Albumin

1. plasma ***oncotic pressure***
2. maintenance of ***vascular volume***
3. regulation of ***endothelial permeability***
4. drug binding
   - phenytoin
   - warfarin
   - phenylbutazone
5. toxin binding
   - free Hb, Fe^{++}, bilirubin
   - arachidonic acid
6. free radical scavenger - O_2 radicals
7. transport
   - FFA
   - hormones, trace elements
   - enzymes, lysosomes
8. heparin-like activity - enhances inhibition of Xa by AT-III
9. inhibition of platelet aggregation
10. gastrointestinal absorptive function
11. longer $t_{½\beta}$ than synthetic colloids

- problems associated with ***hypoalbuminaemia*** in critically ill patients,
  a. decreased oncotic pressure & increased oedema formation
  b. increased endothelial permeability
  c. increased incidence of diarrhoea, decreased tolerance of enteral feeding
  d. ? increased coagulopathy
  e. ? increased damage from ischaemia, reperfusion injury etc.
  f. toxicity
     - drugs
     - bilirubin, free Hb, etc.

- ***problems*** with giving albumin (NSA-5%/20%)
  1. increased blood volume, fluid overload
  2. anaphylactoid responses - less with NSA than with SPPS
  3. expensive as a colloid
  4. salt loading with NSA
  5. may be rapidly metabolized by the liver in severe catabolic states
  6. not effective as TPN
     i. no essential AA's - valine
     ii. low calorie concentration ~ 250 kcal/l

Assessment & Requirements

a. history and observation - poor sensitivity

b. body weight **> 10%** loss chronically
> 6% loss acutely
- affected by fluid changes acutely
- not indicative of cell mass in ICU patients

c. skeletal muscle
   i. arm circumference
      - false assumptions that arm and arm muscle are circumferential and that bone area is fixed
      - high observer variation
   ii. creatinine:height index
      - high variation in creatinine clearance with age
      - difficulties of 24 hour urine collection
   iii. weight:height ratio
      - high variability, eg. excess water

d. triceps skin-fold thickness

e. visceral protein
   i. albumin
      - poor indicator of early malnutrition
      - long plasma half-life (20 days) and large plasma pool (4-5g/kg)
      - rapid fall in serum levels for multiple reasons (loss, redistribution, catabolism, dilution)
   ii. transferrin, prealbumin, retinol binding protein
      - more accurate reflection of acute changes
   iii. haemoglobin
      - poor indicator (haemorrhage, transfusion, haemolysis)
      - ? reticulocyte percentage

f. immune status
   i. lymphocyte count < 1000/µl (N > 1500/µl)
   ii. delayed hypersensitivity response (TB, Candida)
      - significant reduction in malnourished patients

g. vitamin deficiency
   i. WCC - vit. C
   ii. RBC - B_{12}, folate, Fe^{++}, transketolase
      - less useful in assessment of acute nutritional states

- ***Koretz AJRCCM 1995***

• assumed ***nutritional support*** would improve outcome as,

1. observed association between poor nutritional status and clinical outcome
2. NS improves the markers of malnutrition
3. obvious fact that death will follow an indefinite period of no nutrition
4. retrospective / prospective reports of efficacy
5. perspective that doing something is better than nothing

• however, appealing as these are,

1. ***association*** does not prove causation
   - malnutrition may be a marker of more severe disease, not a cause
2. improvement of markers of nutrition does not necessarily correlate with improved clinical outcome
3. death 2° to malnutrition only occurs in extreme circumstances
4. uncontrolled trials do not support interventional efficacy
5. these abnormalities are a ***natural response*** to injury, preserved by evolution

• most of the clinical trials of NS/PNS ***have not*** been able to demonstrate improved outcome
• conversely, several have shown increased risk of ***infection***, especially in the settings of cancer chemotherapy and surgery
• meta-analysis of perioperative PNS trials have suggested a reduction in perioperative morbidity by 5%

NB: reviewing PRCT's of NS versus no support, concluded "although it is likely NS will not provide dramatic benefit, these trials are inadequate to prove that NS has no benefit at all" ie, possiblity of type II error

• comparative studies of PNS versus ENS have shown with PNS,

1. higher death rate
2. more infective complications

• one study only showed an advantage with PNS, however they used bolus feeds through large bore NG tubes → ? ***aspiration***
• this data could not be reproduced when repeated with continuous, higher density feeds, given through fine bore tubes

- there have also been multiple studies of ***special nutrients***,

1. essential amino acids
   - theoretically, in ***renal failure***, provision would enable synthesis of other AA's from urea and glucose
   - studies are almost impossible to assess due to potential confounding factors
   - EAA's are insulin secretagogues, ∴ trials may be comparing glucose with glucose + insulin
   - small benefit was possible in the subgroup requiring dialysis
2. branched chain AA's
   - theoretical advantage in patients with liver failure
   - no differences with respect to ***survival***
   - BCAA group showed some improvement in ***encephalopathy***
   - however, not clear if this is due to "nutritional" aspects, or due to potential blockade of CNS uptake of toxic substances
   - if the later, then BCAA's are very expensive cf. standard R_X of encephalopathy
3. glutamine
   - may be an important intestinal "growth factor"
   - PNS results in GIT mucosal atrophy, ∴ may predispose to ***bacterial translocation***
   - 2 PRCTs compared TPN ± glutamine → no difference in ***survival***
4. ω-3 fatty acids | arginine | RNA ("Impact", Sandoz)
   - some experimental evidence these agents may improve ***immunological function***
   - comparative study → no difference in infection, wound complication
   - other workers have shown a trend toward shorter hospitalisation

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NB: NS products ***do not*** have to meet FDA criteria as medications, ie. demonstrated efficacy in PRCT's, as they are marketed as foods; these are now being altered to contain disease specific 'nutrients'.

Recommendations

1. there are insufficient data to recommend NS as a standard therapy in ICU
2. PRCT's appear to suggest that 1-2 weeks of no NS is ***not*** going to be harmful
   - there is no substantial evidence that nutritional "repletion", or even "prophylaxis", during this period has been beneficial
3. enteral support is probably superior to PNS
4. there may be some advantage to therapeutic feeds, but the present data are inconclusive

"Complications" of Malnutrition

1. poor wound healing
2. immune function depression
3. reduced enzyme synthesis
4. prolonged catabolism
5. increased morbidity & ? mortality
6. intolerance of chemotherapy

NB: many of these may be ***associations*** rather than direct complications *per se*

Daily Requirements		
Water	• 30-35	ml/kg/d
Energy	• **30** • 125	**Cal/kg/d** kJ/kg/d
• basal	• 20	Cal/kg/d
Nitrogen[1]	• 0.2	g/kg/d
Amino acid	• 1.5	g/kg/d
• ~ protein	• 1.25	g/kg/d
• minimum	• 0.5	g/kg/d
glucose	• 3.0	g/kg/d
fat	• 2.0	g/kg/d
K^+	• 0.7-1.0	mmol/kg/d
Na^+	• 1.0-2.0	mmol/kg/d
Ca^{++}	• 0.1	mmol/kg/d
Mg^{++}	• 0.1	mmol/kg/d
$PO_4^=$	• 0.4	mmol/kg/d

[1] Synthamin 17 = 17g N_2 / 1000 ml, $\therefore$ 70kg needs ~ 750 ml/d

Basal Metabolic Rate

Def'n: energy expenditure, fasted, in thermoneutral environment, at rest
~ 18-25 kcal/kg/d
~ 75-105 kJ/kg/d

Resting Energy Expenditure ~ **30 kcal/kg/d**
~ BMR + 10%

- ***Physiological Factors***

a. size, weight, surface area

b. exercise, sleep-wake cycle, work level

c. pregnancy

d. ***specific dynamic action*** of food
   - fat ~ 4 kcal/100 kcal
   - CHO ~ 6 kcal%
   - protein ~ 30 kcal%

e. climate

- ***Pathological Factors***

a. body temperature ~ ↑ 12% per °C > 37
~ 500 kcal/day/°C

b. severe catabolic states ~ 40-55 kcal/kg/day

c. thyroid status

d. renal failure

e. liver failure

Carbohydrate

- ***Energy Substrate***

  a. calorimetry
     - i. *in vitro* ~ 4.182 kcal/g
     - ii. *d*-glucose **~ 3.75** **kcal/g** *in vivo*
       - 500 ml 50% = 250 g ~ 950 kcal
       - 1000 ml 5% = 50 g ~ 200 kcal

  b. SDA ~ 6.0 kcal%

  c. RQ ~ 1.0

- ***Functions***

  a. energy substrate for ***all cells***

  b. protein sparing ~ 30-50g / gram of nitrogen > 100 g/d

  c. prevention of ketosis

  d. lipogenesis
     - 1g glucose → ↓ 45 ml O_2 / ↑ 250 ml CO_2
     - high infusion rates ↑ lipogenesis & CO_2 production

- ***Complications 50% Dextrose***

  a. ***dextrose*** content
     - i. hyperglycaemia - problems of hyperosmolality
     - ii. hypokalaemia, hypophosphataemia
     - iii. rebound hypoglycaemia 2° insulin overshoot

  b. ***hypertonic*** solution
     - i. hyperosmolar syndrome ~ 1250 mosm/l (4.3x)
     - ii. osmotic diuresis - loss of Na^+/H_2O
     - iii. thrombosis - hyperosmolar & acidic state

  c. excess dextrose conversion to ***triglyceride***
     - i. lipogenesis
     - ii. insulin increase - further lipogenesis
     - iii. ↑ CO_2 production |
     - iv. excess hepatic fat deposition | > 5-7 g/kg/min
     - v. elevation of liver enzymes & conjugated bilirubin

  NB: → ***"TPN - hepatitis"***

- effects of high glucose intake on trauma patients,
  a. mild hyperglycaemia is maintained
  b. ↑ oxidative & non-oxidative glucose metabolism
  c. ↑ glycogen deposition
  d. gluconeogenesis from protein suppressed at > 400 g/day, or
     > 4 mg/kg/min

Def'n: ***Maillard reaction:*** glycosylation of amino-acids in TPN solution during autoclaving

Amadori reaction: rearrangement of glycosamino derivative to an aminodeoxyketose; the ***Browning reaction*** then converts this to polymers

Lipids

- ***Energy Substrate***

  a. Energy ~ 9.3 kcal/g
  b. SDA: ~ 4.0 kcal%
  c. RQ: ~ 0.7

- ***Benefits***

  a. high caloric source
  b. essential fatty acid supply * ***linoleic & linolenic acids***
  c. fat soluble vitamin (ADEK) supply
  d. less O_2 utilization and CO_2 production cf. CHO
  e. ***not*** as effective as CHO in protein sparing

  NB: only required for provision of essential AA's, no advantage of dextrose (LIGW)

- ***Intralipid***

  a. soyabean oil derivative - 10% = 100 g/l
     - 20% = 200 g/l
  b. other constituents - 1.2% egg yolk phospholipid
     - 2.5% glycerol
  c. chylomicron sized emulsion
  d. energy value ~ 1 kcal/ml (10%)
     ~ 2 kcal/ml (20%)

- ***Contraindications***

  a. relative
     i. hepatocellular disease
     ii. acute pancreatitis
  b. absolute
     i. hyperlipidaemia
     ii. egg yolk/soyabean allergy

- ***Complications***

1. hyperlipidaemia
2. pancreatitis
3. ***"fat overload syndrome"***
   - i. fever
   - ii. hyperlipidaemia
   - iii. GIT disturbance
   - iv. hepatosplenomegaly, liver dysfunction
   - v. anaemia, coagulopathy, thrombocytopaenia
4. immunological depression
   - ↓ PMN chemotaxis and phagocytosis
   - ↓ RES function
   - enhanced bacterial virulence
5. cardiovascular
   - sinus bradycardia
   - hypoxaemia
   - Warfarin resistance
6. hypersensitivity reactions
7. "cracking" of emulsion - heat, incompatible mixing
8. CVC catheter complications

- ***Medium Chain Triglycerides C_6-C_{10}***

- proposed advantages,

a. more rapidly oxidized

b. independent of ***carnitine*** transport system (useful for muscle)

c. even chain FA's are ***ketogenic***
   - major substrate for muscle, brain and heart
   - ∴ protein sparing

NB: but ***no*** additional benefits cf. standard lipid infusions

- ***Essential FA Deficiency***

a. ***triene:tetraene*** ratio > 0.4

b. deficiency > 1-3 weeks
   - hepatomegaly, fatty liver
   - dermatitis, alopecia, loss of pigmentation
   - growth retardation

c. requirement → ~ 500 ml Intralipid 10% / week

- ***Carnitine in TPN***

Def'n: a naturally ocurring amino-acid required for mitochondrial β-oxidation of ***long-chain*** fatty acids; acts as an acyl carrier allowing transport across the mitochondrial membrane

a. ↑ protein sparing
   i. stimulates fat metabolism
   ii. stimulates hepatic ***ketogenesis***

b. deficiency may result in,
   i. fatty liver
   ii. cardiomyopathy
   iii. growth retardation

c. reduces acute fatty liver from hypercaloric dextrose infusions

d. levels low in,
   i. premature infants
   ii. long-term TPN

• in the fed state →

↑ ***malonyl-CoA*** → ↓ ***carnitine acyltransferase I*** activity
→ ↓ β-oxidation of long chain fatty acids

• in the starved state →

↑ ***glucagon*** → ↓ formation of ***malonyl-CoA***
→ ↑ β-oxidation

• thus, low levels of malonyl-CoA potentiate FFA oxidation and ketogenesis
• ketosis *per se* will only occur if there is also a reduction in serum ***insulin*** levels

Protein - Amino Acids

- ***Energy Substrate***

a. Energy ~ 5.3 kcal/g
b. SDA ~ 30 kcal%
c. RQ ~ 0.82
d. plasma level ~ 0.3-0.4 mmol/l
e. daily requirements
   i. health ~ 20 g/day
   ii. critically ill ? 50-60 g/day

- ***Catabolic States***

• circulating TNFα, IL-1, catecholamines and glucocorticoids
→ ↑ skeletal muscle catabolism → ~ 40% glutamine & alanine
→ ↑ ***gluconeogenesis***

• formed from transamination reactions involving BCAA's

- ***Complications***

a. uraemia - excess non-essential AA's
   - old racemic mixtures
b. hyperammonaemia - excess ***glycine***
   - CNS toxicity
c. hyperchloraemic acidosis - excess Cl^-
   - pH ~ 6.0
d. acetate toxicity
e. hyperosmolar complications
f. infection
g. CVC line complications

- ***Recommendations TPN***

a. ***l-isomers*** only

b. 40-50% as ***essential*** amino acids

c. protein requirement ~ 1 g/kg/day (R: ~ 0.8-3.0 g/kg/day)
~ 750 ml Synthamin 17/70 kg/day

- base on patient total ***calorie*** requirement
- ***calorie:nitrogen ratio*** ~ **150:1** (R: ~ 135-150:1)
- this ratio minimises oxidation of protein for energy purposes
- if assume,

i. 1.0g protein / 70kg ~ 750 ml Synthamin, or 12g N_2

ii. C:N ratio 150:1 **~ 1800 kcal**

NB: estimations based on urinary N-excretion (1.25 x N_U) show ***poor*** accuracy

- ***Synthamin 17***

a. 16.8g of nitrogen / 1000 ml = 100g (AA)/l
= **10%** solution ~ 0.5 kcal/ml

b. 39% essential AA ~ 40% of TPN calories recommended
- normal requirement ~ 20%
- E/T ratio ~ 2.34

c. 15.5% branched chain AA / 6% aromatic AA

d. osmolality ~ 1300 mosmol/l - with electrolytes
~ 1060 mosmol/l - without (*)

e. pH ~ 6.0

f. ***electrolytes***

Na^+	=	70	mmol/l	(3)
Cl^-	=	70	mmol/l	(40)
K^+	=	60	mmol/l	
Mg^{++}	=	5	mmol/l	
$HPO_4^=$	=	30	mmol/l	
Acetate	=	150	mmol/l	(70)

- ***Essential Amino Acids***

NB: recommended content **~ 40%** of TPN

a. leucine / isoleucine
b. valine
c. methionine
d. threonine
e. tryptophan
f. lysine
g. phenylalanine
h. arginine[§]
i. histidine[§] [§]semi-essential, especially in sepsis / severe illness

- ***Branched Chain Amino Acids***

Def'n: leucine, isoleucine, valine (? leucine → most important)

- bypass the liver and are metabolized by ***skeletal muscle*** and kidney
- taken up in skeletal muscle ***independent*** of insulin and liver function
- ***leucine*** stimulates skeletal muscle protein synthesis and inhibits proteolysis, even during sepsis
- low levels are found in sepsis and liver failure
- uses in liver failure,

a. prevention / correction of encephalopathy
b. improvement seen in porta-systemic shunting
c. no improvement in acute hepatic necrosis

- more efficient in reducing the negative ***nitrogen balance*** in burns, sepsis, severe trauma, etc.

→ but ***no*** improvement in survival

- these are essential AA's and should constitute ~ 25% of TPN AA's

NB: prospective randomised trials have shown ***no advantage*** over standard AA solutions in normal, injured or septic patients in terms of ***outcome***

Aromatic Amino Acids

- phenylalanine, tyrosine, tryptophan
- ? causative factor in hepatic ***encephalopathy***, especially tyrosine → ***octopamine***

Alanine

- aliphatic, non-essential amino acid
- required for optimum usage of other AA's
- alanine / pyruvate interconvertable, ∴means of entry for ***gluconeogenesis***

Arginine

- aliphatic, acid & basic AA
- primary AA for ***gluconeogenesis***
- also required for optimal AA usage (ie. ***anabolic***)

NB: l-arginine → substrate for ***nitric oxide*** synthesis

- useful for protein retention in burns patients
- protective against hyperammonaemia in liver failure
- participates in creatine synthesis
- yields glutamic acid
- stimulates immune function,
    a. enhances CMI
    b. T-cell and macrophage

Histidine

- heterocyclic, acidic and basic AA
- essential for infants and uraemic patients
- used in renal failure,
    a. specific deficiency
    b. improves N-balance
    c. reduces ***urea*** production

- stimulates protein synthesis
- precursor to ***histamine***
- O_2 binding on Hb

- ***Glycine***

- non-essential AA
- participates in creatine/creatinine synthesis
- involved in purine/pyrimidine and haem synthesis
- excess leads to hyperammonaemia & CNS toxicity

- ***Glutamic Acid***

- aliphatic, non-essential, acidic AA
- required for optimal utilization of AA's, ie. ***anabolic***
- involved in ***transaminase*** reactions → α-ketoglutarate & AA's
- utilised by ***GIT mucosa***

- ***Hepatic Feeds***

- low aromatic AA content
- high in branched chain AA's and arginine

NB: ***no*** improvement in survival and expensive

Vitamins

	Role	Deficiency
thiamine B_1	• pyruvate decarboxylase • α-ketoglutarate decarboxylase • ***transketolase*** (rbc levels) • structural component of neural membranes	• cardiomyopathy • neuropathy • encephalopathy • lactic acidosis
riboflavin B_2	• flavin nucleotides	• stomatitis • cheilosis
pantothenic acid	• coenzyme A	
niacin	• nicotinamide nucleotides: NAD, NADP	• pellagra[1]
pyridoxine B_6	• AA transaminase cofactor • AA carboxylase cofactor	• dermatitis • cheilosis, glossitis
biotin	• AA carboxylase cofactor	• dermatitis, alopecia
folate	• methyl (1C) group transfer reactions • AA and DNA intermediary metabolism	• megaloblastic anaemia • thrombocytopaenia
cyanocobalamin B_{12}	• methyl (1C) transfer reactions • AA and DNA intermediary metabolism	• macrocytic anaemia • SACD of cord
vitamin C	• connective tissue formation • oxidative/reductive reactions • antioxidant	• scurvy[2]
vitamin A	• retinal pigment formation • epithelial integrity	• night blindness • xerophthalmia, keratomalacia
vitamin D	• Ca^{++} & $HPO_4^{=}$ metabolism	• rickets, osteomalacia
vitamin E	• antioxidant	
vitamin K	• synthesis of clotting factors • II, VII, IX, X and proteins S&C	• coagulopathy • rarely thrombotic disorder

[1] classical traid of ***pellagra*** = dermatitis, diarrhoea & dementia

[2] features of ***scurvy*** = perifollicular haemorrhages & hyperkeratotic papules
petechiae, purpura & splinter haemorrhages
bleeding gums, subperiosteal & joint haemorrhages
anaemia is not uncommon

MVI Ampoules			
Vial 1 (5ml)		**Vial 2 (5ml)**	
vit A	3300 IU	biotin	60 µg
vit B_1	3	folate	400
vit B_2	3.6	B_{12}	5
vit B_6	4		
niacin	40	***no*** vit K	
propanthenate	15		
vit C	100 mg		
vit D	200		
vit E	10		

- ***All B&C***

a.	ascorbic acid	C	- 25	mg/ml
b.	thiamine HCl	B_1	- 5.61	mg/ml
c.	riboflavin-5-PO_4	B_2	- 3.42	mg/ml
d.	pantothenate-Ca		- 2.5	mg/ml
e.	nicotinamide		- 25	mg/ml
f.	pyridoxine HCl	B_6	- 1.52	mg/ml

NB: vials are 2 ml, ∴double above figures

Trace Elements

Def'n: criteria for trace element,

1. present in healthy tissues of all animals
2. constant levels in all animals
3. ***deficiency*** results in reproducible syndrome, associated with,
   - specific biochemical changes
   - syndrome reversal on supply of element

• trace element solution, 5ml vial contains,

a.	Zn^{++}	10	mg
b.	Cu^{++}	2	mg
c.	Mn^{++}	1	mg
d.	I^-	0.28	mg

NB: there is ***no*** iron, chromium, molybdenum, or selenium

• daily requirements for essential trace elements,

a.	zinc	~ 2.5-4.0	mg	(most important early)
b.	copper	~ 0.5-1.5	mg	
c.	manganese	~ 0.15-0.8	mg	
d.	iodine	~ 0.1-0.9	mg	
e.	chromium	~ 10-50	µg	
f.	iron	~ 1	mg	(males)
		~ 2-3	mg	(females)
g.	cobalt	?		
h.	molybdenum	~ 20	µg[§]	
i.	selenium	~ 30	µg[§]	[§]probably essential

• elements not yet proven as essential → nickel, silicon, vanadium, tin

■ ***Aetiology of Deficiency States***

a. catabolism

b. deficient intake, especially TPN solutions

c. fistulae, diarrhoea

NB: plasma levels ***unreliable*** assessment

- ***Zinc***

a.	deficiency	- alopecia, dermatitis - diarrhoea, ileus - depression - low Zn, ALP ? immune function
b.	enzyme systems	- carbonic anhydrase - alkaline phosphatase - alcohol dehydrogenase - superoxide dismutase - glyceraldehyde-3-phosphate dehydrogenase - procarboxypeptidase - retinene reductase

- ***Copper***

a.	deficiency	- neutropaenia, anaemia - subperiosteal haematomas
b.	enzyme systems	- cytochrome oxidase - dopamine hydroxylase, tyrosinase - MAO - urate oxidase - superoxide dismutase

- ***Manganese***

a.	deficiency	~ vitamin K deficiency
b.	enzyme systems	- cholinesterase - pyruvate carboxylase - arginase - superoxide dismutase

- ***Chromium***

a.	deficiency	- neuropathies - diabetes

- ***Molybdenum***

a.	deficiency	? one case reported - tachycardia, tachypnoea - night blindness, scotomata - irritability, coma
b.	enzyme systems	- xanthine oxidase - aldehyde oxidase

- ***Selenium***

  a. deficiency - myositis, cardiomyopathy

  b. enzyme systems - glutathione peroxidase

- ***Cobalt***

  → requirements met if adequate doses of vitamin B_{12} given

ENTERAL NUTRITION

NB: indicated when oral feeding is prohibited but where GIT function is present

a. post-operative patients
b. dysphagia
c. oesophageal problems
d. poor airway reflexes
e. many long-term neurological diseases → bulbar/pseudobulbar palsy

NB: ***contraindicated*** where there is non-functioning GIT

- ***Complications***

a. technical
   i. insertion of NG tube
   ii. trauma to nose, pharynx, larynx, etc.
   iii. inadvertent pulmonary administration
   iv. inadvertent IV administration *Leur-lock connectors since banned
b. vomiting, regurgitation, aspiration
c. diarrhoea
d. hyperglycaemia and hyperosmolar states
e. fluid and electrolyte imbalance
f. uraemia

- ***Benefits Versus TPN***

a. cheaper, safer, more effective
b. maintains GIT function
c. reduces ***stress ulceration***
d. reduces ***nosocomial infection*** *Bonten *et al.*, AJRCCM 1995,
   i. did not alter gastric acidity
   ii. ***increased*** gastric colonization with *Enterobacteriaceae*
   iii. no change in oropharyngeal or tracheal colonization
   iv. ***gastric acidity*** influenced gastric colonization, bot ***not*** colonization of the upper respiratory tract or the incidence of VAP
e. higher caloric intake ? questionable
f. lower morbidity

Feed Types

- feed types are characterised by,
    1. osmolality - isotonic | hypertonic
    2. lactose content - present | absent
    3. molecular form of protein content - intact protein | peptides | amino acids
    4. quantity of protein & calories provided
    5. fibre content - low residue | high residue

- most commercial solutions contain ~ 1000 kcal & 37-45g of protein per 1000 ml

Enteral Feeds				
	Osmolite / Isocal	Jevity	Pulmocare	Nepro
Osmolality	isoosmolar	isoosmolar	hyperosmolar	
Lactose	free	free	free	
Protein	whole	whole	whole	
Calories	~ 1.0 kcal/ml	~ 1.0 kcal/ml	~ 1.5 kcal/ml	
Fibre	low residue	high residue	low residue	low residue

- ***elemental solutions*** contain hydrolysed proteins, or crystalline AA's, with minimal fat content
    a. no benefit except in pancreatic insufficiency, severe malabsorption syndromes
    b. extremely hypertonic & may result in severe diarrhoea
        - low residue, more complete absorption~ 1 kcal/ml
        - optimal absorption if $[Na^+] > 90$ mmol/l
        - expensive

- ***proven*** benefit for,
    a. ***enteral*** versus parenteral
    b. ***continuous*** rather than intermittent feeds
    c. prevention of ***hypoalbuminaemia*** & feed tolerance

- ***no*** proven benefits for,
    a. fibre feeds
    b. high branched chain/low aromatic AA feeds
    c. high essential AA feeds
    d. "therapeutic" feeds

- ***Administration***

a. NG tube
   - large bore for short-term - better aspiration
   - fine bore for long-term - patient comfort
     - sinusitis, mucosal erosion
     - interference with coughing/swallowing
   - confirm position on CXR

b. start with
   - full strength feed ~ 25-33% of desired rate ml/hr
   - administer continuously, preferrably with infusion pump

c. aspirate 4 hourly
   - cease if aspirate ≥ 100 ml

d. consider administration of prokinetic agents
   i. metoclopramide
   ii. cisapride
   iii. domperidone
   iv. erythromycin

e. consider duodenal placement of the feeding tube

f. jejunostomy for long term administration

PARENTERAL NUTRITION

Def'n: complete caloric and nutritional requirements met by IV fluids

- ***Indications for TPN***

NB: absolute ***contraindication*** to TPN → functional GI tract

a. alimentary tract diseases
   - i. acute
     - bowel obstruction, ileus
     - fistulae
     - pancreatitis
   - ii. chronic
     - malabsorption
     - short bowel syndromes
     - inflammatory bowel diseases

b. high caloric requirement patients
   - sepsis, burns, multi-trauma
   - pancreatitis
   - post-operative complications

c. severe malnutritional states
   - cachexia, carcinoma
   - anorexia
   - preoperatively

d. subjects in prolonged coma

e. acute renal failure

f. acute liver failure

• TPN of ? proven benefit for,

1. acute renal failure - outcome, ? rate of recovery
2. acute & chronic GIT disease
3. complicated pancreatic disease - abscess, fistula
4. preoperative patients
   - decreased morbidity & mortality
   - Mullen 1980
5. bone marrow transplant
6. many infant diseases

NB: subsequent studies/reviews would argue ***against*** all of these statements, see review by Koretz, AJRCCM 1995

- theoretical, yet ***unproven*** benefit for,
    a. liver failure
    b. cardiac disease
    c. uncomplicated acute pancreatitis
    d. post-traumatic catabolism
    e. branched chain AA's in severe sepsis or trauma

- ***Assessment of TPN Requirements***

    a. nutritional status
    b. fluid and electrolyte status & on-going losses
    c. limiting factors - organ failure (liver, renal, CVS)
    d. catabolic states - basal, stressed, burns, sepsis, etc.
    e. special requirements - insulin, Fe^{++}, Zn^{++}
    f. route of nutrition

Nutritional Requirements - TPN

- approximate values,

a. water requirement — ~ 30-35 ml/kg/day plus losses
- restore volume status first

b. electrolyte requirement
- Na^+ — ~ 1-2 mmol/kg/day
- K^+ — ~ 0.7-1.0 mmol/kg/day
- $H_2PO_4^-$ — ~ 0.4 mmol/kg/day
- Ca^{++} — ~ 0.1 mmol/kg/day
- Mg^{++} — ~ 0.1 mmol/kg/day

c. protein requirement — ~ 0.5-1.0 g/kg/day minimum
≤ 3.0 g/kg/day (~ AA 1.5-4.0g)

d. caloric requirement — **~ 30 kcal**/kg/day + allowances
~ 15-30% provided by protein
- remainder CHO + lipid

e. glucose requirement — ~ 30% of calories
~ 3g/kg/day or 1200 kcal
~ 500 ml of 50% dextrose

i. ***minimum*** — ~ **1.5 g/kg/day**
* for glucose dependent tissues & protein sparing

ii. maximum — ≥ 4-5 mg exceeds metabolic requirements
→ hyperglycaemia & fatty liver

f. lipid requirement — ~ 30-60% of total calories
~ 50% of non-protein calories
≤ 0.5 g/kg/hr maximum

*eg. 1.5g/kg — ~ 500ml 20% intralipid
~ 1000 kcal

- recommended relative contributions,

a. calorie:nitrogen ratio — ~ 150:1 (R: 80-200:1)

b. CHO:N ratio — ~ 30-50:1
→ CHO:protein — ~ 4-7:1
→ K^+ — ~ 6 mmol/g N

c. glucose — ~ 1.5 g/kg/d

d. fat:CHO ratio — ~ 1:1
? 2:1 optimal

- ***Undefined Parameters***

1. optimum calorie::nitrogen ratio
2. optimum fat::CHO ratio
3. vitamin requirements in critically ill patients
4. trace element requirements in critically ill patients
5. role of branched chain AA's in - liver failure
   - sepsis, severe trauma, burns
6. histidine in liver failure
7. short & medium chain FFA's in - MODS
   - liver failure

• for an average 70kg male,

a. Synthamin 17, 1000 ml = 100 g protein (0.5 kcal/ml)
   ~ 540 kcal
   ~ 1300 osm/l

b. 50% dextrose, 500 ml = 250 g dextrose (2.0 kcal/ml)
   ~ 1025 kcal

c. Intralipid 20%, 500 ml = 100 g lipid (2.0 kcal/ml (10% = 1.0))
   ~ 930 kcal

→ 2500 kcal ~ 20% protein / 40% each CHO & lipid

d. vitamins - MVI-1&2 + vit K 10mg

e. trace elements - Zn, Cu, I, Mn (*Se)

f. others - insulin, heparin, ranitidine
   - aminophylline
   - albumin, Fe^{++}

NB: best guides to success are ***weight gain*** and ***clinical improvement***

- ***TQEH Standard***

a. Synthamin 17, 750 ml = 75 g protein (0.5 kcal/ml)
   ~ 400 kcal

b. 50% dextrose, 750 ml = 375 g dextrose (2.0 kcal/ml)
   ~ 1540 kcal

→ 1900 kcal ~ 20% protein

c. additional H_2O, vitamins, trace elements PRN

Energy & Fluid

- the Harris-Benedict equation provides a good guide to total energy requirements;

1. For Men

   Energy (kcal/24h) = 66.473 + (13.7516 x kg^{wt}) + (5.0033 x cm^{ht}) - (6.775 x age)

2. For Women

   Energy (kcal/24h) = 655.0955 + (9.5634 x kg^{wt}) + (1.8496 x cm^{ht}) - (4.6756 x age)

NB: these predict the requirements for weight maintenance in afebrile patients and there are a number of exceptions;

a. for weight increase → 30% increase

b. for septic patients → 30% increase

c. burns patients > 40% → ~ 100% increase

- in general, **~ 32 kcal/kg/d** is sufficient for weight maintenance, and
  ~ 40 kcal/kg/d is sufficient for weight gain or septic patients

- basal fluid infusion should ~ 1-1.2 ml/kcal, plus the volume of any losses from diarrhoea, stomal losses, fistula drainage, N-G suction etc.
- in oliguric patients ~ 750-1000 ml, plus volume of urine output and other losses
- with cardiac failure ~ 40 ml/kg can be infused providing Na^+ is restricted to 20-40 mmol/d

Amino Acids

- normal function requires visceral & musculoskeletal integrity, plus normal levels of enzymes, hormones and plasma proteins
- all of these are dependent upon new protein synthesis and provision of adequate AA's is a major objective of TPN
- although the requirement is influenced by a number of factors, nitrogen balance and protein synthesis are proportional to the amount of AA infused between the range 0-2 g/kg/day
- the pattern is important as ***unbalanced mixtures*** do not support protein synthesis
- enrichment of mixtures with branch-chain AA's or keto-acids may aid protein synthesis in septic patients, however ***no benefit*** in outcome
- AA's are more efficiently utilised when infused with adequate non-protein energy to meet caloric requirements
- a positive nitrogen balance is achieved in most malnourished patients by infusing 0.5-1.0 g/kg ideal body weight of AA, together with optimal nonprotein calories
- as the input of nonprotein energy is increased, nitrogen retention is augmented at all levels of AA intake, the most marked effects seen between the range of zero calories and an amount = the BMR
- beyond 50-60 kcal/kg, additional calories do not significantly improve nitrogen balance

Relation of Nitrogen Retention to Nonprotein Energy

• both CHO and lipids can be used and are of equal efficacy in malnourished or septic patients after an initial 3-4 day period of adaptation to the energy source
• thus, the factors governing the choice of calories are other than the effects on nitrogen balance;

a. osmotic pressure
b. CHO requirement for insulin
c. CHO may increase BMR and CO_2 production, thus ventilation

• concentrated glucose solutions are hyperosmolar and will cause thrombosis of peripheral veins, thus necessitating an SCV line
• obviously CHO loads are not ideal for diabetic individuals and the use of lipid infusions reduces the requirement for frequent BSL monitoring and additional insulin
• glucose infusion mixtures consist of 25% dextrose, 2% AA's, plus vitamins and minerals
• lipid infusions are mixtures of TG's, phospholipid as an emulsifying agent, and glycerol to maintain isotonicity, ∴may be given ***peripherally***
• these can be administered concurrently using a Y-connector
• ***insulin*** is not required for fat metabolism and plasma levels are low, and those of FFA's and ketones high, when lipid is the major nonprotein source
• also, lipid infusions can be ceased abruptly without the danger of hypoglycaemia
• essential FFA's are met if as little as 500 ml of "Intralipid" is given weekly

Recommendations for Nonprotein Energy

• lipid free systems are only required in patients with hyperchylomicronaemia
• infusions of ~ 80% lipid can be given peripherally, thereby minimising the treat of catheter sepsis and other complications
• Harrison's recommends a 1:1 ratio through a CV line as this approximates the normal dietary ratios of CHO & fat and cause neither hyperglycaemia or hyperinsulinaemia

■ ***Other Requirements***

• ***vitamins*** must be added to the administered solution
• excessive amounts of the fat soluble group should be avoided because of the danger of hypercalcaemia and other toxic effects
• a combination of 5 ml Multivitamin Infusion (MVI) + 10 ml Soluzyme + Vit C on alternate days meets most requirements
• these should be supplemented with **Vit K** (5 mg) and Vit B_{12} (200 µg), initially at intervals of 3 weeks
• ***trace elements*** are only needed if TPN is to exceed 2 weeks
• these include Zn, Cu, Mn, Cr, Se

Routes of Administration

a. central venous line
   - has the advantages that fluids may be infused irrespective of osmolality and the need for repeated venipuncture is obviated
   - however, carries the risks of septicaemia and thrombosis
   - the basic principles of insertion are as follows;

   i. aseptic technique
   ii. position documented radiologically
   iii. introduced via a large central vein, not peripherally
   iv. the catheter should not be used to withdraw blood or measure the CVP
   v. barium impregnated silicon rubber catheters are less likely to be surrounded with fibrin clot and are relatively atraumatic

b. peripheral venous infusion
   - this route is safe and unlikely to be associated with sepsis or thrombosis
   - however, the infused fluids must be isotonic or only mildly hypertonic
   - therefore, the majority of nonprotein calories must be lipid

Complications

Technical Complications

- most relate to placement of the CV line,

a. damage to other structures
   - artery
   - nerves
   - pleura
   - lymphatics

b. air embolism

c. catheter embolism due to shearing off of the tip

d. subclavian vein or SVC thrombosis

e. venous or atrial perforation (late)

f. TPN hydrothorax

- incorrect placement and infusion into the pleura or mediastinum can be avoided by infusing saline until placement is confirmed radiologically
- problems which can arise late include thrombosis around the catheter, air embolism and venous perforation

Septic Complications

• incidence **~ 2.8%** and is influenced by,

a. catheter site, duration and catheter type

b. the use of sterile technique

c. subsequent catheter care

• the presence of a foreign body within the central veins provides considerable risk of sepsis, thus insertion and regular cleansing and dressing of the site should be done under strict aseptic technique
• sepsis in a patient with a central line is often ***not*** due to catheter sepsis and other causes should be excluded prior to the catheter being removed
• on removal there should be prompt defeveresence if the catheter was the origin of the sepsis
• a new catheter may be inserted 48 hrs after the fever has subsided
• it is important not to withhold TPN from such patients as further malnutrition will further predispose them to sepsis

Metabolic Complications

a.	hydration	- deficit or excess
b.	electrolyte imbalance	- Na^+, Cl^-, K^+, Ca^{++}, Mg^{++}, $HPO_4^=$
c.	osmolar imbalance	- high/low, Na^+, urea, glucose
d.	acid/base balance	- Cl^-, lactate, ketosis, acetate
e.	glucose metabolism	- hyper/hypoglycaemia
f.	trace elements	- Zn^{++} (drains, fistulae, diarrhoea) - Fe^{++}
g.	vitamin deficiency	- thiamin, folate, K (coagulopathy) - B_{12}, A, D, E occur later
h.	hyperammonaemia / uraemia	
i.	metabolic bone disease	? hypervitaminosis D
j.	cardiac failure	- fluid overload - LQTS (Mg^{++}, Ca^{++}, K^+) - hypo-$PO_4^=$, selenium
k.	respiratory failure	- hypo-$PO_4^=$, ? hypo-K^+ ? high CO_2 production
l.	fatty liver	- glucose induced steatosis - carnitine deficiency - essential AA deficiency
m.	acalculous cholecystitis	

Metabolic Complications

• in septic patients, ***hyperglycaemia*** may occur owing to insulin resistance and high levels of CA's and cortisol
• management is to replace CHO calories with lipid, and/or add insulin
• during TPN the blood glucose levels should not be allowed to fall below 150 mg/dl due to the danger of hypoglycaemia
• the sudden appearance of hyperglycaemia may herald the onset of ***sepsis***
• hypoglycaemia is apt to occur when hypertonic glucose infusions are ceased, or rarely when a patient receiving TPN and insulin has their sepsis removed
• ***hyperammonaemia*** and a picture resembling hepatic encephalopathy may occur in patients receiving a mixture of AA's deficient in ***arginine***
• hypertriglyceridemia may occur with over-feeding
• anabolism is associated with cellular uptake of phosphorus, magnesium and potassium
• this can result in low plasma levels of any or all of these
• ***hypophosphataemia*** results in low RBC levels of 2,3-DPG and thus reduced oxygen transfer to the tissues
• in the brain this may result in disorientation, convulsions and/or coma

• ***acidosis*** results from Cl^- excess, lactate production, or ketosis
• ***alkalosis*** from Cl^- deficiency, excess lactate/acetate administration
• the metabolism of the basic AA's in their chloride form produces both chloride ions & protons, which, if unbuffered, can result in a hyperchloraemic acidosis
• for this reason all current AA mixtures contain ***sodium acetate***, the conversion of acetate to bicarbonate serves to buffer the protons produced by the metabolism of the basic AA's

Liver Disease

• minimal elevations of ALP and AST (70-90%) are common in TPN
• rarely associated with ***jaundice***
• only in the occasional patient, ~ 1.5-2.0%, does ***cholestasis*** develop and this is only associated with minimal hepatocellular dysfunction
• hyperbilirubinaemia is common in septic patients
• "sludge" accumulates in the gallbladder and may lead to obstructive changes in the biliary tract
• the liver may become fatty, enlarged and tender if excess calories are given as CHO

Hypercalcaemia & Pancreatitis

• pancreatitis associated with hypercalcaemia can occur during TPN and this may be relieved by removing Vit. D from the supplementation

Metabolic Bone Disease

• in some patients receiving home TPN, osteomalacia & osteoporosis have occurred, leading to bone pain and fractures
• the mechanism for these changes is unclear

- ***Complications of 50% Dextrose***

1. those related to the ***dextrose*** content
   - i. hyperglycaemia - problems of osmolality
   - ii. hypokalaemia / hypophosphataemia
   - iii. rebound hypoglycaemia 2° insulin overshoot
2. those due to the ***hypertonic*** solution
   - i. hyperosmolar syndrome ~ 1250 mosmol/l (>4 x plasma)
   - ii. osmotic diuresis - loss of Na^+ and water
   - iii. venous thrombosis - hyperosmolar & acidic (6.0)
3. excess conversion to ***triglyceride***
   - i. lipogenesis
   - ii. increased insulin - further lipogenesis
   - iii. increased CO_2 production[§]
   - iv. excess hepatic fat deposition[§] > 5-7g/kg/min[§]
   - v. elevated LFT's & bilirubin ~ "TPN" hepatitis

- ***Complications of Lipid Emulsions***

1. hyperlipidaemia
2. pancreatitis
3. "fat overload syndrome"
   - hyperlipidaemia
   - GIT disturbance
   - hepatosplenomegaly
   - liver dysfunction, fever
   - anaemia, coagulopathy
   - thrombocytopaenia
4. essential FA deficiency > 1-3 weeks
   - dermatitis, alopecia
   - fatty liver, hepatomegaly
   - loss of pigmentation
   - growth retardation
5. "cracking" of emulsion
   - heat
   - incompatible mixing

- ***Complications of Amino Acid Solutions***

a.	uraemia	- excess non-essential AA's - racemic mixtures
b.	hyperammonaemia	- excess ***glycine*** - CNS toxicity
c.	hyperchloraemic acidosis	- Cl^- excess, pH ~ 6.0
d.	acetate toxicity	
e.	hyperosmolar	

Causes of "TPN Liver Disease"

1.	fatty liver	- glucose induced steatosis - carnitine / essential AA deficiency
2.	gallstones	- calculous cholecystitis
3.	cholestasis	- acalculous cholecystitis
4.	non-specific inflammatory changes	
5.	sepsis	- septicaemia - cholangitis - biliary tract sepsis
6.	concomitant liver d.	- viral (CMV, Hep.B, C) - drugs, tumour, obstruction
7.	long-term	? progressive liver disease ? cirrhosis ? MODS

- ***Management***

1.	regular LFT's	
2.	U/Sound	- gallbladder - fatty infiltration
3.	hepatitis serology	
4.	reduce CHO administration	
5.	change to enteral feeds ASAP	
6.	? hormones	- glucagon, secretin
7.	? metronidazole	