The Lennard-Jones
Intestinal Failure Unit

St MARK'S
HOSPITAL

Formulating a PN Prescription

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Case

17 year old male

Date	Age	Problem
1997		Congenital myasthenia syndrome
1997	10 days	Tracheostomy on BiPAP
1998	8 months	Gastrostomy insertion (later removed)
2002	5 years	Nissen Fundoplication
2009	12 years	Adhesiolysis (small bowel obstruction)
2012	14 years	Adhesiolysis (small bowel obstruction)
Jan 2014	16 years	Correction of scoliosis
June 2015	17 years	SB resection due to obstruction from volvulus leaving 40cm from DJ flexure with 280cm of distal bowel to colon

Multichamber bag

	Volume (ml)	N (g)	Energy (kcal)	Na (mmol)	K (mmol)	Ca (mmol)	Mg (mmol)	PO_4 (mmol)
Kabiven 9	2400	9	1500	53	40	3.3	6.7	18
Additrace	1 vial							
Solivito	1 vial							
Vitlipid	1 vial							
Requirements	**3000**	**9.3**	**1750**	**207**	**31-47**	**3.1-4.7**	**3.1-6.2**	**12**
Prescription	2430	9	1500	53	40	3.3	6.7	18

Inadequate energy	• Monitor weight, anthropometrics and oral diet
Inadequate fluid & sodium	• Request additions to the bag • Run additional saline
Too much phosphate	• Monitor blood concentrations

How to provide this regimen?

- Difficult to provide from MCB
- High fluid / electrolyte requirements
- Lipid free bags
- PN needs to be tailored to individual requirements
- Depends on pharmacy compounding facilities

Tailored/Scratch bags

- Depends on compounding facilities/cost/storage
- Use when ‘all-in-one’ does not fit:
  - ↓ Fluid/ electrolyte requirements e.g. renal
  - ↑ Fluid/ electrolyte requirement e.g. high output stoma/fistula
- More flexibility with amounts but still limited by product selection:
  - Lipids available in 250 & 500ml bottles (550-1000kcal)
  - Nitrogen set amounts

Formulating a PN prescription

- Choose the amino acid solution
- Choose the glucose solution
- Choose the lipid emulsion
- Electrolytes (min & max)
- Vitamins and trace elements
- Volume

Amino acids/nitrogen

- Wide range of solutions available
- Variable nitrogen content
  - Some contain electrolytes
- Differing ratio of essential & non-essential amino acids
- Type of solution used can impact stability

Glutamine

- Most abundant amino acid in the body
- Main source is skeletal muscle (>60%) evidence of depletion during stress
- Major fuel for rapidly proliferating tissues, e.g. enterocytes & immune cells
- Precursor for glutathione (antioxidant)
- Substrate for renal ammonia production (regulation of acid-base balance)
- ‘Conditionally essential’ in times of injury and sepsis
- Safe IV dose 0.28-0.57g/kg/d

Glutamine in HPN

To determine if the inclusion of 10 g of glutamine in HPN reduces infectious complications

Methods

- RCT (crossover)
- 35 HPN patients
- Patients given 0.14g/kg/day

Results

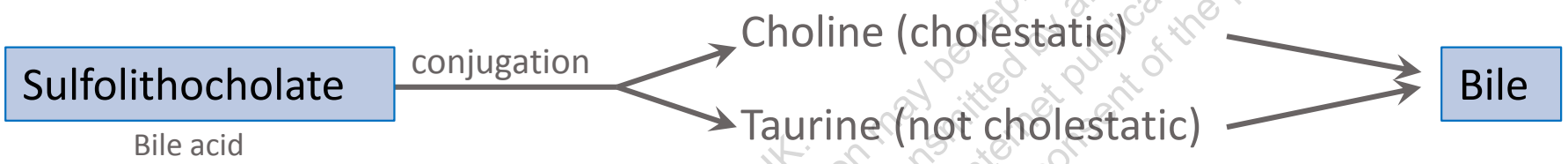
- No difference in infective complications
- No change in intestinal permeability
- No difference in plasma glutamine concentrations

Conclusion

- Glutamine is safe but no effect on infective complications over 6 months

Culkin *et al* (2008) *Eur J Clin Nutr*, **62,** 575

Taurine



Deficiency

- Shown to occur in patients with short bowel
- Do not reabsorb bile acids normally
- ↑ losses of taurine conjugates of bile acids

Correcting the deficiency

- Children: LFTs improve[1]
- Adults: Plasma concentrations restored with 10mg/kg/d[2]

1. Heird *et al*, 1987, *Pediatrics,* 80:401. 2. Kopple *et al,* 1990, *Am J Clin Nutr*. 52:846

Taurine in HPN

To determine if the inclusion of IV taurine in HPN improves abnormal LFTs

Methods

- RCT (crossover)
- Patients with chronic cholestasis given 16mg/kg/d
- 11 patients completed both arms

Results

- No change in LFTs
- No adverse events
- 90% taurine deplete & plasma concentration restored after IV supplementation

Conclusion

- Taurine is safe but no effect on LFTs over 3 months

Culkin *et al* (2009) Proc Nut Soc, 69: OCE2, E167

ESPEN guidelines: Nitrogen

	Grade of evidence	Strength of recommendation
Do not suggest the routine addition of amino acids glutamine, cysteine or taurine in the PN to decrease complications in adults HPN	Low	Weak

Pironi *et al* (2016) *Clin Nutr*; 35: 247

Choose a nitrogen source

	Volume (ml)	N (g)	Energy (kcal)	Na (mmol)	K (mmol)	Ca (mmol)	Mg (mmol)	PO_4 (mmol)
Vamin 18EF	500	9						
Requirements	3000	9.3	1250	207	31-47	3.1-4.7	3.1-6.2	12
Total (so far)	500	9	0	0	0	0	0	0

Carbohydrate

- Glucose
- Cheap
- Range of concentrations (5-70%)
- Initiation of PN – use glucose oxidation rate (GOR) as a guide

$$\frac{4\text{-}7\text{mg} \times \text{kg} \times 60\text{min} \times 24\text{hr}}{1000} = \text{g of glucose}$$

- Can exceed GOR if normal blood glucose, liver function is reasonable and patient metabolically stable

Wolfe *et al* 1979 *Metabolism*, 28:210

Choose a glucose source

	Volume (ml)	N (g)	Energy (kcal)	Na (mmol)	K (mmol)	Ca (mmol)	Mg (mmol)	PO_4 (mmol)
Vamin 18EF	500	9						
Glucose 10%	500		200					
Glucose 40%	500		800					
Requirements	3000	9.3	1250	207	31-47	3.1-4.7	3.1-6.2	12
Total (so far)	1500	9	1000	0	0	0	0	0

Lipids

- **10-30% emulsions – energy dense & isotonic**
- **Expensive**
  - Do not split bottles
- **Reduced respiratory quotient (RQ)**
  - 0.7 (CO_2 eliminated / O_2 consumed)
- **Less risk of refeeding**

Evolution of parenteral lipid emulsions

Generation	Description	Lipid types	Brands
1st	Conventional lipid	LCT (soybean oil) LCT (soy/safflower oil)	Intralipid
2nd	Lipid emulsions with reduced PUFA	Structured lipids (MCT/LCT) Olive oil based emulsion	Structolipid Clinoleic
3rd	Lipid emulsions with reduced PUFA & specific ω6/ω3 FA ratio	Fish oil Soy/MCT/olive oil/fish oil	Omegaven SMOF

ASPEN: Clinical role for alternative intravenous fat emulsions (2012) *Nut Clin Pract*; 27: 150-192. Waitzberg D *et al* (2006) *JPEN;* 30: 351-367

Lipid emulsions in PN

Which one should we use?

Strength of evidence

Critical appraisal

ESPEN support the use of olive and fish oil in ICU[1]

Recent review: Very little high quality evidence that fish oils have a more beneficial effect on clinical outcomes[2]

1 Calder *et al* (2017) *Clin Nutr* Pub ahead of print. 2 Abbasoglu *et al* (2017) *JPEN*, Pub ahead of print

Evidence base in ICU

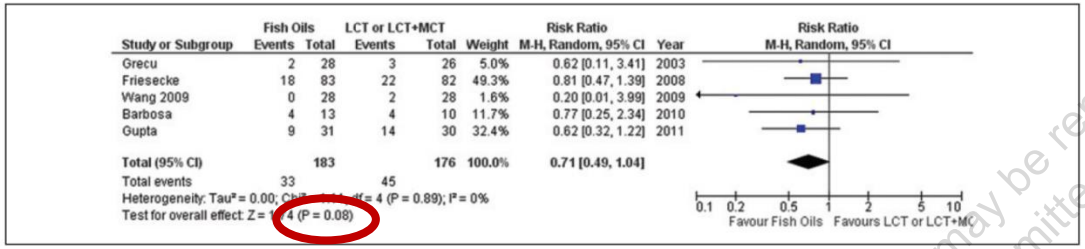


Figure 1. Effects of fish oil lipid emulsion strategies on mortality (n = 5). CI, confidence interval; LCT, long-chain triglyceride; MCT, medium-chain triglyceride.

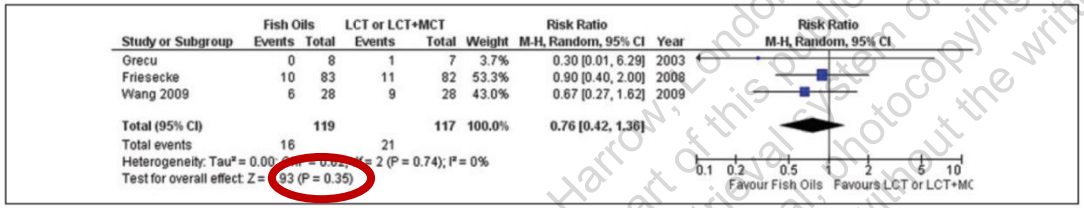


Figure 2. Effects of parenteral fish oil lipid emulsions on infections (n = 3). CI, confidence interval; LCT, long-chain triglyceride; MCT, medium-chain triglyceride.

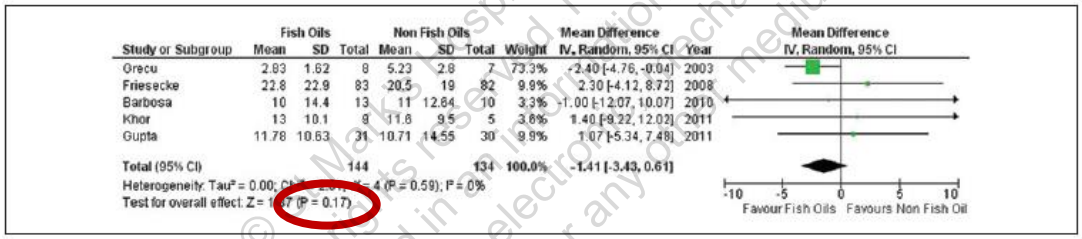


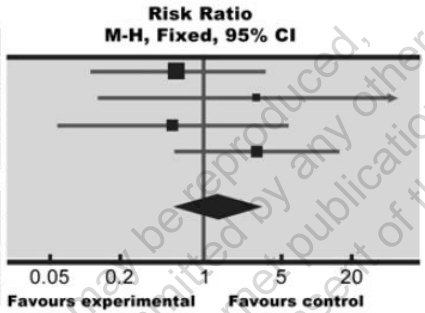
Figure 3. Effects of parenteral fish oil lipid emulsions on ventilation days (n = 5). CI, confidence interval.

No difference in mortality, infectious complications or ventilator days

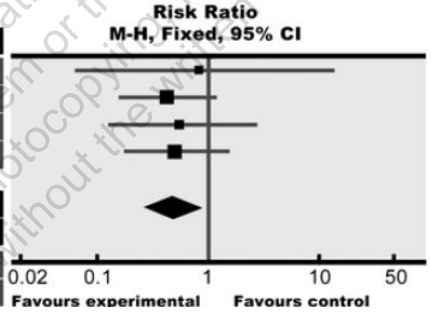
Manzanares *et al* (2015) *Crit Care*;19:167

Evidence base in surgery

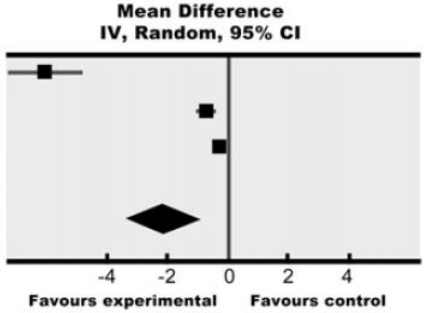
Study or Subgroup	Fish Oil Events	Fish Oil Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Grecu I 2003	2	28	3	26	41.7%	0.62 [0.11, 3.41]
Jiang ZM 2004	1	101	0	103	6.6%	3.06 [0.13, 74.21]
Kelbel I 2002	1	14	2	16	25.0%	0.57 [0.06, 5.65]
Wichmann 2007	6	127	2	129	26.6%	3.05 [0.63, 14.82]
Total (95% CI)		**270**		**274**	**100.0%**	**1.42 [0.57, 3.53]**
Total events	**10**		**7**			
Heterogeneity: Chi^2 = 2.63, df = 3 (p = 0.45); I^2 = 0%						
Test for overall effect: z = 0.75 (P = 0.46)						



Study or Subgroup	Fish Oil Events	Fish Oil Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Heller AR 2004	1	24	1	20	4.1%	0.83 [0.06,12.49]
Jiang ZM 2004	5	101	12	103	44.6%	0.42 [0.16, 1.16]
Keibel I 2002	2	14	4	16	14.0%	0.57 [0.12, 2.66]
Wichmann 2007	5	127	10	129	37.3%	0.51 [0.18, 1.44]
Total (95% CI)		**266**		**268**	**100.0%**	**0.49 [0.26, 0.93]**
Total events	**13**		**27**			
Heterogeneity: Chi^2 = 0.27, df = 3 (p = 0.97); I^2 = 0%						
Test for overall effect: z = 2.18 (P = 0.03)						



Study or Subgroup	Fish Oil Mean	Fish Oil SD	Fish Oil Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Grecu I 2003	3	1	28	9	3	26	28.5%	-6.00 [-7.21, -4.79]
Berger MM 2008	1.6	0.4	12	2.3	0.4	12	35.5%	-0.70 [-1.02, -0.38]
Heller AR 2004	4.3	0.29	24	4.6	0.36	20	36.0%	-0.30 [-0.50, -0.10]
Total (95% CI)			**64**			**58**	**100.0%**	**-2.07[-3.47, -0.67]**
Heterogeneity: Tau^2 = 1.41; Chi^2 = 84.70, df = 2(p < 0.00001); I^2 = 98%								
Test for overall effect: z = 2.89 (P = 0.004)								



No difference in mortality.
Reduction in infectious complications & ICU days

Wei *et al* (2010) *Nutrition*;26:474-81

Systematic review: Lipids in HPN

Summary of results from the three included studies.

Reference	Study details	IVLEs used	Liver function tests	Inflammation and peroxidation indices	Clinical outcomes
Rubin et al., 2000 [13]	RCT, adults, n = 22, 4 weeks	SO vs structured SO-MCT	SO: ALP, ALT, AST & γ-GT abnormal in 2 patients	Similar lipid peroxidation	Similar clinical safety and AEs (Vomiting n = 5 for SO-MCT, n = 4 for SO).
Vahedi et al., 2005 [15]	RCT, adults, n = 13, 3 months	SO vs OO-SO	No differences	No change or difference in C-reactive protein	Similar AEs
Klek et al., 2013 [14]	RCT, adults, n = 75, 4 weeks	SO vs SMOF	Normal but ALT, AST & total bilirubin lower with SMOF (p = 0.049, 0.027 and 0.043)	Increase in serum α-tocopherol with SMOF (p < 0.05) No change or difference in IL-6, sTNF-RII or C-reactive protein	Serious AEs more frequent with SO (p = 0.03)

ALP = alkaline phosphatase, γ-GT = gamma glutamyl transpeptidase, AST = aspartate transaminase, IL-6 = interleukin-6, sTNF-RII = soluble tumour necrosis factor receptor II.

Conclusion: There may be benefits in using alternative lipids rather than pure soya oil in adults on HPN, but there are currently too few RCTs to reach a firm conclusion

Jones & Calder 2016 *Clin Nutr* In press http://dx.doi.org/10.1016/j.clnu.2016.12.026

Choose a lipid source

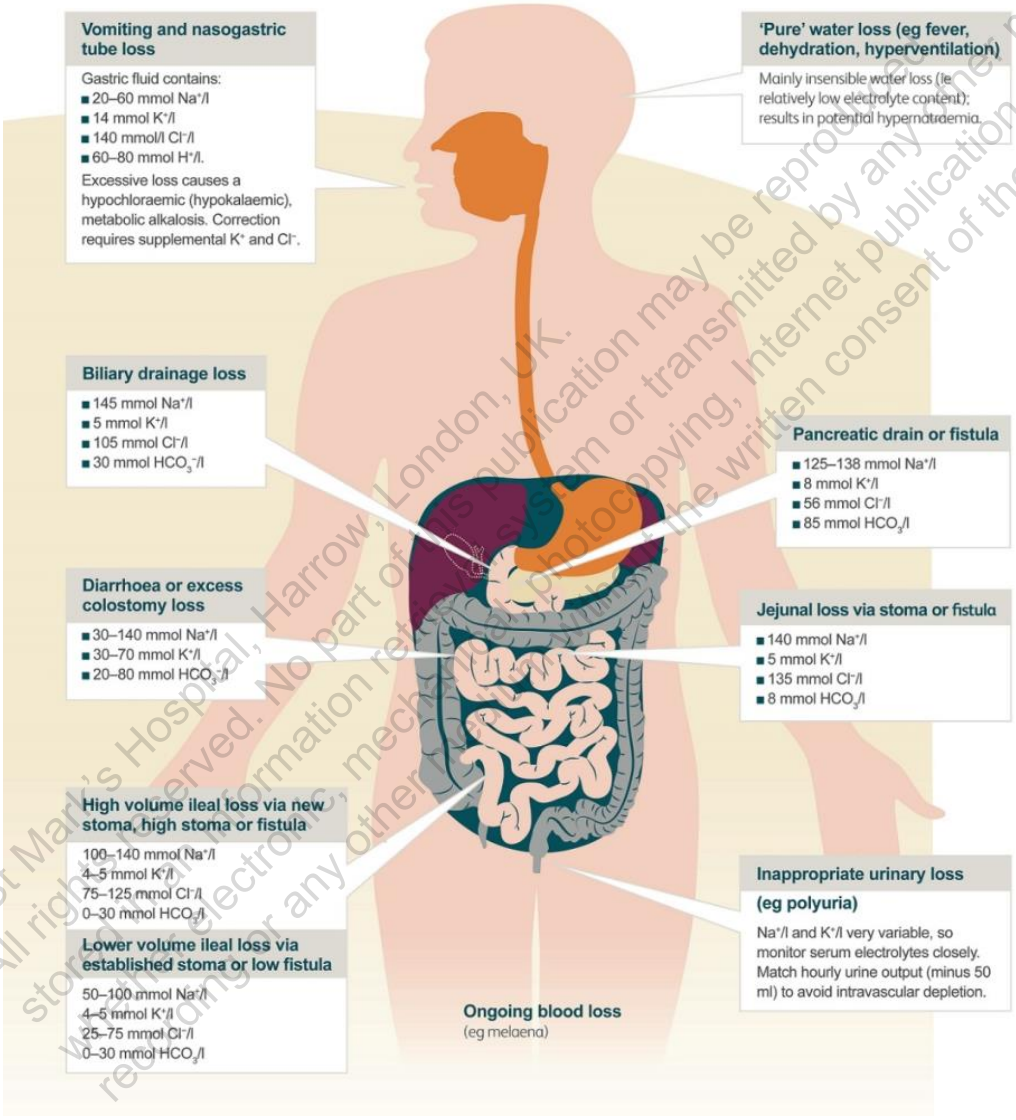
	Volume (ml)	N (g)	Energy (kcal)	Na (mmol)	K (mmol)	Ca (mmol)	Mg (mmol)	PO_4 (mmol)
Vamin 18EF	500	9						
Glucose 10%	500		200					
Glucose 40%	500		800					
SMOF Lipid 20%	500		1000					7.5*
Requirements	3000	9.3	1250	207	31-47	3.1-4.7	3.1-6.2	12
Total (so far)	2000	9	2000	0	0	0	0	0

* Not thought to be metabolically available

Electrolytes

Requirements	Losses	Other			
Sodium Potassium Calcium Magnesium Phosphate	Sodium Potassium Magnesium	Re-feeding	Renal function	Medication	Stability

Right fluid for losses



NICE 2013 IV Fluid therapy in adults in hospital

Electrolytes & fluid

	Volume (ml)	Nitrogen (g)	Energy (Kcal)	Na (mmol)	K (mmol)	Ca (mmol)	Mg (mmol)	PO4 (mmol)
Vamin 18EF	500	9						
Glucose 10%	500		200					
Glucose 40%	500		800					
Water	1000							
SMOF Lipid 20%	500		1000					7.5*
Sodium chloride 0.9%	500			77				
Sodium chloride 30%	18			92				
Potassium chloride 15%	30				60			
Calcium Chloride 1mmol/ml	5					5		
Magnesium sulphate 50%	3						6	
Sodium glycerophosphate 21.6%	15			30				15
Requirement	3000	9.3	1250	207	31-47	3.1-4.7	3.1-6.2	12
Total	3571	9	2000	199	60	5	6	22.5*

* 7.5 from lipid not thought to be metabolically available

Vitamins & trace elements

- Requirements are different to oral/enteral
- Assess patients individually
- Large amounts needed in short bowel (selenium/zinc)
- Use standard preparations in fixed doses but adjust if:
  - Deficiency (acute/chronic)
  - Toxicity (acute/chronic)
  - Effect of acute phase response on requirements / plasma concentrations(CRP <20 for accurate interpretation)

Shenkin (2001) *Clin Nutr*, 20:47, Fuhrman (2006) *Nut Clin Pract*, 21:566, Hardy *et al* (2009) *Nutrition*, 25:1073

Micronutrients: effect of inflammatory response

CRP	Interpretation
<15mg/L	Reliable
15-50mg/L	Unlikely to be reliable
>50mg/L	No value

Duncan *et al* (2012) *Am J Clin Nutr*, 95:64 www.trace-elements.co.uk

Vitamins

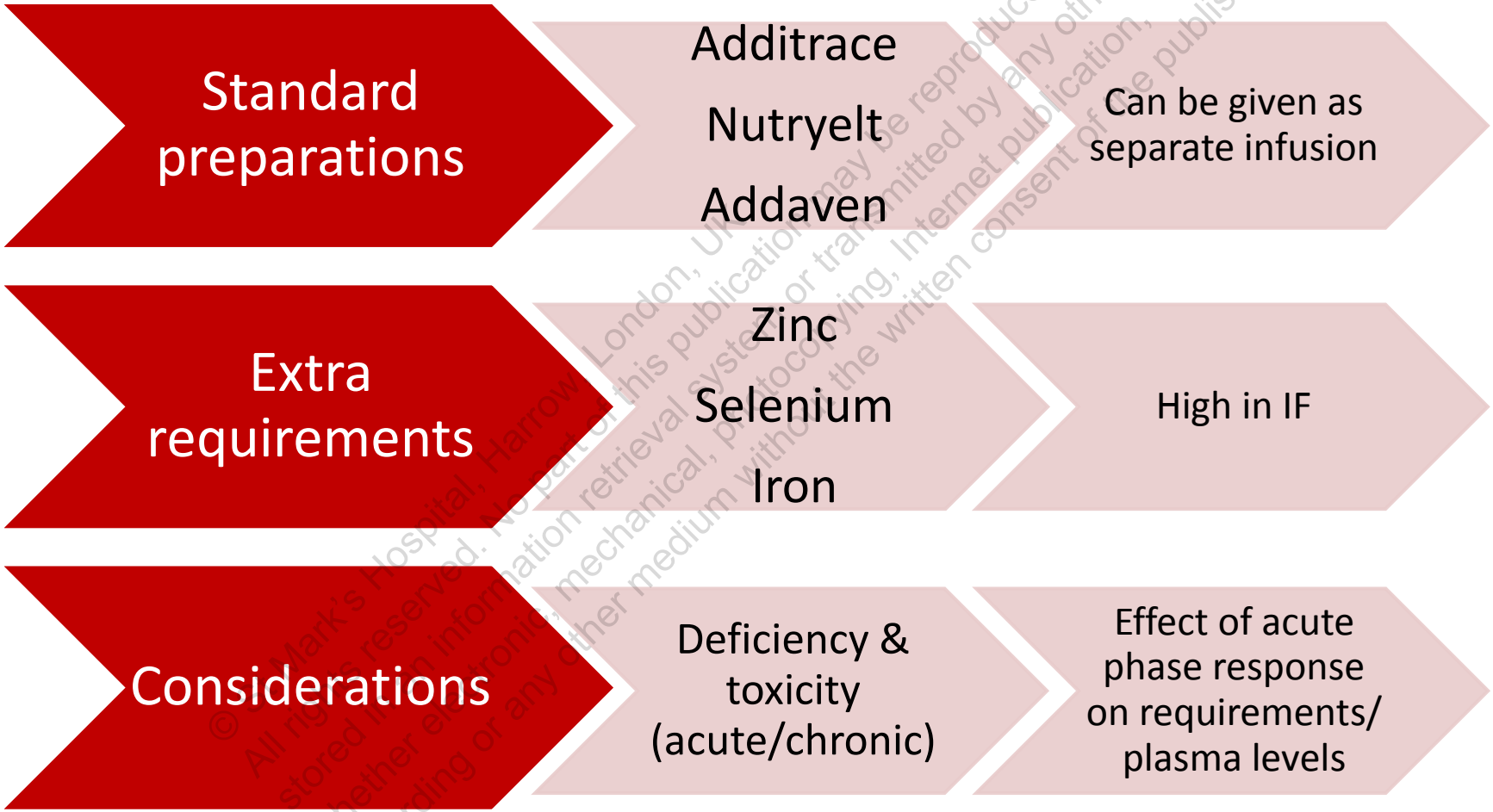
Standard preparations	Solivito N Vitlipid Adult Cernevit	Can be given as separate infusion
Extra requirements	Vitamin D Vitamin B_{12} Folic acid	Degradation during storage
Considerations	Deficiency & toxicity (acute/chronic)	Effect of acute phase response on requirements/ plasma levels

Vitamins in PN

	ASPEN Guidelines[1]	Solivito N + Vitlipid Adult	Cernevit
Vitamin A (IU)	3300	3300	3500
Vitamin B1 (mg)	6	2.5	3.5
Vitamin B2 (mg)	3.6	3.6	4.1
Vitamin B3 (mg)	40	40	46
Vitamin B5 (mg)	15	15	17.3
Vitamin B6 (mg)	6	4	4.5
Vitamin B12 (µg)	5	5	6
Vitamin C (mg)	200	100	125
Vitamin D (IU)	200	200	220
Vitamin E (IU)	10	10	11.2
Vitamin K (µg)	150	150	0
Folate (µg)	600	400	414
Biotin (µg)	60	60	69

1 Vanek *et al* (2012) *Nutr Clin Pract*, 27:440.

Trace elements



Shenkin (2001) *Clin Nutr*, 20:47, Fuhrman (2006) *Nut Clin Pract*, 21:566, Hardy et al (2009) *Nutrition*, 25:1073

Trace elements

Element	ASPEN guidelines[1]	Additrace	Nutryelt	Addaven*
Zinc (µg)	250-500	650	1000	500
Selenium (µg)	60-100	32	70	79
Copper (µg)	300-500	1240	300	380
Manganese (µg)	55	275	55	55
Chromium (µg)	10-15	10	10	10
Molybdenum (µg)	Not added	19	20	19
Iron (µg)	Not added	1100	1000	1100
Iodine (µg)	Not added	130	130	130
Fluorine (µg)	Not added	950	950	950

* Not licensed in the UK

1 Vanek *et al* (2012) *Nutr Clin Pract*, 27:440

Micronutrient deficiencies

Prevalence	• High in short bowel & HPN[1,2]
Causes	• Underlying condition • Increased intestinal losses • Inadequate provision
Prevention & treatment	• Important to provide adequate micronutrients when weaning off HPN[3]
Monitoring	• Lack of reliable biochemical assays especially during acute phase[4]
AGA guidelines	• Observe for clinical manifestation of deficiencies & regular monitoring[5]

1. Braga *et al* (2011) *JPEN,*35:493, 2. Buchman *et al* (2009) *Gastroenterology,* 137,5 Suppl:S1. 3. DiBiase *et al* (2006), *J Clin Gastroenterol*, 40,S94. 4. Duncan *et al* (2012) *Am J Clin Nutr*, 95:64. 5. Buchman *et al* (2003) *Gastroenterology.* 124:1111

Our lipid PN Regimen (2/7)

	Volume (ml)	Nitrogen (g)	Energy (Kcal)	Na (mmol)	K (mmol)	Ca (mmol)	Mg (mmol)	PO4 (mmol)
Vamin 18EF	500	9						
Glucose 10%	500		200					
Glucose 40%	500		800					
Water	1000							
SMOF Lipid 20%	500		1000					7.5*
Sodium chloride 0.9%	500			77				
Sodium chloride 30%	18			92				
Potassium chloride 15%	30				60			
Calcium Chloride 1mmol/ml	5					5		
Magnesium sulphate 50%	3						6	
Sodium glycerophosphate 21.6%	15			30				15
Additrace	10							
Cernevit	5							
Requirement	3000	9.3	1250	207	31-47	3.1-4.7	3.1-6.2	12
Total	3586	9	2000	199	60	5	6	22.5

Our aqueous PN Regimen (5/7)

	Volume (ml)	Nitrogen (g)	Energy (Kcal)	Na (mmol)	K (mmol)	Ca (mmol)	Mg (mmol)	PO4 (mmol)
Vamin 18EF	500	9						
Glucose 50%	500		1000					
Water	1000							
Sodium chloride 0.9%	1000			154				
Sodium chloride 30%	3			15				
Potassium chloride 15%	30				60			
Calcium Chloride 1mmol/ml	5					5		
Magnesium sulphate 50%	3						6	
Sodium glycerophosphate 21.6%	15			30				15
Additrace	10							
Cernevit	5							
Requirement	3000	9.3	1250	207	31-47	3.1-4.7	3.1-6.2	12
Total	3071	9	1000	199	60	5	6	15

Summary

Formulate a PN prescription to meet requirements

More robust RCT regarding lipid emulsions

Micronutrients essential

Stability

- Important to have a basic knowledge of stability
- Important to be aware of restrictions
- Every PN bag requires a stability check before administration
- Patient safety is paramount

Basic stability

- Complex solutions with >50 chemical components
- Environment, storage time and container can also affect stability
- Main risks:
  - Calcium/phosphate interaction
  - Lipid
  - Electrolytes
  - Trace elements
  - Vitamins

Stability

Ca & Phosphate

- Factors affecting this:
- Calcium salt
- Phosphate salt
- Temperature
- Other PN components (amino acid and magnesium)
- Mixing order
- Risk:
  - Catheter occlusion
  - Pulmonary deposition of calcium phosphate crystals

Lipid

- Electrolyte and trace element concentrations
- Volume
- Amino acid composition (balance, pH)
- Glucose concentration (pH and viscosity)
- Buffering agents (PO4, acetate)
- Lipid emulsion composition
- Light
- Temperature & storage/delivery times

Electrolyte

- Maximum values that can be added are available from manufacturers
- Related to lipid stability and reactivity between species
- Higher electrolyte content in an aqueous bag than a lipid containing bag

Trace element

- Particularly a problem with Vamin® amino acid solutions
- Cysteine interacts with copper to form copper sulphide precipitate
- Additions e.g. Zinc, Selenium, Iron

Vitamin

- Vitamins degrade within hours of addition to PN mixture
- Need to protect from light and oxygen
- Oxidation can be reduced by using multilayer bags and removing air from the bag after filling
- Use light protection bags
- What about protecting the giving sets?