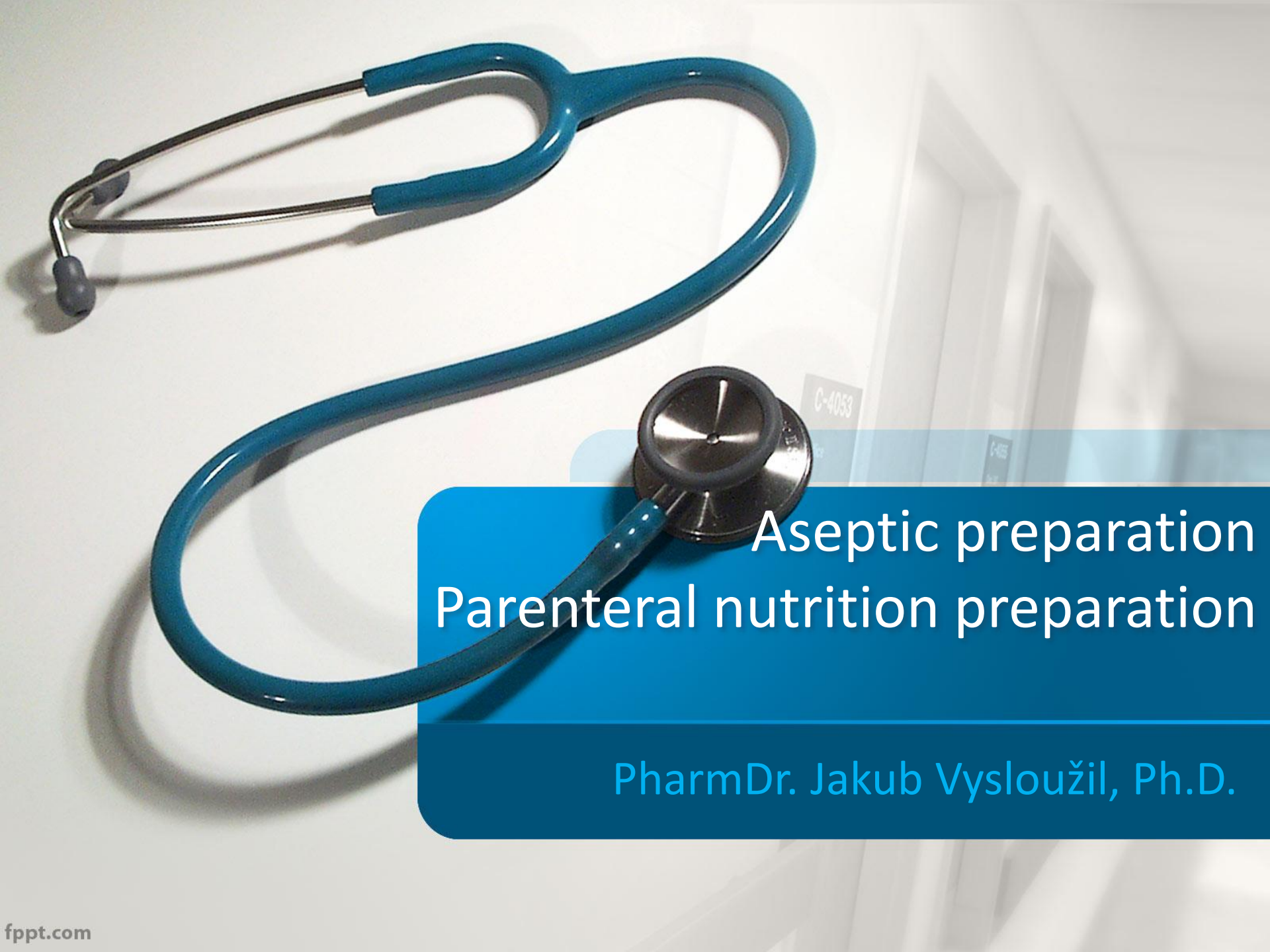


Aseptic preparation
Parenteral nutrition preparation

PharmDr. Jakub Vysloužil, Ph.D.

Sterile preparations
Aseptic preparation

Sterile preparation

Sterile preparation

- Parenteral administration
- Eye drops
- Dosage forms for prematurely born children
- Preparations for wound treatment

PE 010-4 PIC/S

- PE 010-4 PIC/S: GUIDE TO GOOD PRACTICES FOR THE PREPARATION OF MEDICINAL PRODUCTS IN HEALTHCARE ESTABLISHMENTS
  - Council of Europe

Clean Area Grades

Grade	Maximum permitted number of airborne particles/m^3 equal to or above:			
	At rest		In operation	
	0,5 µm	5,0 µm	0,5 µm	5,0 µm
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not defined	Not defined

Preparation environment

- **Grade A:** Workspace for high-risk activities, such as a filling site, a stopper container, open ampoules and bottles or creating aseptic connections.
  - These conditions can be provided by ventilation systems with laminar air flow. Laminar air flow systems provide a homogeneous air flow rate of 0.36 - 0.54 m/s (recommended value) at the workstation in an open work environment. The preservation of laminar flow has to be proven and validated.
- **Grade B**: For aseptic preparation and filling, space surrounding the class A environment.
- **Grade C and D:** Workspace for performing less critical activities in the preparation of sterile medicinal products.

Preparation environment

- The form of the built-in construction, the individual spaces of clean grades separated by partitions/bulkheads
- Tight cassette ceiling, part of the ceiling are HEPA or ULPA air filters for clean air intake to clean grade space
- The clean grade areas are in overpressure with a difference of 10-15 Pa at the boundaries. Overpressure increases with increasing grade class (except for special cases).
- Ventilation
  - The laminar field is a one-way homogeneous air stream at a velocity of 0.45 m / s ± 20%. The laminar field ensures a high level of product protection
- Laminar Box
  - Horizontal x vertical; HEPA filters
  - The highest degree of protection is provided by so-called insulators/izolators, closed systems, into which air is fed through the HEPA filters, and work is carried out under vacuum and sleeves.

Laminar flow

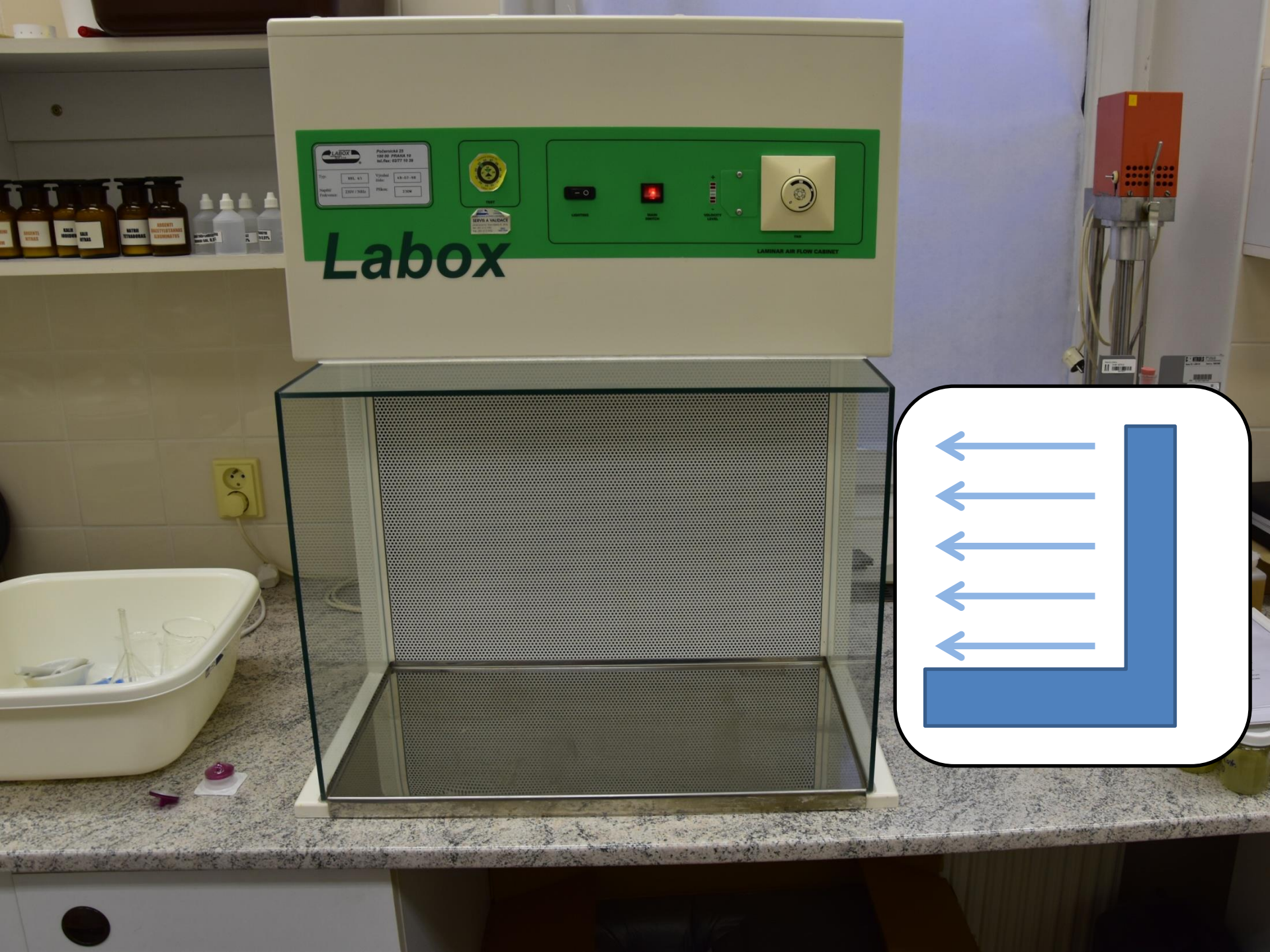
- It is the movement of the fluid in layers; parallel-flowing streamers
- Lower speed
- Ideal for removing contamination

- On the other hand, the turbulent flow is characterized by higher velocity and the formation of vortices, the particles may not get out of space at all

Preparation in laminar box

- Work takes place in the middle of a laminar box in the area of laminar air flow
  - –At least six inches from the edge of the workplace
  - –Nothing is allowed to obstruct the HEPA filter from flowing through the preparation area
  - –Additionally, any other object (horizontally and vertically) must not be placed between the sterile preparation and the laminar flow source,


Labox
LAMINAR AIR FLOW CABINET


Labox
LAMINAR AIR FLOW CABINET

Izolators

Ventilation

HEPA filter (High Efficiency Particulate Arrestance)

- is capable of removing 300 nm particles from the air with at least 99.97% efficiency. Larger particles are filtered with greater efficiency.
- The basis is the folded fabric most often made of laminated glass fiber

ULPA (Ultra Low Penetration Air)

- is capable of removing 100 (120) nm particles from the air with at least 99.999% efficiency.

Preparation of sterile medicinal products

Sterile preparation of medicinal products is divided into:

- preparation of **terminally sterilized medicinal products**
  - The preparation of components and preparations is carried out in the purity class D (C)
  - The filling of the products for terminal sterilization should be performed at least in the C (A)
- **aseptic preparation**
  - Manipulation and filling of aseptically prepared medicinal products (open and closed procedures) should take place in a Class A environment in a laminar flow, in a pressurized biohazard box or in an insulator.
    - Overpressure gradient

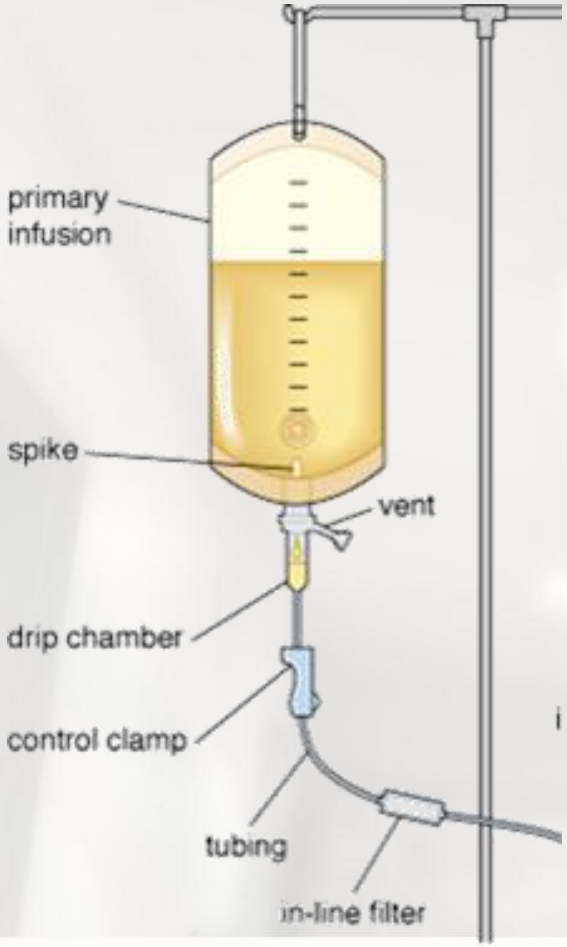
Other recommendations + requirements

- Sanitation
- Workers
- Documentation
- Monitoring

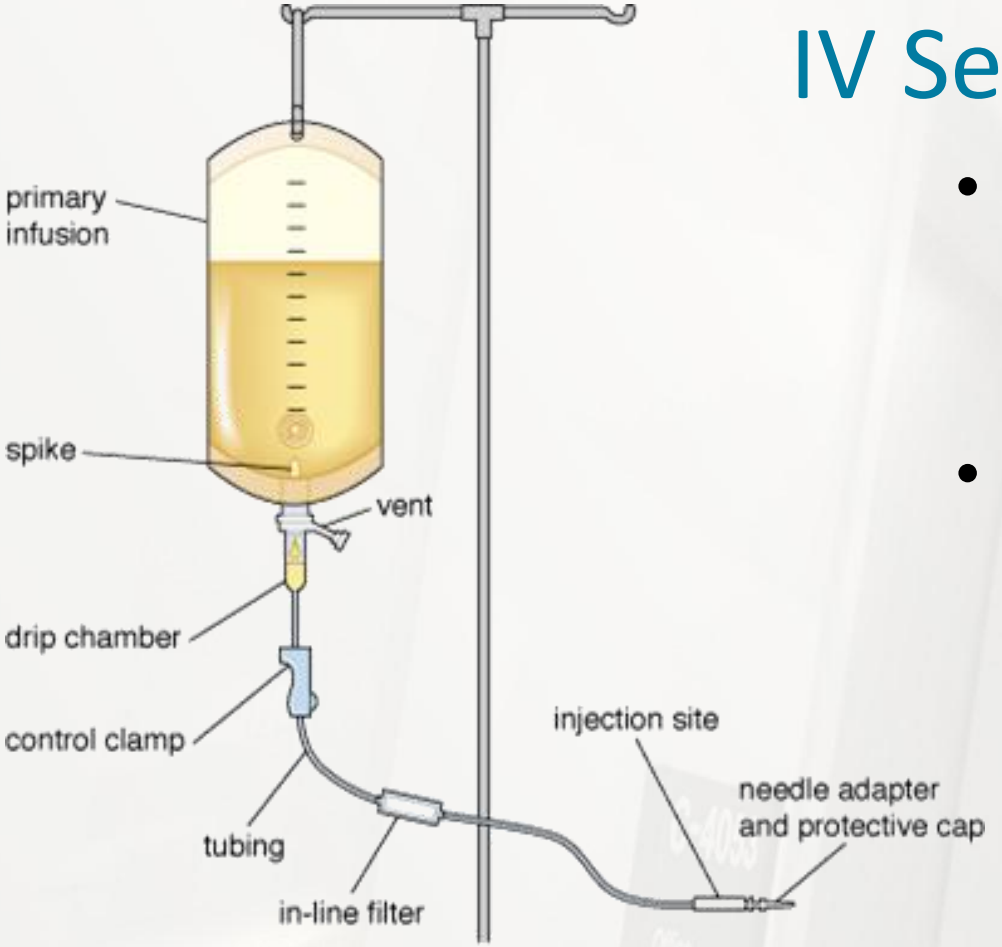
IV preparations

IV Sets

- A spike to pierce the rubber stopper or port on the IV container
- A drip chamber for trapping air and adjusting flow rate
- A control clamp for adjusting flow rate or shutting down the flow
- Flexible tubing to convey the fluid



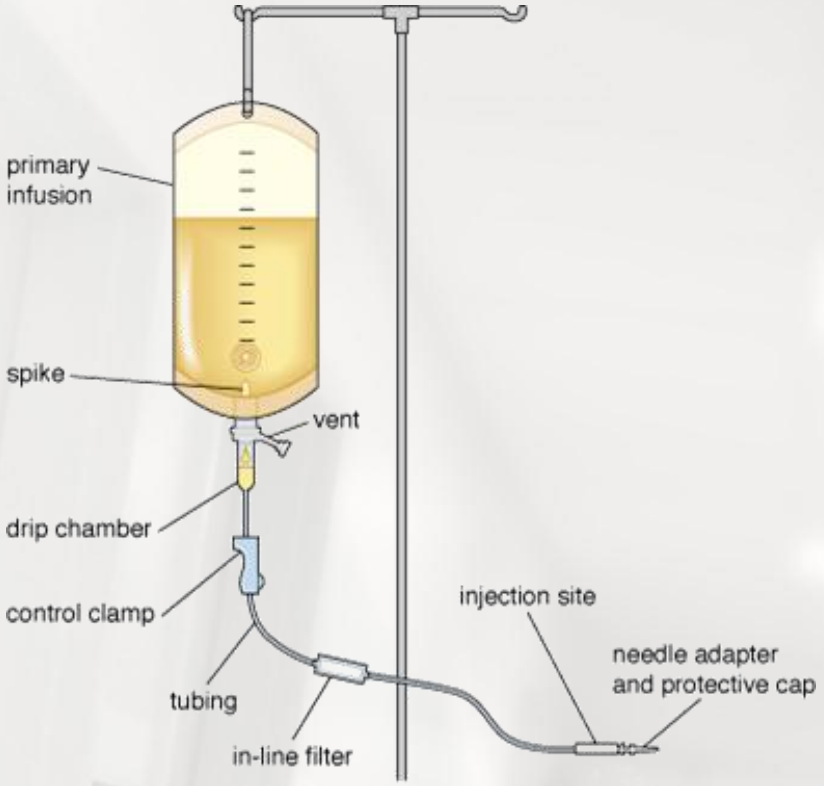
IV Sets



- A needle adapter for attaching a needle or a catheter
- A catheter, or tube, may be implanted into the patient and fixed with tape to avoid need to repuncture the patient each time an infusion is given

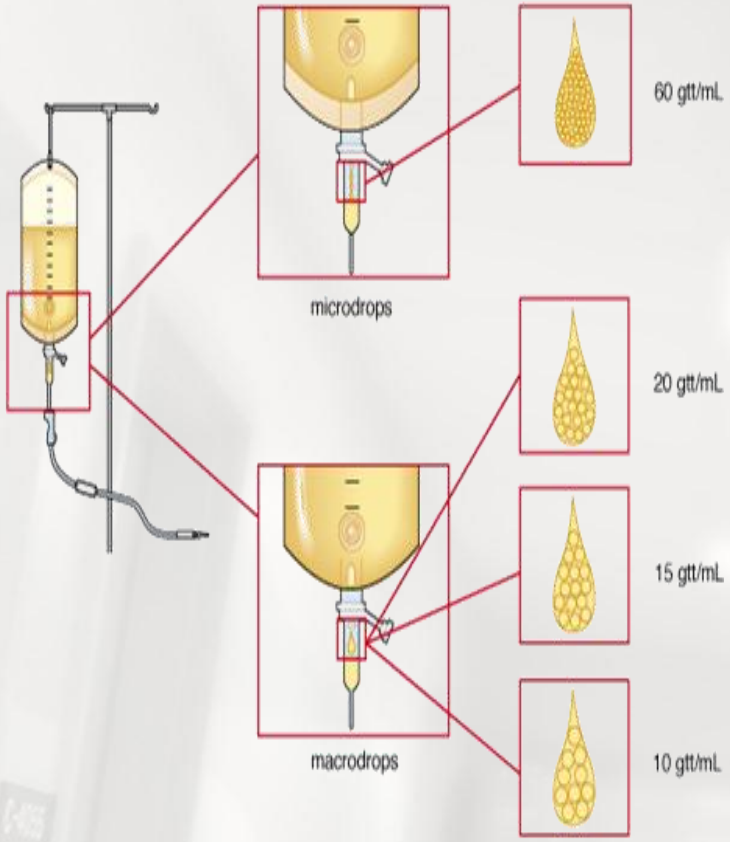
IV Sets

- The drip chamber is a transparent, hollow chamber located below the set's spike
  - drops of fluid fall into the chamber from an opening at the uppermost end, closest to the spike
  - number of drops it takes to make 1 mL identifies an IV set



IV Sets

- The most common IV drop sets are
  - 10 (10 gtt/mL)
  - 15 (15 gtt/mL)
  - 20 (20 gtt/mL)
  - 60 (60 gtt/mL)
- An opening that provides 10, 15, or 20 gtt/mL is commonly used for adults
- An opening that provides 60 gtt/mL is used for pediatric patients and is called a mini-drip set



IV Solutions

- A ***piggyback*** is a small-volume parenteral admixture that is attached to an existing IV line
- The piggybacked solution is infused into the tubing of the running IV
  - usually over a short time, from 30 minutes to 1 hour
- Some IV piggybacks are prepared in 250 mL solution because they contain a medication that is irritating to the veins
- In some cases, syringes are used instead of piggyback containers to deliver medication into a running IV

Preparing a Label for an IV Admixture

Labels for IV admixtures should bear the following information:

- patient's name and identification number
- room number
- fluid and amount
- drug name and strength (if appropriate)
- infusion period
- flow rate (e.g., 100 mL/hr or infuse over 30 min)
- expiration date and time
- additional information as required by the institution or by state or federal guidelines

IV preparation shortcuts:

Preparation	*shortcut*
2,5% glucose in water	$D_{2.5}W$
5% glucose in water	D_5W
5% glucose and Ringer solution with lactate	D_5RL or D_5LR
10% glucose in water	$D_{10}W$
5% glucose in normal saline	D_5NS
2,5% glucose and 0,45% NaCl	$D_{2.5}$½ NS
5% glucose and 0,45% NaCl	D_5 ½ NS

IV preparation shortcuts:

Preparation	*shortcut*
Normal saline (0.9%)	**NS**
0.45% NaCl	**0.45%NS or ½ NS**
Ringer solution with lactate	**RL or LR**
Aqua sterilisata pro injectione	**SWFI**
Bacteriostatic water for injection	**BWFI**
Sterile water for irrigation	**SW for irrigation**
NS for irrigation	**NS for irrigation**

IV preparation shortcuts: electrolytes

Preparation	*shortcut*
Potassium Chloride	**KCl**
Potassium phosphate	**K phos or KPO_4**
Potassium acetate	**K acet**
Natrium phosphate	**Na phos or $NaPO_4$**
Natrium chloride	**NaCl**

IV preparation shortcuts: other

Preparation	***shortcut***
Multivitamine for injection	**MVI**
Trace element	**TE**
Zinc (Trace element)	**Zn**
Selenium (Trace element)	**Se**

Ringer solution

Natrii chloridum	8,60 g/l
Kalii chloridum	0,30 g/l
Calcii chloridum dihydricum	0,33 g/l

Hartmann solution

Natrii chloridum	6,00 g/l
Kalii chloridum	0,40 g/l
Calcii chloridum dihydricum	0,27 g/l
Natrii lactas	3,20 g/l

Total parenteral nutrition

Malnutrition

- condition resulting from diet in which nutrients are either missing or are too abundant that the diet causes health problems
  - Undernutrition (undernourishment)
    - WHO, Unicef - malnutrition
  - Overnutrition
    - obesity

Malnutrition

- Malnutrition of pregnant woman and children up to 2 years causes permanent complications of physical and mental development
  - Iron deficiency – anemia – damaging brain function
  - Folate deficiency – neural tube defects
  - Iodine deficiency – lowers IQ by 10-15 points

Malnutrition

- Malnutrition in elderly people
  - Changes in body composition
  - Organ functions
  - Lower ability to process food
  - Loss of taste and smell
  - Dental health
  - Depression
  - Appetite loss
  - Swallowing problem

- Healthy and active elderly people usually do not have malnutrition problems

Malnutrition types

- Hypovitaminosis
- Avitaminosis
  - Vitamin A: xerophthalmia and night blindness
  - Vitamin D (cholecalciferol) deficiency is a known cause of rickets, and has been linked to numerous health problems.
  - Vitamin E: poor conduction of electrical impulses along nerves due to changes in nerve membrane structure and function
  - Vitamin K (phylloquinone or menaquinone): impaired coagulation, osteoporosis

  - Vitamin B1 (thiamine): beriberi
  - Vitamin B2 (riboflavin) ariboflavinosis
  - Vitamin B3 (niacin): pellagra
  - Vitamin B5 (panthotenic acid): paresthesia
  - Vitamin B7 (biotin): lower fertility, hair/skin growth
  - Vitamin B9 (folate): neural tube defects
  - Vitamin B12 (cobalamin): megaloblastic anemia, combined degeneration of spinal cord
  - Vitamin C (ascorbic acid): scurvy

Nutritional support - history

- 1831 – T. Latta – water and electrolytes
- 1847 – I. Semmelweiss – aseptic conditions
- 1896 – Biedle, Krause – glucose i.v.
- 1920 – Yamakava – fat emulsion i.v.
- 1939 – Elman, Weiner –protein hydrolyzate
- 1960s – S. Dudrick – complete nourishment
- 80s of 20. cent. – all in one

Goal of nutritional support

- maintain long-term satisfactory nutritional condition and suitable condition of the internal environment of the patient
- in patients at risk it may be advantageous to introduce parenteral nutrition in the preoperative period

Comparison of enteral and parenteral nutrition

- Enteral
  - Advantages
    - Physiological for intestines and liver
    - Natural nutriment for intestines
    - Lower cost
  - Disadvantages
    - Aspiration danger
    - GIT intoleration
    - Metabolical disturbances

Comparison of enteral and parenteral nutrition

- Parenteral
  - Advantages
    - Precise determination of individual nutriments amount
    - Quick adjustement of individual nutriment deficiency
    - Alternative to bowel loss
  - Disadvantages
    - Complications - catheter-sepsis, thrombosis, phlebitis
    - Metabolical complications- glycemia, potassium and phosphate levels
    - Less physiological
    - Higher cost

Indications for parenteral nutrition

- Malnutrition
- Digestive disorders
- Malabsorbtion
- Anorexia
- Intestinal fistula
- GIT stenosis
- Ileus
- Operations, GIT operations
- Intestinal inflammation
- Polytrauma
- Sepsis
- Peritonitis
- Head trauma
- Burns
- Pancreatitis
- Liver and renal failure

Prerequisities for nutritional support

- Inability to receive enteral nutrition
- Malnutrition
  - Anamnesis
  - Somatic examination, examination of nutriment, biochemistry, examination of organ function
- Evaluation of origin of malnutrition and impressibility by parenteral nutritional support
- Quality evaluation of periphery and central bloodstream

Contraindications

- Possibility of enteral nutrition
- Terminal disease
- Refusal
- Shock, instability of circulatory system

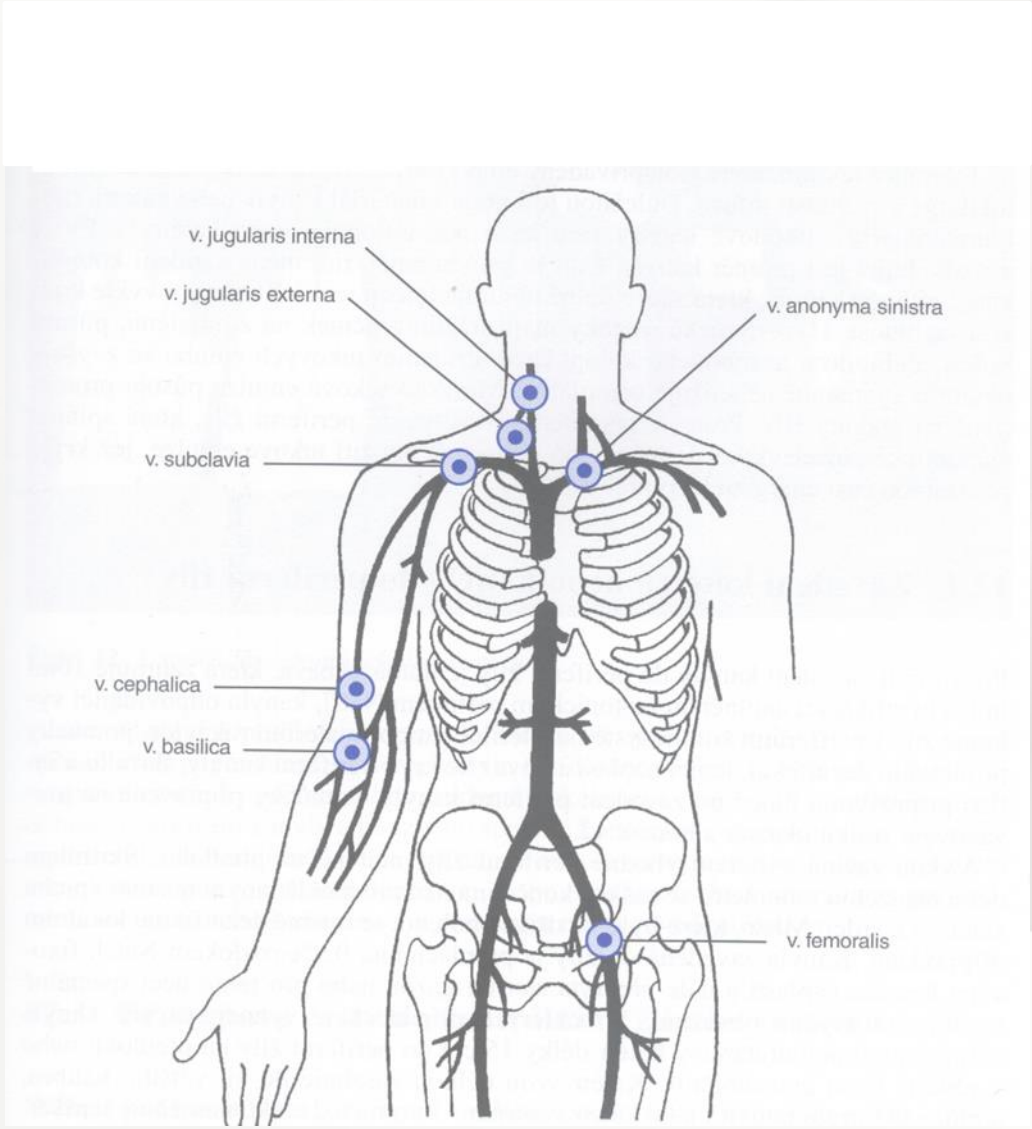
Types of prepration according to:

- Route of administration
  - Periphery nutrition (limbs)
  - Central nutrition (v. subclavia)
- Origin
  - Multiple bottles
  - A-I-O bags
    - » Adults
    - » Prematuruly born
- According to composition
  - » Supplementary
  - » Total
  - » Organ specific treatment (glutamine, ω-3 FA)

Why A-I-O?

- Better utilization of nutrients
- Lower incidence of metabolic complications
- Lower risk of infection
- Lower price (consumption of syringes, sets, needles)
- If possible, can be served in cycles with night pause

Routes of administration



Routes of administration

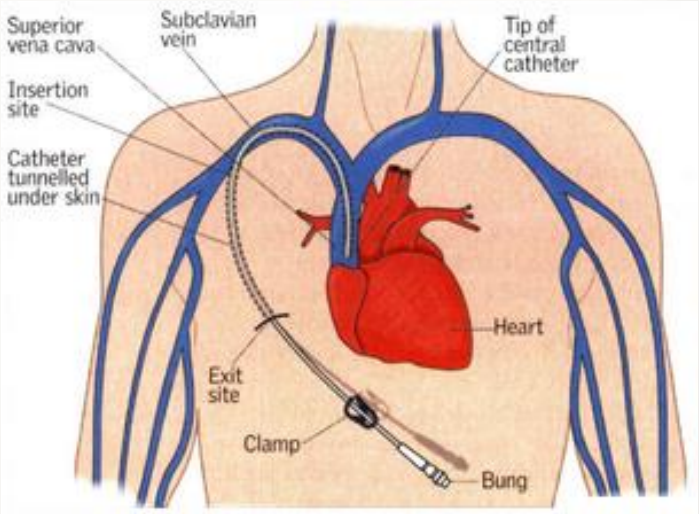
Periphery (limbs)

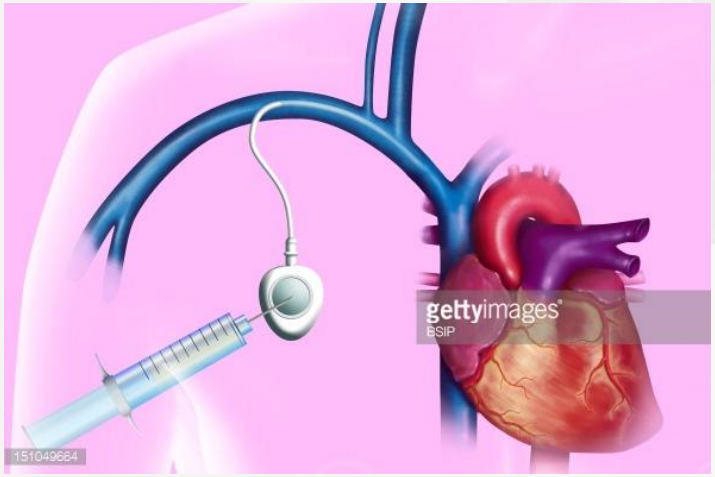
- Short term nutrition
- Osmolality max 900 mosmol/l (adults)
- Osmolality max 600 mosmol/l (children)
- For hydratation, vitamins, proteins

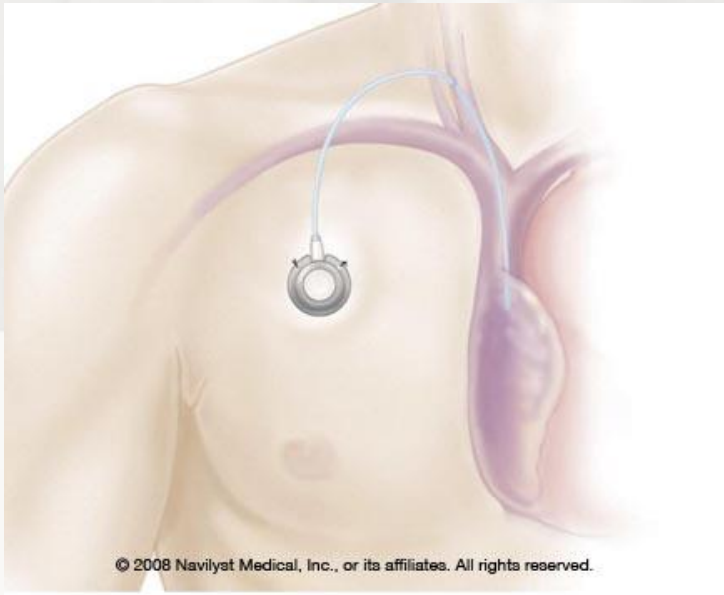
Central

- Long term nutrition
- Osmolality can be over 900 mosmol/l (adults)
- Has to be under sterile conditions (catheter sepsis)

Routes of administration







Formulation of parenteral nutrition preparation I

- Determine total energy need
  - 25-30 kcal/kg/day in stabilized patient, 35-40 kcal/kg/day in stressed patient
- Determine N and amino acids need
  - 0,75-1,75 g proteins/kg/day
  - Nutramines – AA for nutrition
  - Glutamine – in heavy sepsis, polytraumas = to overcome hypercatabolic condition

Formulation of parenteral nutrition preparation II

- Determine saccharide and lipide need
  - Sacharides = mainly glucose 3-5 g/kg/day
    - » Fructose, sorbitol, xylitol – not often, adverse effects
  - Lipid emulsion 2g/kg /day, max. speed 0,15g lipids/kg/hour
    - » Soybean oil (LCT) or comb. with MCT (medium chain triglyceride
    - » Olive oil
    - » Contraindication: acute liver failure, hypercholesterolemia…
- Consideration of suitability of specific nutritional substrates
  - Glutamine, arginine, branched AAs
- Determine dose of vitamins and trace elements
  - » depending on the length of administration, malnutrition degree, clinical status of the patient

Formulation of parenteral nutrition preparation III

- Determine the consumption of the ions and liquid
  - » Basal need according to Holiday-Segar equation:
  - » 100 ml/kg for first 10 kg
  - » 50 ml/kg second 10 kg
  - » 20 ml/kg for the rest of the weight (tj. weight over 20 kg)
  - » 30-40 ml of water/kg/day (can be raised up to 100 ml, usually should not exceed 45 ml/kg/day), sum up with metabolical water (107 ml in oxidation of 100 g of lipids, 55ml/100g sacharides, 41 ml/100g proteins)
  - » Ions
  - – take into account: fever, hydration level, phototeraphy, diuretics
- Determine dose of vitamins and trace elements
  - » depending on the length of administration, malnutrition degree, clinical status of the patient

Formulation of parenteral nutrition preparation IV

- Emulsifier
  - Only a in limited number (IV applications)
  - In fat emulsion
  - Lecithin
    - Biodegradable, can be metabolized, non toxic
    - Highly purified egg lecithin
    - Allergy! (plant oils on skin – transdermal transport)
  - X! Synthetic Emulsifiers
    - Risk of toxic effect on kidneys

Preparation of A-I-O bags

- Requirements
  - strictly sterile; controlled area A
- Filling precision
- System stability

  order of filling, pH, storage
- Sensitivity of emulsion

Preparation of A-I-O bags

Preparation of A-I-O bags

- Modern devices
  - Multi-channelled
  - Automatized
  - No need for manual solution addition
  - Macro & micro volumes
  - Computer with dedicated software (calculations)
  - Barcode reader

Preparation of A-I-O bags

Preparation of A-I-O bags

- Bags
  - Sterile
  - Easy handling; safety
  - Preferably plasticizer free (fat emulsions)
  - EVA
  - To ensure long shelf life
  - Several ports (injection/outlet)
  - Various volumes
  - Multi chamber bags

Preparation of A-I-O bags

Preparation of A-I-O problems

- Fat emulsion – surface potential (zeta) -35 mV in pH 5-8
- Majority of AA is electrically negative at pH 5,4 - 6,5; cysteine, asparagic a glutamic acid have negative charge at pH higher than 5,5
- Solubility of calcium phosphate at higher pH – shift from well soluble $Ca(H_2PO_4)_2$ to almost insoluble $CaHPO_4$

Monitoring of patients

- Clinical monitoring
  - Clinical examination
  - Observation of physical functions
  - Balance of liquids
  - Observation of weight
- Laboratory monitoring
  - Biochemical blood examination – mineralogram, glycemia, urea, creatinine, liver tests, prealbumine
  - Hematological examination

Parenteral Nutrition Risks

- Metabolical complications
  - Sacharide, lipide or protein metabolism disruption
- Venous cathether insertion
  - Infection, flebitis (periphery), sepsis, pneumothorax, embolism, thrombosis
- GIT disorder
  - Intestinal
  - Liver

Preparation of A-I-O for prematurely born children

Preparation of A-I-O for prematurely born children REQUIREMENTS

- The stability of the water management balance
- The stability of the internal environment at the immaturity of biochemical regulatory systems
- To secure energy resources to sustain a high level of growth
- Minimal risk of complications in vulnerable patients

Preparation of A-I-O for prematurely born children: specifics

- A high proportion of water on the body weight
- High water losses due to immature skin
- Rapid reduction in extracellular fluid without big changes of osmolality
- Maintenance of an adequate circulating volume enabling fetal circulation reconstruction

Preparation of A-I-O for prematurely born children

- Individual preparations according to protocols
- Mix of vitamins and lipids
- Diluted solutions of heparine 50UI/ml

• Water	120-150	ml/kg
• Energy	90-100	kcal/kg
• Proteins	2.5-3.5	g/kg
• Sacharides	10-15	g/kg
• Lipids	2.0-3.5	g/kg

Preparation of A-I-O for prematurely born children

- Carbonhydrates 50 - 55%
- Proteins 10 - 15%
- Lipids 30 - 40%
- A positive nitrogen balance is secured ratio 1 g AMK + 25-30 kcal of nonprotein energy.

Preparation of A-I-O for prematurely born children

Stage 1 - to prevent catabolism
(Day 0 - 30 kcal / kg - glucose + AA)

Stage 2 - to ensure claims of basal metabolism
(Day 3 - 50 kcal / kg - glucose + AA + lipids)

Stage 3 - after stabilization to initiate anabolism and growth
(Day 7 - 75 kcal / day - glucose + lipids + AA)

Further changes in the representation of the various energy sources according to actual usage

Adequate energy, water, minerals, vitamins and trace elements in the transition to full enteral nutrition, providing quality growth. Optimum is above the maximum

Pharmacist as a member of nutrition team

- Tasks
  - Parenteral nutrition preparation
  - Compatibility and stability of A-I-O preparations
  - Helps to devise new formulas of parenteral preparations
  - Economical analysis of treatment
  - Monitoring new trends in parenteral treatment

Pharmacist as a member of nutrition team

- Controls
  - Correct content of A-I-O during and after the preparation
  - Sterility of preparation
  - Pyrogenity of preparation
  - Purity and contamination of preparation workplaces

Thanks for your attention