nutrition

3 Types of malnutrition

1. **Marasmus**: lack somatic proteins
2. **Kwashiorkor**: lack visceral proteins
3. **Mixed Marasmus/Kwashiorkor:** a bit of both

3 Protein compartments

1. **Somatic**: muscle proteins
2. **Visceral**: produced by organs, e.g. albumin, transferrin
3. **Immunity**: a subset of visceral, e.g. antibodies, clotting factors

5 Steps to assess nutritional status

1. **Visual assessment**
    - Marasmus vs. Kwashiorkor
2. **Patient's history:** present and past weight
3. **Physical exam**
4. **Protein compartments**
    - Weight/Height measurements
        - Edema/obesity/pathologies distort results
    - Anthropometric measurements: muscle vs. fat amounts
        - Triceps skin fold
        - Mid-arm circumference
        - Creatinine/height index (CHI)
            - Urinary creatinine is decreased in malnutrition and renal disease
            - Better in terms of height than weight
            - CHI = actual/normal mg excreted (where 90%-100% is normal)
    - Albumin: 50-60% of total serum proteins
        - Normal conc. = 3.4-5g/100ml of blood
        - Catabolic stress = ↓albumin = ↑insulin = further ↓aa
        - Interplay between 2 types of malnutrition: somatic aa used as building blocks for visceral aa
        - Easier to detect drop in serum conc. of transferrin than albumin
5. **Immune competence** (*anergy*=inability of a patient to respond to an infection)
    - Lymphocyte counts
    - Antigen-skin tests: Multitest CMI system (think Cooties game)
        - Ability of lymphocytes and immunoglobulins to respond to antigens
        - >1 grade of swelling/redness indicates some immune response
        - 0 grade = lack of response = indicative of anergy and malnutrition

4 Roles of pharmacists in nutrition

1. Help diagnose type/degree of malnutrition
2. Recommend treatment/method
3. Evaluate treatment, suggest changes
4. Management

If the GI tract works, use it!

- Into mouth (**nasogastric tube**)
- Into stomach (**gastrostomy**)
- Into small intestine (**jejunostomy**)

If not, use parental/IV administration

- **Protein sparing**
    - Mild patients

- Peripheral arm vein
- Isotonic: 2.75-3.5% solution (+vitamins, minerals, electrolytes)
- Not a TPN modality: no fat or dextrose given

- **Peripheral TPN**
  - Mild to moderate patients for limited time (<10 days)
  - Patients wit septicemia
  - No fluid restrictions
- **Central TPN**
  - Moderate to severe patients
  - Burn patients (no peripheral veins available)
  - Longer duration (2-3 weeks)
  - Subclavian or internal jugular vein

Numbers to know

Nitrogen balance = [Protein intake x 16%] – [$N_{excreted}$ + C] → should have positive $N_{balance}$ of 4-6g

Caloric conversions:

- Dextrose: 3.4kcal/g
- Lipid emulsion: 9kcal/g

Nutritional requirements:

- **Protein** (supplied in 3.5-15% conc.)
  - Maintenance 0.8-1.6g aa/kg/day
  - Mild trauma 1.6g-2.0g aa/kg/day
  - Severe trauma 2.0-3.0g aa/kg/day
- **Nitrogen**
  - 16% of protein -or- protein/6.25 (in grams)
- **Calories**
  - Mildly stressed 125-150kcal/gN_2
  - Highly stressed 80-100kcal/gN_2 (note: less calories needed for severe pts because less mobilized)
  - Provided as dextrose and fat (50/50, 40/60)
    - **Dextrose** supplied as 5-70% concentration (e.g. D_5W=50g/L, $D_{50}W$=500g/L)
    - **Lipid emulsion** supplied as 10-20% concentration
      - 200 extra kcal from glycerin and emulsifiers
      - Now favored over dextrose because
        - ↓Hyperglycemia risk
        - Dextrose → fat (accumulates in liver)
        - ↓Osmolarity of aa/dextrose solutions to facilitate peripheral admin
        - ↓Severity and frequency of phlebitis
        - ↓Chance of essential FA deficiency
- **Molecular weights**
  - Dextrose: 180g/mol
  - NS: 58.5g/mol

CALCULATIONS

Solve for nutrition

1. Solve for volume (ml) of **amino acids** needed [use: degree of trauma, weight of pt, concentration]
2. Solve for amount (g) of **nitrogen** needed [use: grams of amino acid from part 1]
3. Solve for **kcal** needed [use: degree of trauma, grams of nitrogen from part 2]
   a. Determine **ratio** of dextrose/lipid

4. Solve for volume (ml) of **dextrose** needed [use: ratio, concentration, caloric conversion]
5. Solve for volume (ml) of **lipid emulsion** needed [use: ratio, concentration, caloric conversion]

Solve for tonicity

- **Amino acids:** will be given mOsm/L, use known volume to solve
- **Dextrose:** solve knowing D5W=280mOsm/L, multiply by known volume
- **Lipid emulsion:** 2.25g glycerin/100ml…

Incompatibility charts

		ANIONS		
CATIONS		Monovalent Cl^-	Divalent CO_3^{2-}	Trivalent PO_4^{3-}
	Monovalent Na^+, K^+	Soluble	Soluble	Soluble
	Divalent Ca^{2+}, Mg^{2+}	Soluble	Insoluble	Insoluble
	Trivalent	Soluble	Insoluble	Insoluble

Mg2+ behaves differently → important when considering lactate ringers and ringer solutions

Ion pair incompatibilities

Mixing of a weak acid drug with a weak basic drug

Barbiturates: weak acids

Heparin: weak bases

Na+Phenobarb- + Morphine+SO4- → big insoluble salt

Na+Phenobarb- + Tetracycline+Cl- → big insoluble salt

90% of reactions are some form of ion pair incompatibility

		LVP			
S V P		D5W + 5%$NaHCO_3$ (basic)	0.9% NaCl (neutral)	D5RL (neutral, Ca^{2+})	D5W + 15000 NaHeparin (basic)
	Dopamine HCl (basic)	I (free base)	C	C	I (ion pair precip)
	NaPhenytoin (acidic)	I (insoluble)	C	I (insoluble)	I (insoluble)
	KPenG (acidic)	I (base hydrolysis)	C	C	I (base hydrolysis)

SVP: have added sodium hydroxide (basic) but drug itself may be acidic

Penicillins: beta lactams or lactones, cyclic esters or amides

Beta lactam rings are sensitive to both acids and bases which cause hydrolysis

A lot of lactates are soluble: low enough molecular weight

NaPhenytoin is only soluble in NS and needs to be given w/in a ½ hr of making it up

NaPhenytoin is a weak acid but likes base, it is a very insoluble drug (in order to keep it ionized, need a lot of cosolvents and need to raise the pH really high)

		LVP			
S V P		0.9% NaCl (neutral)	D5RL (neutral)	D5W + 15000 NaHeparin (basic, w.acid drug)	
	NaSucc of Hydrocortisone (w. acid)	C	I Ca3(PO3)2	I (ester hydrolysis)	
	Cimetidine HCl (w.base)	C	C	I (ion pair)	
	Tetracylcine HCl (w.base)	C	I (tet reacts w/ Ca2+)	I (ion pair, free base)	
	NaAmp + NaSucc of Hydrocortisone	C	I (amp inc	I (amp inc w/dextrose,	

	(w.acid)		w/dextrose)	hydrolysis)	

Benzyl alcohol: preservative
Sodium biphospahte anhydrous: buffer (phosphates are trivalent)
Ascorbic acid: antioxidant
Ampicillin can't be given in dextrose: it will hydrolyze the ampicillin
Hydrocortisone is an ester: ester hydrolysis
Tetracylcine: don't take with milk or cheese because of it reacts with calcium
Barbituates: weak acid
Morphine sulfate: weak base

	LVP			
S V P		RL +20000 NaHep (basic)	D20W + 4.25%aas (acid)	NS+50mg Hydrocortisone NaSucc ((acid)
	Lidocaine HCl (base)	I (ion pair, free base)	C	I (ion pair)
	NaKochalate (acid)	C	I (free acid)	C
	Haloperiodl lactate ester	I (base hydrolysis of ester)	I (acid hydrolysis of ester)	C

When have big amounts of heparin → probably basic
If small amounts → not going to make it basic
In general, not good to put drugs in TPN

IMMUNE STIMULANTS

Vaccines

- Attenuated(live) or inactivated (killed)
- Whole or fractions
- Take virus → sonicate to death → differential centrifugation to isolate portion important for immune response

Toxoid

- Modified exotoxin rendered non-toxic
- Easy for companies to make
- Require refrigeration and/or reconstitution (freeze dried powder)

Passive immunity

- **Human immune sera**
  - Immuneglobulin: e.g. measles, hepatitis A
  - Hyper immune serum: e.g. hepatitis B, rabies
- **Animal immune sera**
  - Antitoxin: e.g. botulism, diphtheria, tetanus
  - Antiviral serum: e.g. rabies
  - Antivenin: e.g. rattle snake, black widow spider, scorpion
- **Viral vaccines** e.g. measles, mumps, influenza
  - Isolated by: disintegration, column filtration, differential centrifugation
- **Viral vaccines in human tissue culture**

Allergen extracts

- **Types:** food, animals, grasses, insects, molds, trees, weeds, inhalants
- **Extraction process**: percolation/decoction
- **Diagnosis**: scratch/prick test using very dilute solutions of allergen extracts

Immunotherapy

- Treatment of disease by inducing, enhancing, or suppressing an immune response
- Goal: to increase IgG
- Small subcut doses → weak dose qwk → increasing strength or # of doses over a few months
- IgG competes with IgE IgG>>>IgE with increased dosing with allergen
- Problems: difficult to standardize and establish potency
- Dosage forms: solutions, suspensions, lyophilized powders requiring reconstitution
- Additives
    - Human serum albumin: protein preservative
    - Normal saline: tonicity
    - Phenol: antimicrobial
    - Glycerin: protein preservative
    - Aluminum precipitated allergen: slows absorption/action of allergen
- Use & Handling
    - Aseptic and sterile procedures
    - Proper documentation
    - Generally require refrigeration (never frozen)
    - Sterility testing required (particulate/pyrogen testing not)

Hymenoptera venoms

- Honeybee, wasp, hornets
- Purified, lyophilized
- Usually only venom collected, not whole insect (exception: fire ants)

PROTEIN PHARMACEUTICALS

Biotechnological products techniques

- Recombinant DNA
- Monoclonal antibodies
- PCR
- Gene therapy
- Nucleotide blockade/antisense (mRNA)

Chemical instability

Change in structure due to breaking of bonds

- Proteolytic cleavage
    - Proteases
    - Hydrolysis: solution is to lyophilize the product
- Deamidation: cleave NH3 group
- Oxidation: Met, Cys (also His, Trp, Tyr)

Physical instability

Change in structure *not* due to bond breaking/forming

- Aggregation: precipitation, normal Brownian motion
- Conformational stability: denaturing/unfolding of protein

Additives in biotech formulations

- **Serum albumin**
  - Flood the system so active proteins won't be bound, i.e. inhibit adsorption
  - Adsorption binding sites may be hydrophilic or lipophilic, proteins have both, which makes it a problem
  - Tubing: use polyester or nylon, not PVC, which has more binding sites
  - Resembles nascent complexing proteins: w/o nascent proteins, active proteins are more active
  - Cryoprotectant: protects while freeze drying, almost as good as mannitol
  - Examples when albumin is used: interferon, IL-2, TPA
- **Amino acids (Gly)**
  - Chelate trace elements to prevent aggregation : trace elements allow aggregation, e.g. Zn in insulin
  - Take up adsorption sites to reduce surface adsorption
  - Inhibit aggregate formation
  - Inhibit thermal induced inactivation: neutral amino acids like glycine protect the formulation if heated
- **Fatty acids & phospholipids**
  - 7-8 carbon length is optimal
  - Liposomal systems help stabilize proteins and peptides through nonpolar interactions
  - Protection of non-polar portion of protein interacting with non-polar lipid (emulsifiers for lipids are phospholipids)
- **Surfactants**
  - Charged surfactants (cationic/anionic) cause denaturation
  - Non-ionic surfactants stabilize by reducing interfacial tension
  - Reduce tendency for protein to unfold, help retain structure
  - Examples: Tween 80, Brij, poloxamer)
- **Metals**
  - Ca^{2+} and Cu^{3+} stabilize proteins
  - Bridge between disulfide bonds: helps stabilize bonds and tertiary structure
- **Polyols**
  - Polyhydroxyl groups: carbohydrates, sorbitol, mannitol, glycerol
  - Used in lyophilized dosage forms to prevent aggregation by adding bulk
  - Aids reconstitution: polyols are very water soluble, help the water get to the amino acid very quickly
  - Protects against oxidation
  - Strengthens intra hydrophobic bonds by reducing the interaction between water and protein
  - Humectant: helps hydrate the protein for protection and stabilization
- **Reducing agents**
  - Reduce disulfide bond formation, which tends to lower protein activity
  - Agents: glutathione, thioethanolamine, thiodiglycol, thioacetic acid, N-acetylcysteine
- **Chelating agents**
  - Problem: Cu, Fe, Ca, Mn act as catalysts in oxidation reactions by using up the oxygen
  - Chelating these metals help stabilize the formulation by using up the active sites on the metals
  - Agents: EDTA, diNa, CadiNa, tetraNa
- **Miscellaneous**
  - Hydrolyzed gelatin: available amino acids
  - Ammonium sulfate: adjusts pH