
Fish oil (%)	-	-	-	-	-	-	-	15	15
Fatty acid distribution									
SFA:MUFA:PUFA	60:10:30			17:23:60			15:65:20	40:30:30	
Egg phospholipid (g/Bot)	6	3	6	6	3	6	3	1.2	3
PO_4 (mMol/Bot)	7.5	3.75	7.5	7.5	3.75	7.5	3.75	1.5	3.75
Glycerol (g/L)	25	25	25	22	22	22	5.6	2.5	2.5
Energy (kcal/Bot)	550	500	1000	550	500	1,000	500	200	500
Osmolarity (mOsm/L)	345	380	380	-	-	-	270	290	290
Osmolality (mOsm/kg water)	-	-		300	350	350	-	380	380

Energy Substrates: Intravenous Fat Emulsion (IVFE)

- Emulsions containing
  - Soybean oil:
    - ~50-55% Linoleic acid
    - 4-9% Linolenic acid
  - Safflower oil:
    - ~66% Linoleic acid
    - 4% Linolenic acid.
- Higher amounts of circulating phospholipids are associated with impaired triglyceride clearance in neonates & infants, 20% IVFE is the preferred product for this population.
- Both IVFE types are effective for treatment or prevention of essential fatty acid deficiency (EFAD).

Energy Substrates: Intravenous Fat Emulsion (IVFE)

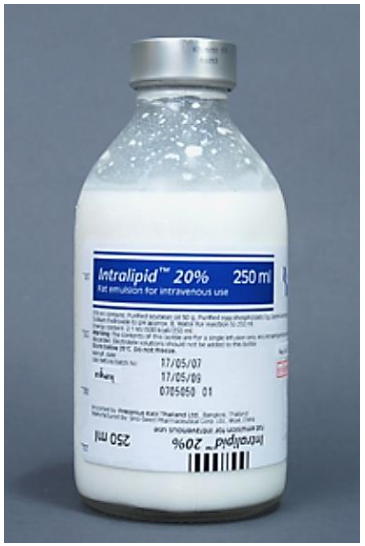
- EFAD may be prevented by providing 2-5% of total calories as Linoleic acid & 0.25- 0.5% as Linolenic acid.
- This may be achieved in most adults by giving ~100 g IVFE weekly.
- Neonates & infants require minimum of 0.5-1 g/kg daily.
- Risk of hypertriglyceridemia decreases with longer infusion times.
- Rapid IVFE infusions are reported to contribute to ↓ oxygenation in neonates.

Energy Substrates: Intravenous Fat Emulsion (IVFE)

- **Adverse pulmonary effects** are thought to be caused by polyunsaturated fatty acid (PUFA)-driven prostaglandin production, which results in altered vascular tone.
- Rapid infusion of long-chain fatty acid formulations may have negative impact on **immunocompetence** by saturating reticuloendothelial system.
- Initiation of IVFE earlier than 4-7 days of life in **infants with birth weight <800 g** remains controversial because of potential ↑ risk of **chronic lung disease & death**.

Energy Substrates: Intravenous Fat Emulsion (IVFE)

- IVFE use may facilitate provision of adequate calories & minimize complications of nutrition therapy such as hyperglycemia, hepatotoxicity, or ↑ carbon dioxide production.
- IVFE use is **c/i** in patients with impaired ability to clear fat emulsion, such as patients with pathologic hyperlipidemia & hypertriglyceridemia associated with pancreatitis.
- 10% & 20% IVFE products may be administered either by central or peripheral route.


Intralipid™ 20% 250 ml
Fat emulsion for intravenous use
17/05/07
17/05/09
0705050 01


Lipofundin® MCT/LCT 20%
MCT 10
LCT 10
250 ml


04-2011


SMOFlipid 20%
Emulsion for infusion
Fresenius Kabi
Manufactured by:
Fresenius Kabi Austria GmbH
Fresenius Kabi AB, Uppsala, Sweden


149GA0288
SMOFlipid 20%
Emulsion for infusion
FRESENIUS KABI
Manufactured by:
Fresenius Kabi Austria GmbH
Fresenius Kabi AB, Uppsala, Sweden

Energy Substrates: Intravenous Fat Emulsion (IVFE)

- They may be added directly to PN solution as total nutrient admixture (TNA) or 3-in-1 system (lipids, protein, glucose, & additives), or they may be piggybacked with CAA-dextrose solution.
  - **MCT**s are hydrolyzed & cleared > rapidly than LCTs, & they do not accumulate in liver.
    - MCTs do not require **carnitine** for entrance into mitochondria for oxidation.
    - MCTs are not source of essential fatty acids.
  - **Omega-3 PUFAs (linolenic acid)** are metabolized to cytokines, which may be < inflammatory & immunosuppressive than those derived from **omega-6 PUFAs (linoleic acid).**

Electrolytes

- Maintenance or Therapeutic amount of various electrolytes are added to PN formulations depending on the patient's requirements

Electrolyte	Parenteral	Salt form
Sodium	1-2 mEq/kg	▪ 3%NaCl → 0.51 mEq/mL ▪ 20%NaCl →3.42 mEq/mL ▪ 25%NaOAc →3 mEq/mL
Potassium	1-2 mEq/kg	▪ 15%KCl → 2 mEq/mL ▪ 30%KOAc → 3 mEq/mL
Chloride, Acetate	As needed to maintain acid-base balance	
Calcium	10-15 mEq	▪ 10%Calcium Gluconate → 0.45 mEq/mL ▪ 5%Calcium Levulinate → 0.327 mEq/mL
Magnesium	8-20 mEq	▪ 50%Magnesium Sulfate → 4 mEq/mL
Phosphate	20-40 mMol	▪ 8.7%K_2HPO_4 → K 1 mEq/mL, HPO_4^{2-} 0.5 mMol/mL ▪ Fructose 1,6 Diphosphate trisodium → Phophate 0.47 mMol/mL, Na^+ = 1 mEq/mL ▪ Glycophos® → $H_2PO_4^-$ 1 mMol/mL, Na^+ 2 mEq/mL

Daily Electrolyte and Mineral Requirements for Pediatric Patients

Electrolyte	Preterm Neonates	Infants/Children	Adolescents and Children, >50 kg
Sodium	2-5 mEq/kg	2-5 mEq/kg	1-2 mEq/kg
Potassium	2-4 mEq/kg	2-4 mEq/kg	1-2 mEq/kg
Calcium*	2-4 mEq/kg 650 mg Calcium Gluconate/100 mL PN	0.5-4 mEq/kg	10-20 mEq
Phosphorus* K_2HPO_4	1-2 mmol/kg	0.5-2 mmol/kg	10-40 mmol
Magnesium	0.3-0.5 mEq/kg	0.3-0.5 mEq/kg	10-30 mEq
Acetate	As needed to maintain acid-base balance		
Chloride	As needed to maintain acid-base balance		

- A calcium to phosphorus ratio of at least 1.7:1 (mg/mg) to achieve adequate bone mineralization in neonatal period
- **The equation for determining calcium phosphorus ratio to ensure the precipitation does not occur:**
  Calcium (mEq/L) X Phosphorus (mmol/L) ≤300.
- Phosphate should be added when serum P less than 5 mg/dL

Gargasz A. AACN Advanced Critical Care 2012. 23; 4: 451-464.

Vitamins

- Commercially available:
  - Single
  - Multivitamins (With and Without vitamin K)
    - Water soluble vitamins
      - Soluvit N: vit B1 2.5 mg, vit B2 3.6 mg, vit B6 4 mg, vit B12 5 mcg, vit C 100 mg, biotin 60 mcg, folic acid 0.4 mg, nicotinamide 40 mg, pantothenic acid 15 mg
    - Fat soluble vitamins
      - Vitalipid N **Adult:** Per 10 mL Vit A 3,300 IU, vit D2 200 IU, vit E 10 IU, vit K1 150 mcg
      - Vitalipid N **Infant:** Per 10 mL Vit A 2,300 IU, **vit D2 400** IU, vit E 7 IU, vit K1 200 mcg

Commercial Parenteral Multivitamins

Each vial contains:	Cernevit®	OMVI
Vitamin A (Retinol)	3500 IU	3,300 IU
Vitamin D3	220 IU	200 IU
Vitamin E (α tocopherol)	11.20 IU (10.2 mg)	10 mg
Vitamin K	-	2 mg
Vitamin C (Ascorbic acid)	125 mg	100 mg
Vitamin B1 (Thiamine)	3.51 mg	3.1 mg
Vitamin B2 (Riboflavin)	4.14 mg	3.6 mg
Vitamin B6 (Pyridoxine)	4.53 mg	4 mg,
Vitamin B12 (Cyanocobalamin)	6 µg	5 µg
Folic Acid	414 µg	400 µg
Pantothenic acid	17.25 mg	15 mg
Biotin	69 µg	60 µg
Vitamin PP (niacin)	46 mg	40 mg

Vitamins for premature infants and Adults receiving Parenteral Nutrition

Vitamin	Premature infant (Units/kg/day)		Full term and children (Units/day)	Adults and children ≥11 years* (Units/day)
	▪ Am J Clin Nutr. 1988;48:1324-1342. ▪ Ayers P, Adams S, Boullata JI, et al. A.S.P.E.N. Parenteral nutrition safety consensus recommendations. JPEN J Parenter Enteral Nutr. 2014;38;296-333			
Fat-soluble vitamin	**EAR**	**Current**		
A (mcg) 1 mcg = 3.33 IU	500	280	700	1000
E (mg)	2.8	2.8	7	5
K (mcg)	80	10	200	150 mcg daily or 5-10 mg weekly
D2 (mcg)	4 **or** 160 IU	4 **or** 160 IU	10 **or** 400 IU	none
Water-soluble vitamins				
C Ascorbic acid (mg)	25	32	80	**200**
B1 Thiamine (mg)	0.35	0.48	1.2	**6**
B2 Riboflavin (mg)	0.15	0.56	1.4	3.6
B6 Pyridoxine (mg)	0.18	0.4	1	**6**
B3 Niacin (mg)	6.8	6.8	17	40
Pantothenate (mg)	2	2	5	15
Biotin (mcg)	6	8	20	60
Folate (mcg)	56	56	140	**600**
B12 (mcg)	0.3	0.4	1	**100-1000 mcg IM monthly**

Trace Elements

- **Adult:**
  - **Addamel N Per 10 mL** Essential trace elements: iodine 1 micromole, selenium 0.4 micromole, Fe 20 micromole, Zn 100 micromole, chromium 0.2 micromole, copper 20 micromole, fluoride 50 micromole, manganese 5 micromole, molybdenum 0.2 micromole
- **Pediatric:**
  - **Peditrace®: Per mL** Copper Cl 53.7 mcg, manganese Cl 3.6 mcg, K iodide 1.31 mcg, Na fluoride 126 mcg, Na selenite 6.66 mcg, $ZnCl_2$ 521 mcg

Daily Trace Element Requirements for Neonate, Pediatric and Adults Patients

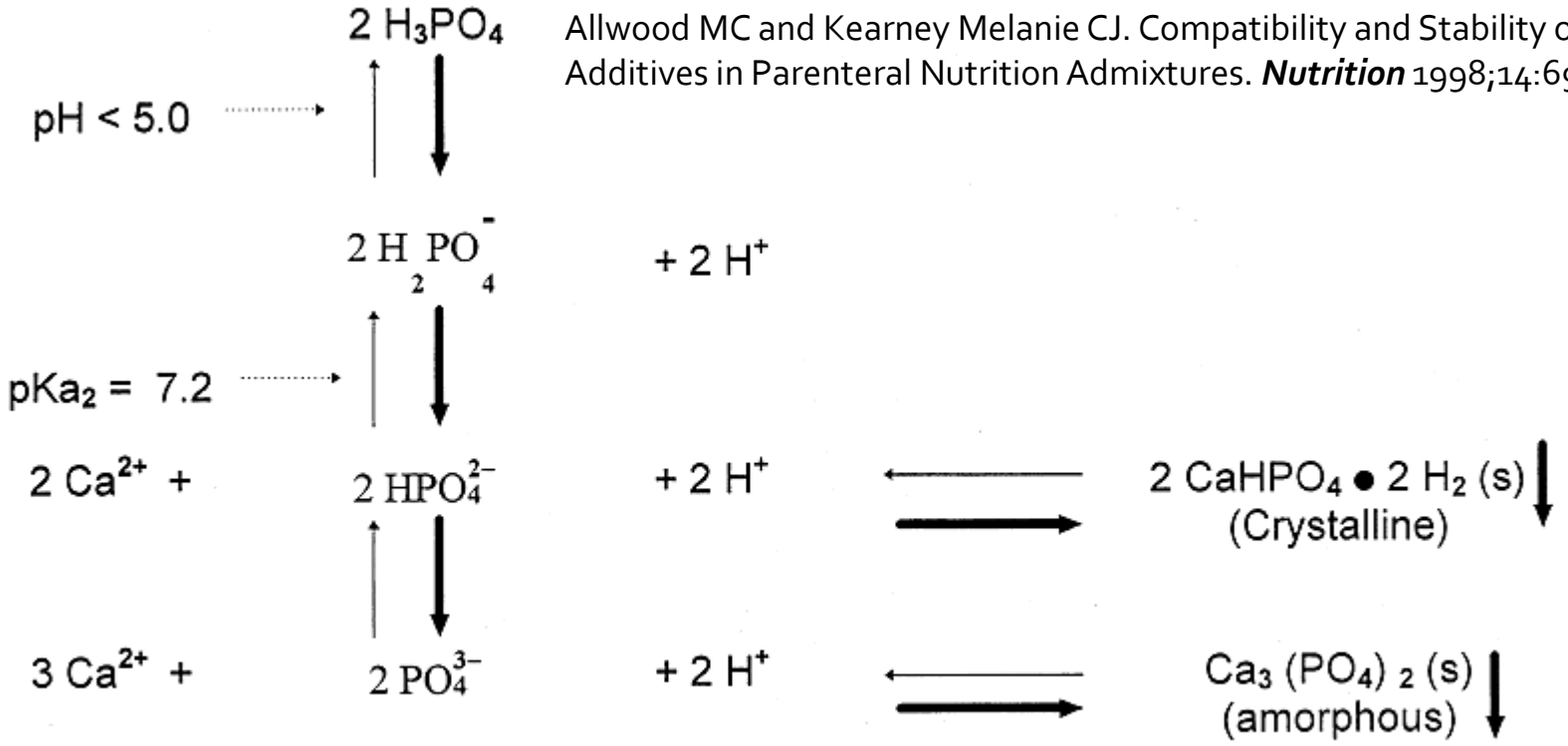
Trace Element	Preterm neonates < 3 kg (mcg/kg/d)	Term neonates 3-10 kg (mcg/kg/d)	Children 10-40 kg (mcg/kg/d)	Adolescent > 40 kg and Adult (per day)	
Zinc	400*	50-250	50-125	2-5 mg	2.5 -5 mg
Copper	20	20	5.0-20	0.2-0.5 mg	0.3-0.5 mg
Manganese	1 (Should be withheld in cholestasis or liver function impairment)	1	1	40-100 mcg	60-100 mcg
Chromium	0.05-0.2 Caution with renal dysfunction	0.2	0.14-0.2	5-15 mcg	10-15 mcg
Selenium	1.5-2*	2	1.0-2	40-60 mcg	20-60 mcg
Carnitine	8-20 mg/kg/day				
Choline		125-150 mg/day			
Heparin	0.25-1 Units/mL of PN To enhance the clearance of lipid emulsions, increase lipoprotein lipase levels and lipolytic activity				

* For Early PN for VLBW premature infant containing: Dextrose, Amino acids, Calcium, Heparin

Mixture Stability in Parenteral Nutrition

The most important interactions in the aqueous phase are as follows.

1. Precipitation of Calcium Hydrogen Phosphate.



Allwood MC and Kearney Melanie CJ. Compatibility and Stability of Additives in Parenteral Nutrition Admixtures. ***Nutrition*** 1998;14:697–706.

FIG. 1. Speciation of inorganic phosphate in parenteral nutrition mixtures.

Mixture Stability in Parenteral Nutrition

The most important interactions in the aqueous phase are as follows.

1. Precipitation of Calcium Hydrogen Phosphate.

Results:

- The 38,019 parenteral orders contained 36,909 PN with y-sited fat emulsion and 1110 PN orders without fat emulsion. **Sixty percent of the patients weighed between 1 and 5 kg, 20% were between 5 and 10 kg, 16% were between 10 and 25 kg, and 6% were >25 kg**.
- The addition of fat emulsion to the parenteral solution had a pH of 5.5, the addition of cysteine had a final pH of 5, and the addition of cysteine and fat emulsion remained at a pH of 5.
- Solutions that are compounded and tested at room temperature

Nutr Clin Pract. 2011;26:708-713

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Mixture Stability in Parenteral Nutrition

Nutr Clin Pract. 2011;26:708-713

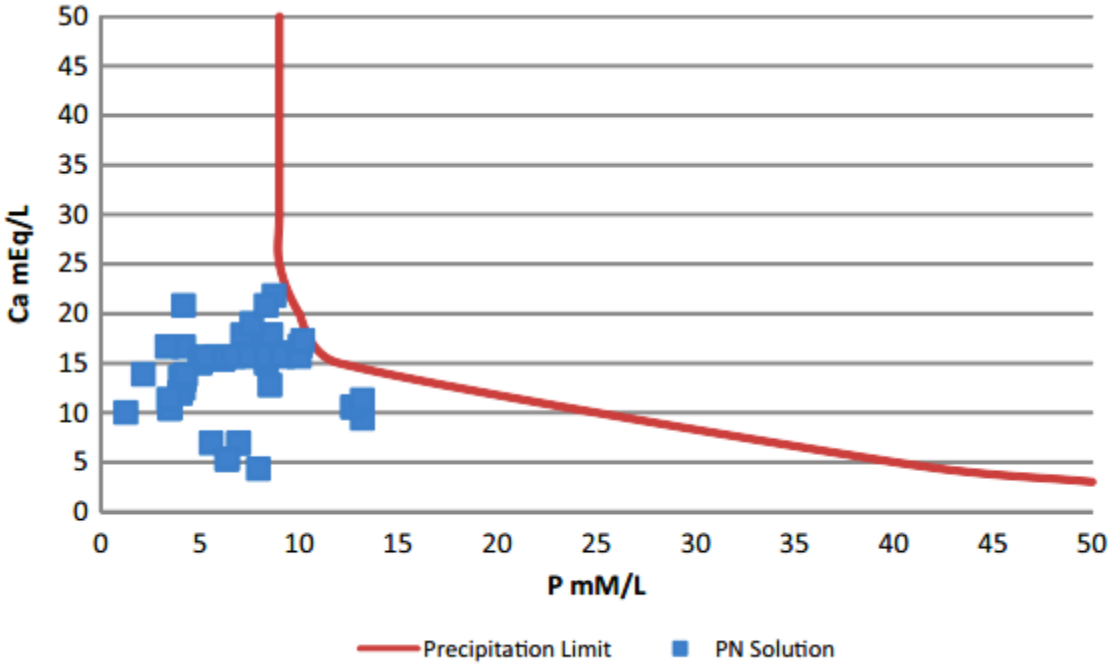
1. Precipitation of Calcium Hydrogen Phosphate.

Standard Amounts of Calcium and Phosphorus in Parenteral Solutions

			Patient Weight, kg					
Ion	Unit	Usual Daily Requirement	<2.5	2.51– 4.9	5.0–10.0	10.1–20	20.1>60	>60.1
Calcium	mEq/kg/d	1–3	2.8	2.5	1.5	1	0.5	0.4
Phosphorous	mM/kg/d	0.5–3	1.2	1	0.5	0.5	0.5	0.4

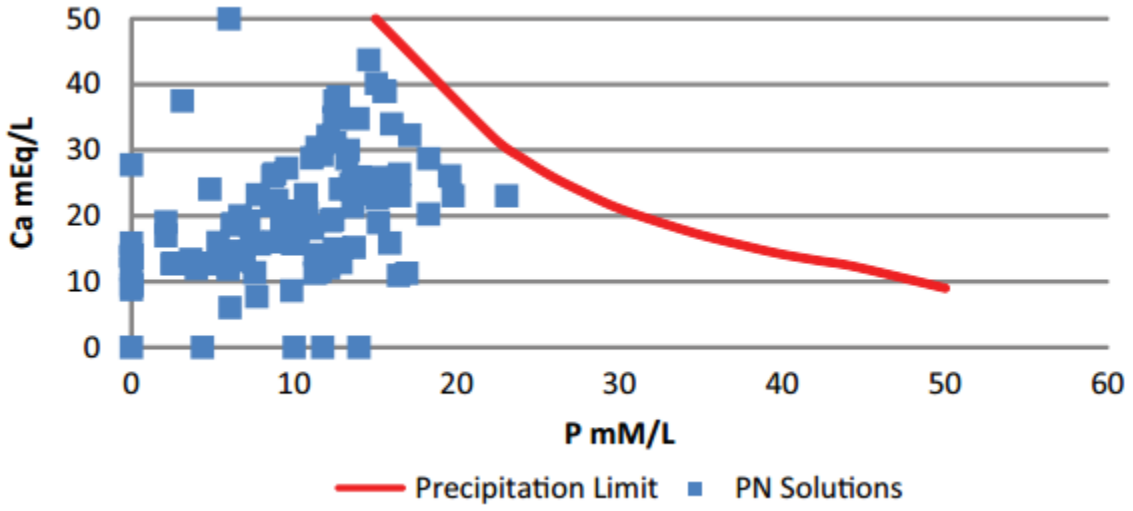
Standard Amounts of Trace Minerals and Iron in Parenteral Solutions

			Patient Weight, kg			
Ion	Unit	Usual Daily Requirement	<3.0	3.0–9.9	10.0– 24.9	>25.0
Zinc	mcg/kg/d	100–900	400	300	100	—
	mg/d	—	—	—	—	2.5
Copper	mcg/kg/d	20	20	20	20	—
	mcg/d	—	—	—	—	500
Manganese	mcg/kg/d	2–10	5	5	5	—
	mcg/d		—	—	—	150
Chromium	mcg/kg/d	0.14–0.2	0.14	0.14	0.14	—
	mcg/d		—		—	10
Selenium	mcg/kg/d	3–6	5	5	5	—
	mcg/d				—	30
Iodine	mcg/kg/d	2	2	2	2	1



TrophAmine 1.5%
Dextrose 10%

TrophAmine 4%
Dextrose 25%



Nutr Clin Pract. 2011;26:708-713

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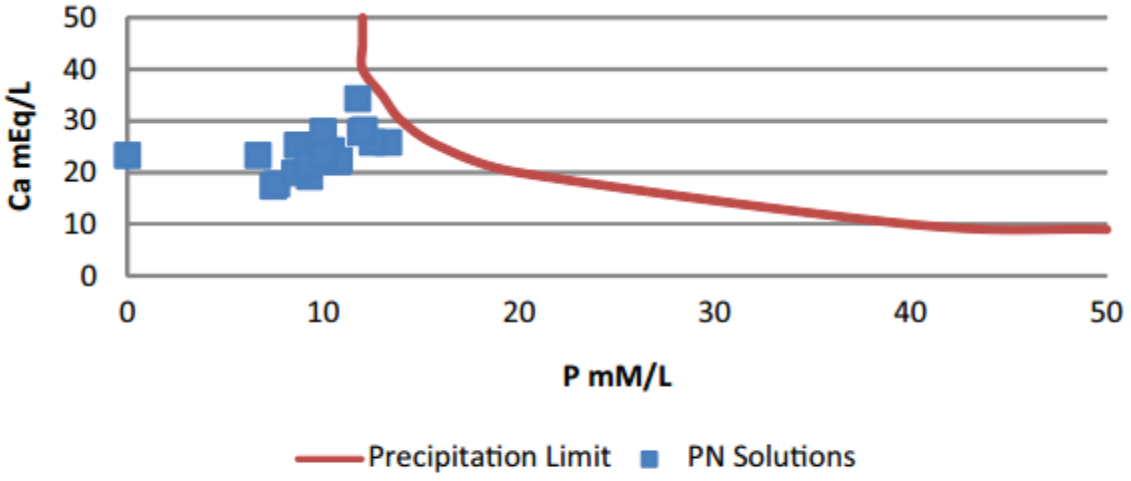

Figure 10. TrophAmine 2%, cysteine (40 mg/g amino acids), and dextrose 10%. PN, parenteral nutrition.

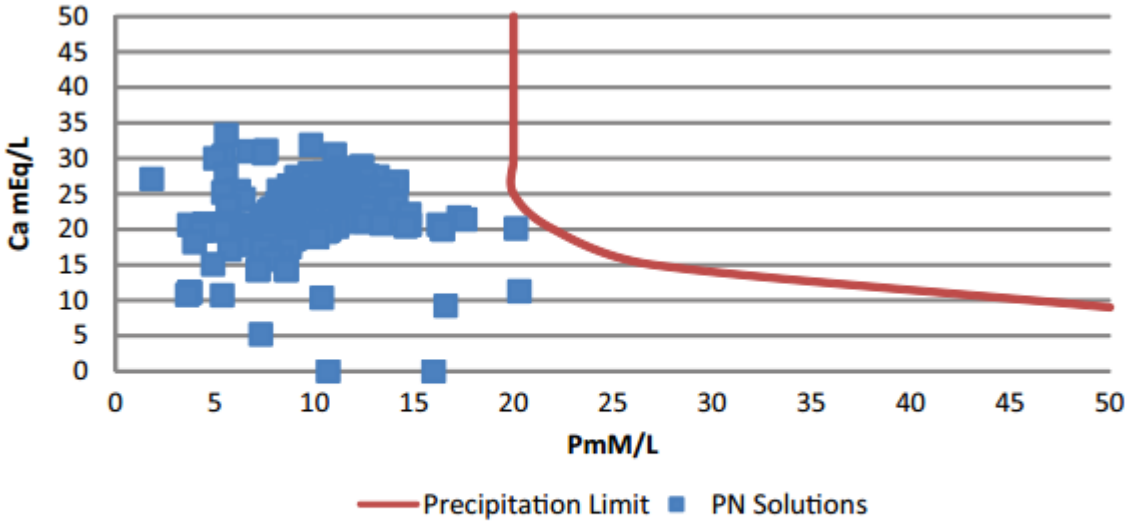

Figure 14. TrophAmine 2%, cysteine (40 mg/g amino acids), fat emulsion (3 g/kg/d), and dextrose 10%. PN, parenteral nutrition.

Nutr Clin Pract. 2011;26:708-713

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American Society for Parenteral and Enteral Nutrition

Probability-Based Compatibility Curves for Calcium and Phosphates in Parenteral Nutrition Formulations

Thomas Gonyon, BS; Phillip W. Carter, PhD; Gerald Phillips, MSc; Heather Owen, MSc; Dipa Patel, BS; Priyanka Kotha, MSc; and John-Bruce D. Green, PhD

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Table 2. Formulations for the 100-mL and 1-L Systems.

Component	Target Concentration	100-mL Actual Value or Range	1-L Actual Value or Range
Amino acid, %	4	4	4
Dextrose, %	12	12	12
Calcium, mEq/L	Varies	0–46.5	0–35.3
Phosphates, mmol/L	Varies	0–36	0–42
Sodium, mEq/L	150	148	148
Potassium, mEq/L	80	78.8–80.8	78.8–81.6
Magnesium, mEq/L	5	4.1	4.2
Acetate, mEq/L	34	33.6	33.6
Chloride, mEq/L	Varies	192–234	193–234

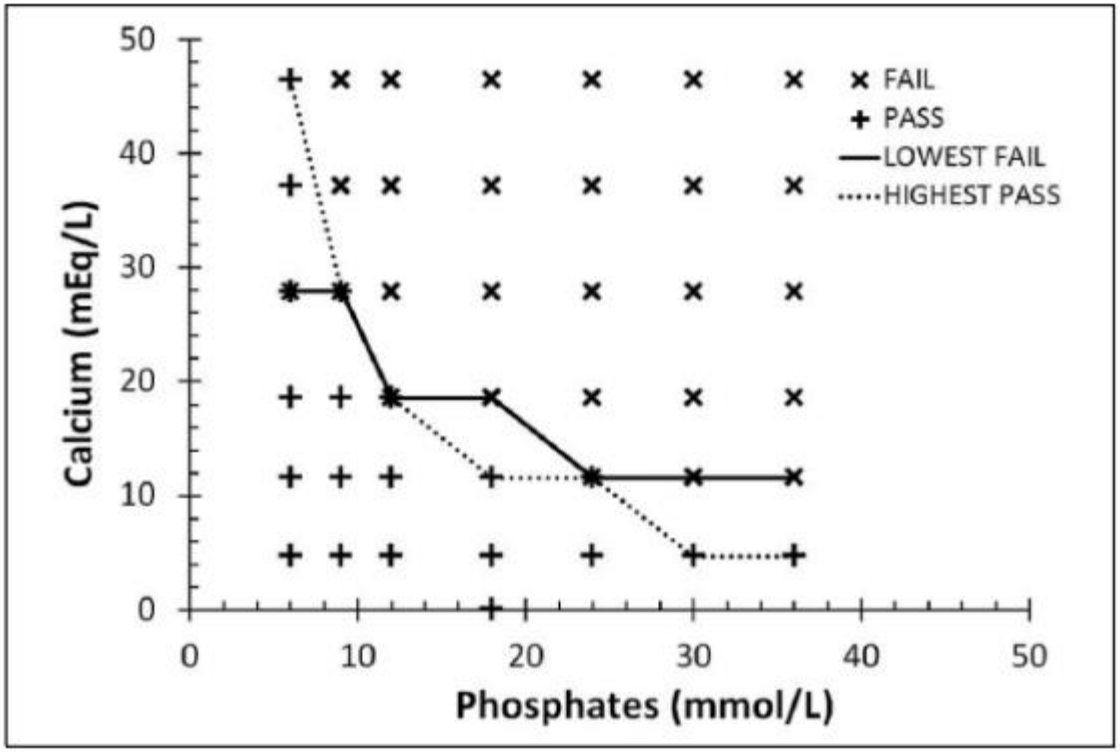


Figure 1. Compatibility curves are generated from triplicate microscopic measurements labeled as all pass (+), all fail (×), or at least 1 pass and 1 fail (*). Connecting the highest calcium that passed at a given phosphate creates the highest pass curve (dotted line), and connecting the lowest calcium that failed creates the lowest fail curve (solid line).

Mixture Stability in Parenteral Nutrition

The most important interactions in the aqueous phase are as follows.

1. Precipitation of Calcium Hydrogen Phosphate.

- 3-in-1 Formulations
  - 16%Aminoplasmal
  - 70% glucose solution + Electrolytes
  - 20% lipid emulsion as a 50:50 mixture of medium-chain and long-chain triglycerides (Lipofundin MCT, B. Braun, lot 2042A81)

Final Concentrations of Selected Additives in Weight-Based Total Nutrient Admixtures for Fluid-Restricted Patients

Additive	Amount per Liter				
	40-kg Pt.	50-kg Pt.	60-kg Pt.	70-kg Pt.	80-kg Pt.
Amino acids (g)	71.2	73.4	74.9	76.0	76.8
Dextrose (g)	196.9	203.5	208.2	210.0	213.2
Lipids (g)	24.9	25.4	25.8	26.8	26.9
Sodium (meq)	118.6	97.8	83.3	72.4	64.0
Potassium (meq)	71.2	58.7	49.9	43.5	38.4
Calcium (meq)	11.9	9.8	8.3	7.2	6.4
Magnesium (meq)	11.9	9.8	8.3	7.2	6.4
Phosphate (mmol)	28.5	23.5	19.9	17.4	15.4
Chloride (meq)	118.6	97.8	83.3	72.4	64.0
Trace elements (mL)	3.6	2.9	2.5	2.2	1.9
Multivitamins (mL)	11.9	9.8	8.3	7.2	6.4

Am J Health-Syst Pharm. 2006; 63:79-85

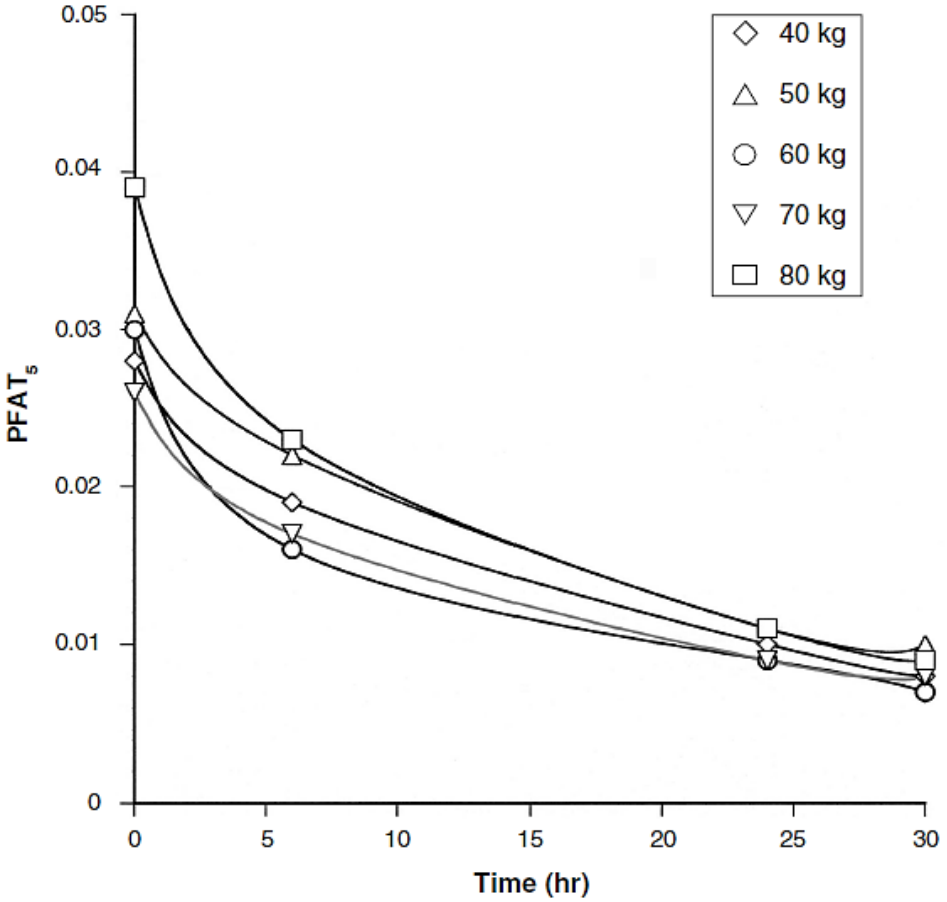
Mixture Stability in Parenteral Nutrition

Am J Health-Syst Pharm. 2006; 63:79-85

Results

- No significant changes in the physicochemical stability of the TNAs were observed by **D**ynamic **L**ight **S**cattering (DLS) or **L**ight **E**xtinction with **S**ingle-**P**article **O**ptical **S**ensing (LE-SPOS) mean droplet size (large diameter tail) from time 0 (immediately after compounding) to 30 hours

- According to the USP proposal, a (commercial) lipid injectable emulsion (as used in the TNAs in this study) must have a mean droplet diameter below 500 nm.



Calcium and phosphate stability

- **There are a number of factors which affect the formation of calcium phosphate, including:**
  - Amino acid concentration
  - Amino acid product composition (i.e. pH or Phosphorus content)
  - Concentration of the electrolytes (Calcium, Phosphorous, Magnesium)
  - Calcium salt used
  - Dextrose concentration
  - pH of formulation
  - Temperature of formulation
  - Order of mixing

Calcium and phosphate stability

- **The risk of calcium phosphate precipitation may be reduced by:****
  - Keeping the final amino acid concentration at 2.5% or greater.
  - Maintaining a final pH of 6.0 or lower.
  - Infusing the solution within 24 hours of preparation.
  - Using Calcium gluconate instead of Calcium chloride.
  - Avoiding mixing calcium and phosphorus in close sequence during preparation.
  - ***Keeping the calcium:phosphorus ratio greater than 1:2.***
  - ***Keeping the total amount of calcium and phosphorus less than 45 mEq/L.***
  - ***Keeping the calcium:phosphorus solubility product less than 150.***
  - ***Adding cysteine to the amino acids.***

PN: Order of mixing

- **Gravity Transfer/Manual Compounding**

1. Combine Dextrose , Amino acid, and Sterile Water for injection
2. Add Phosphate
3. Add Sodium, Potassium and Magnesium (in any order)
4. Add Trace minerals
5. Agitate the solution well
6. Add Calcium and agitate the solution well again
7. Observe the solution for precipitates of contaminants, if either is present, discard the solution, if precipitate is present, review the quantities of additives for incompatibilities and adjust nutrient doses as needed to achieve compatibility
8. If a TNA is being admixed, add the IVFE next, gentle agitate, and observe for signs of the emulsion cracking
9. Add Vitamins last
   - Vitamin B1 degraded by Daylight,
   - Vitamin C degraded by Oxygen, Temperature, Lack of Cysteine, Reducing agent: Copper

Mixture Stability in Parenteral Nutrition

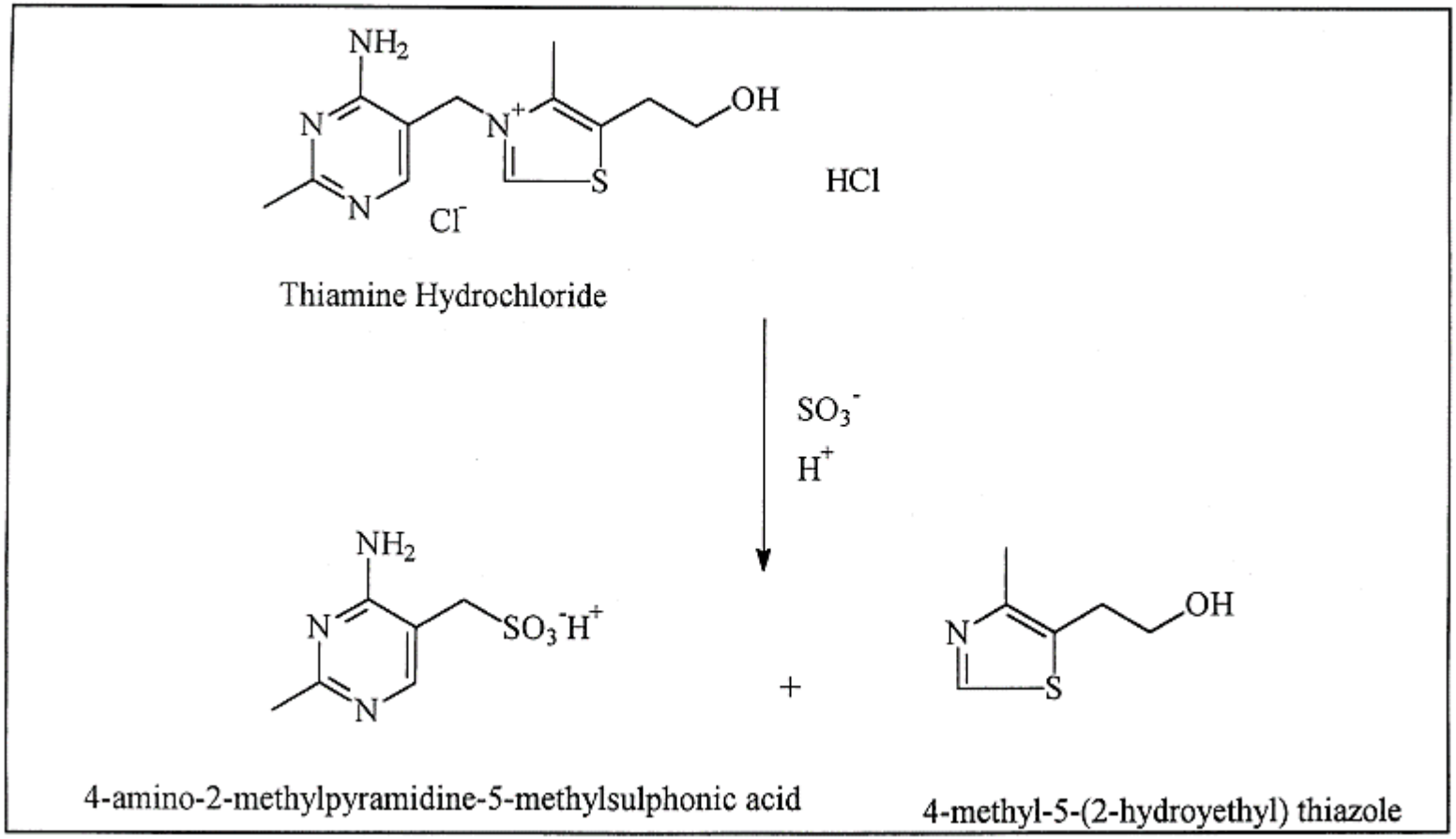
2. Inactivation of Vitamins, as They Are Highly Susceptible to Degradation.

- Sometimes the clinical state of the patient requires additional supplementation with high doses of some vitamins:
- Vitamin B1 in severe malnutrition
- Vitamin C in patients with increased cell catabolism.
- Inactivation of vitamins may follow many mechanisms:
  - **Photolysis of vitamin A, B1, B2 (Riboflavin is degraded by exposure to daylight)**
  - **Oxidation of vitamin C**
  - **Reduction of vitamin B1**
  - **Adsorption of vitamin A onto the surface of the container**

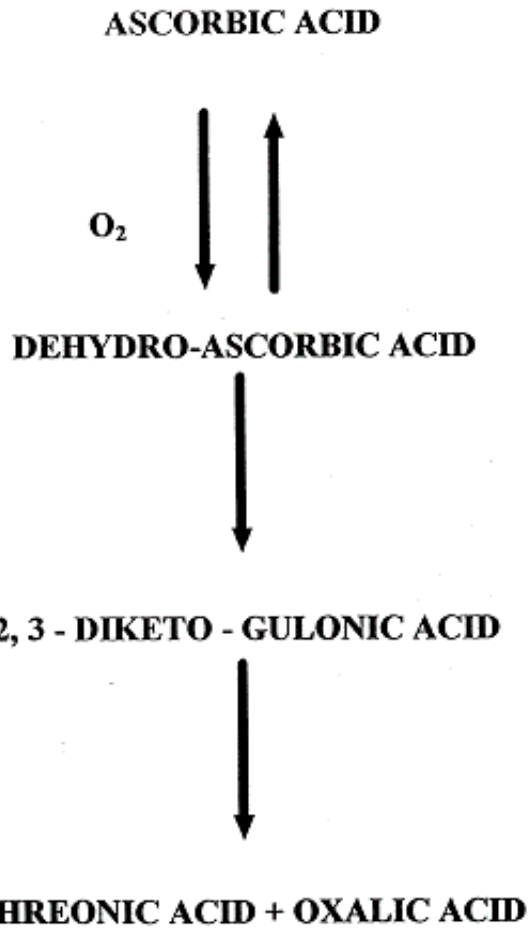
Thiamine Degradation

↑ Unstable as the pH rises and is decomposed by oxidizing or reducing agents.

-The predominant cause of degradation in TPN mixtures is by reduction, caused in particular by sodium metabisulfite



Ascorbic acid degradation pathway



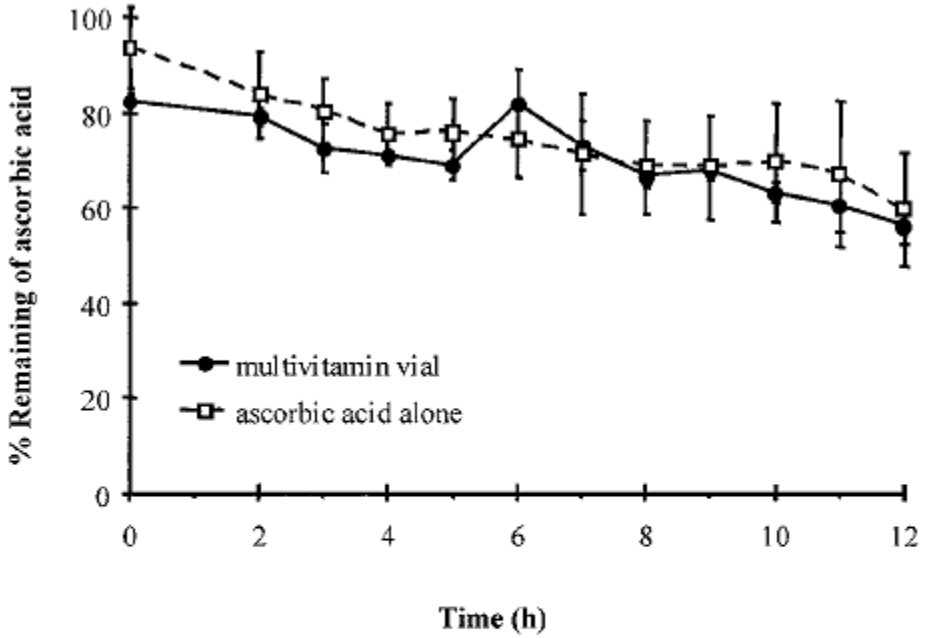


FIG. 3. Degradation of ascorbic acid in 2500-mL capacity multilayered (ML) bags stored at 21°C and filled with the total parenteral nutrition (TPN) mixture (NuTRIflex Lipid plus [B. Braun, Melsungen, Germany] + Tracutil [B. Braun, Melsungen, Germany]) supplemented with 1 multivitamin vial (Cernevit, Hoffman La Roche, Basel, Switzerland) or with 125 mg ascorbic acid (Fluka Chemie AG, Buchs, Switzerland). The results represent the mean ± SD of 4 to 13 duplicated bag analyses per time interval expressed as percentage of the initial multivitamin dose.

YM Dupertuis, A Morch, M Fathi, C Sierro, L Genton, UG Kyle and C Pichard. Physical Characteristics of Total Parenteral Nutrition Bags Significantly Affect the Stability of Vitamins C and B1:A Controlled Prospective Study* ***JPEN J Parenter Enteral Nutr*** 2002; 26; 310

Stability & Compatibility

- **C**rystalline **A**mino **A**cid-dextrose solutions generally are stable for 1-2 months if refrigerated at 4°C & protected from light.
- TNA formulations are complex mixtures that are inherently unstable.
- Several factors affect stability of TNA solutions, including pH, electrolyte charges, temperature, & time after compounding.
- US Pharmacopeia 797 standards recommend **storage times of not > 30 hours at controlled room temperature (15°C to 30°C) & not more than 9 days at refrigerated temperatures (2°C to 4°C)** for all medium-risk compounded sterile preparations, including PN solutions.

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Stability & Compatibility (cont'd)

- Because of differences in pH among various CAA products & differences in phospholipid content among lVFE products, specific manufacturers should be consulted for compatibility & stability information prior to routine mixing of components.
- One approach to compounding TNA formulations manually is to first combine CAA, dextrose, & sterile water (if necessary).
- Add electrolytes, vitamins, & trace elements & then **visually inspect solution for precipitate**.

Stability & Compatibility (cont'd)

- Finally, add IVFE & visually inspect solution to ensure uniform emulsion exists.
- But: this specific order & time sequence may not be possible with use of automated compounders.
- PN solutions for neonates & infants tend to have larger calcium & phosphorus amounts, as well as other divalent cations, that limit use of TNA formulations.
- **Use of 2-in-1 formulation** with separate administration of IVFEs is recommended for neonates & infants.

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Stability & Compatibility (cont'd)

- Addition of bicarbonate to acidic PN solutions → carbon dioxide gas & insoluble calcium & magnesium carbonates → **Sodium Bicarbonate use in PN solutions is not recommended (use bicarbonate precursor such as acetate).**
- Because of variable stabilities of individual vitamins, **IV vitamin solutions should be added to PN solution near to time of administration, & should not be in PN solution longer than 24 hours.**
- Peroxide formation in dextrose-amino acid solutions depends on concentration of IV multivitamins, CAA, & dextrose, & presence of IVFEs.

Stability & Compatibility (cont'd)

- Peroxides have negative effects on organ & immune function: e.g., neonatal hypoxic–ischemic encephalopathy, intraventricular hemorrhage, chronic lung disease, retinopathy of prematurity & necrotizing enterocolitis.
- **Protecting PN & IVFE solutions from light is recommended** to minimize peroxide formation.

Stability & Compatibility (cont'd)

- Compatibility of IV medications & other IV solutions is an important concern in delivering safe & effective drug and nutritional therapy.
- IV medications are infused most often as separate admixture piggybacked in PN line.
- **For adding medications directly to PN solution, specific criteria should be considered: dosage regimen should be stable for each 24-hour period & should have pharmacokinetic properties appropriate for continuous infusion.**
- There should be documented chemical & physical compatibility of medication with PN mixture.
- PN regimen should be infused continuously over 24 hours.

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Drug Stability in Parenteral Nutrition

Physical Compatibility of Parenteral Nutrition with mixed Selected Medications via Y-site Administration

Medication	Admixture Type	
	Dextrose-Amino Acids	TNA
Acyclovir 7 mg/mL D5W	I	I
Amikacin 5 mg/mL D5W	C	C
Amphotericin B 0.6 mg/mL D5W	I	I
Ampicillin 20 mg/mL NaCl 0.9%	C	C
Cefazolin 20 mg/mL D5W	I	C
Ceftazidime 40 mg/mL D5W	C	C
Cimetidine 12 mg/mL D5W	C	C
Ciprofloxacin 1 mg/mL D5W	I	C
Cyclosporine 5 mg/mL D5W	I	I
Dopamine 3200 mcg/mL D5W	C	I
Dobutamine 4 mg/mL D5W	C	C

Drug Stability in Parenteral Nutrition

Physical Compatibility of Parenteral Nutrition with mixed Selected Medications via Y-site Administration

Medication	Admixture Type	
	Dextrose-Amino Acids	TNA
Famotidine 2 mg/mL D5W	C	C
Fentanyl 12.5 mcg/mL D5W	C	C
Fentanyl 50 mcg/mL undiluted	C	C
Ganciclovir 20 mg/mL D5W	I	I
Gentamicin 5 mg/mL D5W	C	C
Haloperidol 0.2 mg/mL D5W	C	I
Heparin 100 units/mL undiluted	C	I
Insulin 1 U/mL D5W	C	C
Midazolam 2 mg/mL D5W	I	I
Morphine 1 mg/mL D5W	C	C

Drug Stability in Parenteral Nutrition

Physical Compatibility of Parenteral Nutrition with mixed Selected Medications via Y-site Administration

Medication	Admixture Type	
	Dextrose-Amino Acids	TNA
Morphine 10 mg/mL undiluted	NA	I
Ofloxacin 4 mg/mL D5W	C	C
Ondansetron 1 mg/mL D5W	C	I
Ranitidine 2 mg/mL D5W	C	C
Sodium bicarbonate 1 mEq/mL	I	C
Tacrolimus 1 mg/mL D5W	C	C
Trimethoprim/sulfamethoxazole 0.8/4 mg/mL D5W	C	C
Vancomycin 10 mg/mL D5W	C	C

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Drugs compatible with NuTRIflex Lipid Special after 1 hour contact mixed in 1:1 (v/v) proportions

Drug	Dose	Drug	Dose
Calcium chloride	0.13 mmol/mL Ca	Midazolam	2.5 mg/mL
Cefepime	100 mg/mL	Morphine sulfate	5 mg/mL
Cyclosporine	2.5 mg/mL	Noradrenaline	1 mg/mL
Fentanyl	0.05 mg/mL	Octreotide	25 μg/mL
Furosemide	10 mg/mL	Ondansetron	2 mg/mL
Tropisetron	1 mg/mL	Paracetamol	10 mg/mL
Magnesium sulfate	0.4 mmol/mL Mg	Piperacillin/Tazobactam	80 mg/mL (piperacillin)
Meropenem	50 mg/mL	Potassium phosphate	0.12 mmol/L PO_4
Metoclopramide	5 mg/mL	Tacrolimus	0.1 mg/mL
Metronidazole	5 mg/mL	Vancomycin	10 mg/mL

Composition of NuTRIflex Lipid Special (B.Braun Medical) per 1000 mL: amino acids 57.4 g; Lipids 40 g; glucose 144 g; sodium 54 mmol; potassium 38 mmol; calcium 4.2 mmol; magnesium 4.2 mmol; phosphate 16 mmol; chloride 48 mmol; Acetate 48 mmol; zinc 0.03 mmol.

S. Muhlebach, "Basics in clinical nutrition: drugs and nutritional admixtures," *e-SPEN Journal*, vol. 4, no. 3, pp. e134–e136, 2009.

Should Insulin be added to Parenteral Nutrition?

Insulin Indications for PN

- Manage hyperglycemia
- Protein accretion (anabolism)
- Anti-inflammatory activity

Insulin in PN

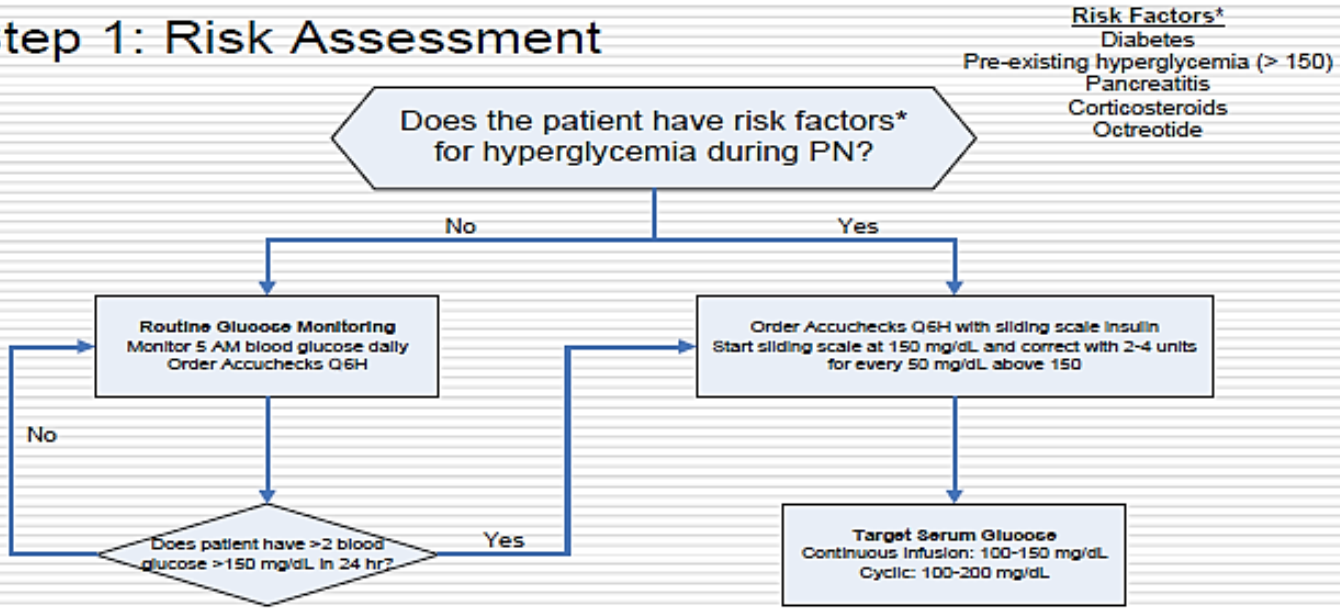
- Criteria for medications added to PN
- Stable and compatible
- Evidence supports clinical value of medication administered in PN
- Frequency of dosage adjustment no more than every 24 hours
- Insulin is associated with frequent harmful events in PN

Evidence Supporting Insulin Use: Insulin protocol

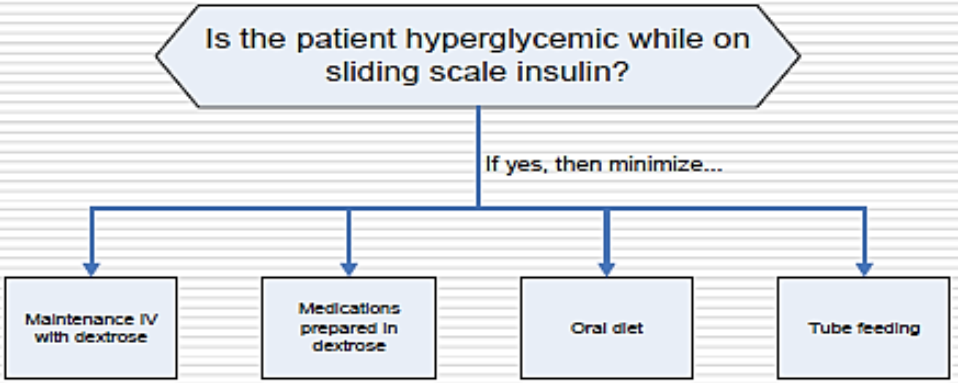
- NSS: primarily pharmacist
- Capillary Blood glucose (CBG) every 6 hrs
  - Criteria: glucose > 140 mg/dl
- Insulin dose per g Carbohydrate (CHO)
  - PN induced hyperglycemia
    - 1 U/20 g CHO
- Diabetes/glucocorticoids
  - CBG <11.1 mmol/L (200 mg/dl)
    - 1 U/10 g CHO + 0.15 U/kg/d
  - CBC > 11.1 mmol/L
    - 1 U/5 g CHO + 0.25 U/kg/d
- 2/3 insulin dose in PN, 1/3 separate as long-acting insulin

Algorithm – Steps 1 and 2

Step 1: Risk Assessment

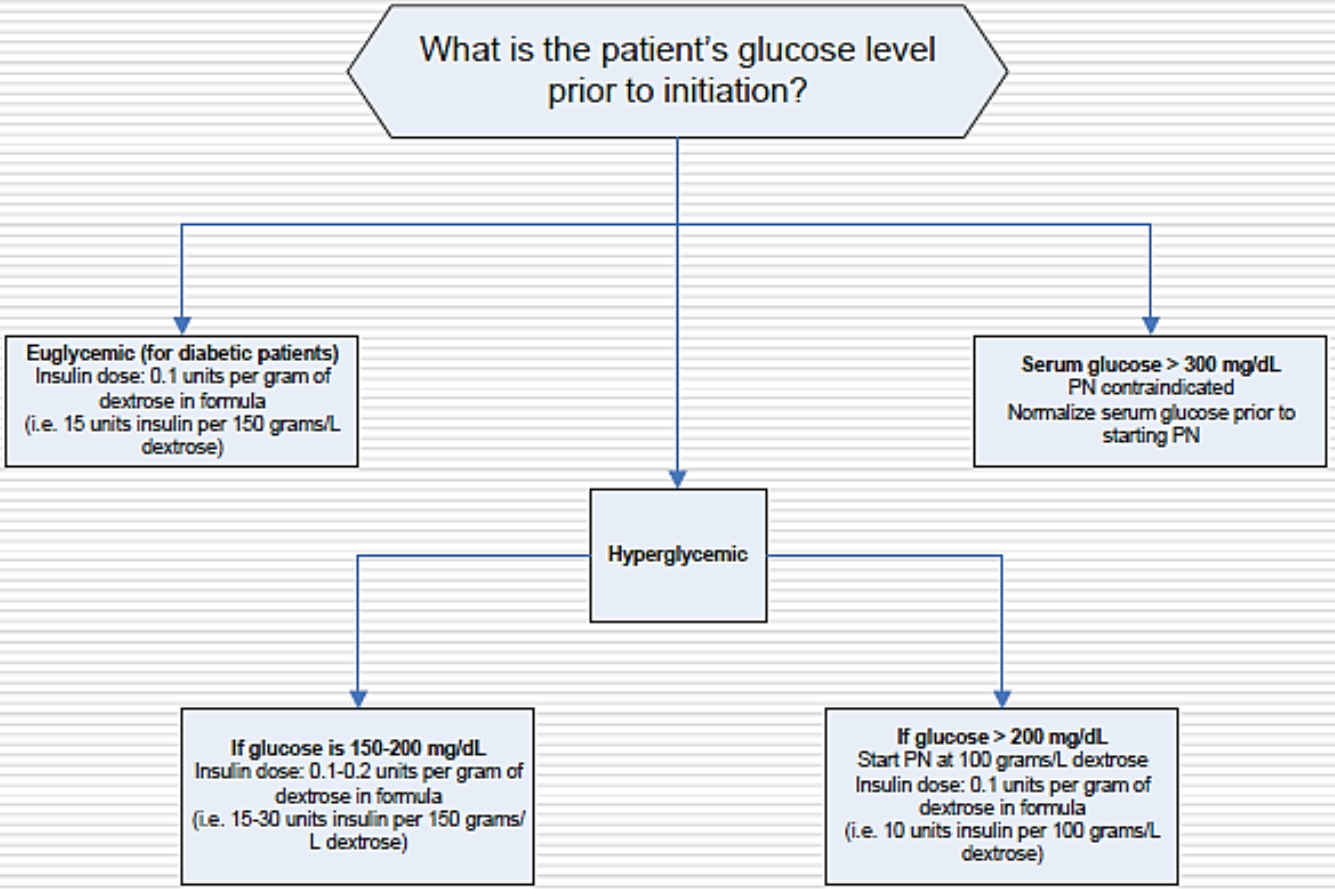


Step 2: Minimize glucose from other sources



Glucose Algorithm – Step 3

Step 3: Adding insulin into PN



Summary

- The use of insulin in PN is a controversial topic
- Primary indication: hyperglycemia associated with PN
- Original issues with bioavailability from PN
- Little evidence evaluating outcomes of insulin use in PN
- Considerable variability in types of patients and PN practices

Thank you for your attention

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