Therapeutic options for patients with end stage renal disease (ESRD)

Renal replacement therapy

- RRT began in 1950
- Evolving method - continuous method
- Better access to RRT

Renal replacement therapy (RRT) - dialysis

- HD was the prototype of RRT
- Does HD replace all kidney function?

Renal replacement therapy options

- Hemodialysis hemofiltration, hemodiafiltration and hybrid treatments

- Peritoneal dialysis
  - continuous ambulatory peritoneal dialysis (CAPD)
  - automated peritoneal dialysis (APD)

- Kidney transplantion
  - Deceased Donor DD
  - Living Donor LD

Initiation of dialysis in chronic kidney disease (CKD)

The decision to initiate dialysis in a patient with chronic renal failure involves the consideration of subjective and objective parameters by the physician and the patient.

These parameters are often modulated by the patient's perception of his/her quality of life and by possible anxiety about starting new therapy that is technologically complex.

Dialysis modality and patient outcome

Most patients with ESRD can be treated with either hemodialysis or CAPD.

The choice of dialysis modality is in part influenced by nonmedical factors, including:

- patient preference,
- the location and ownership of the ambulatory facility,
- the availability of a training program for CAPD, and interfacility rivalry.

Initiation of dialysis in chronic kidney disease – when?

- Patients with CKD should be closely followed and the GFR estimated:

- GFR <50 ml/min (serum creatinine concentration 2-3 mg/dl)→ nephrologist care, education

Initiation of dialysis in chronic kidney disease – when?

- GFR<25 ml/min

  → we begin preparing the patient for RRT

(including discussion of the choice between HD or PD, and creation of an arteriovenous fistula with native vessels or a synthetic graft, KTx preemtive?)

- GFR<20 ml/min → vascular access or acces to peritoneal cavity or kidney transplantation

- GFR< 10 ml/min or GFR<20 ml/min in DM → start RRT

CLINICAL INDICATIONS

- Pericarditis
- Fluid overload or pulmonary oedema refractory to diuretics
- Accelerated hypertension poorly responsive to antihypertensive drugs
- Progressive uremic encephalopathy or neuropathy, with signs such as confusion, myoclonus, wrist or foot drop, or, in severe cases, seizures, brain oedema
- A clinically significant bleeding diathesis attributable to uremia – risk of bleeding to the CNS
- Persistent nausea and vomiting
- Arrhythmia due to hyperkalaemia

Indication for initiation of dialysis

Biochemical indication

- SCr>12 mg/l (>1060umol/l)
- Blood urea nitrogen concentration >250 mg/dl (>50 mmol/l)
- Serum bicarbonates concentration HCO3<13 mmol/l
- Hyperkalaemia>6.5 mmol/l (in AKI)

Contraindication

- Disseminated cancer
  (with metastasis)
- Severe dementia

Contraindications to dialysis modalities

Absolute	Relative
Peritoneal dialysis	
Loss of peritoneal function producing inadequate clearance	Recent abdominal aortic graft
Adhesions blocking dialysate flow	Large polycystic kidneys
Surgically uncorrectable abdominal hernia	Ventriculoperitoneal shunt
Abdominal wall stoma	Intolerance of intra-abdominal fluid
Diaphragmatic fluid leak	Large muscle mass
Inability to perform exchanges in absence of suitable assistant	Morbid obesity
	Severe malnutrition
	Skin infection
	Bowel disease
	Carriage of *S.aureus*
Hemodialysis	
No vascular access possible	Difficult vascular access
	Needle phobia
	Cardiac failure
	Coagulopathy

(Adapted from NKF-DOQI: NKF-DOQI Clinical Practice Guidelines for Peritoneal Dialysis Adequacy, 2000. Am J Kidney Dis 2001;37(Suppl 1):S65–S136.)

J.Feehally/J.Floege/R.J.Johnson

CLINICAL IMPORTANCE OF RESIDUAL RENAL FUNCTION

- The loss of residual renal function effects upon patient survival
- Remaining GFR may only be 4 to 5 mL/min, but is sufficient to make a significant contribution to the removal of potential uremic toxins since filtration is continuous as opposed to the 12 hours per week that the patient is undergoing hemodialysis
- Continued urine output facilitates the regulation of fluid and electrolyte balance, and may enhance nutritional status and

Renal replacement therapy options

- Hemodialysis, hemofiltration, hemodiafiltration and hybrid treatments

- Peritoneal dialysis
  - continuous ambulatory peritoneal dialysis (CAPD)
  - automated peritoneal dialysis (APD)

- Kidney transplantation
  - DD
  - LD

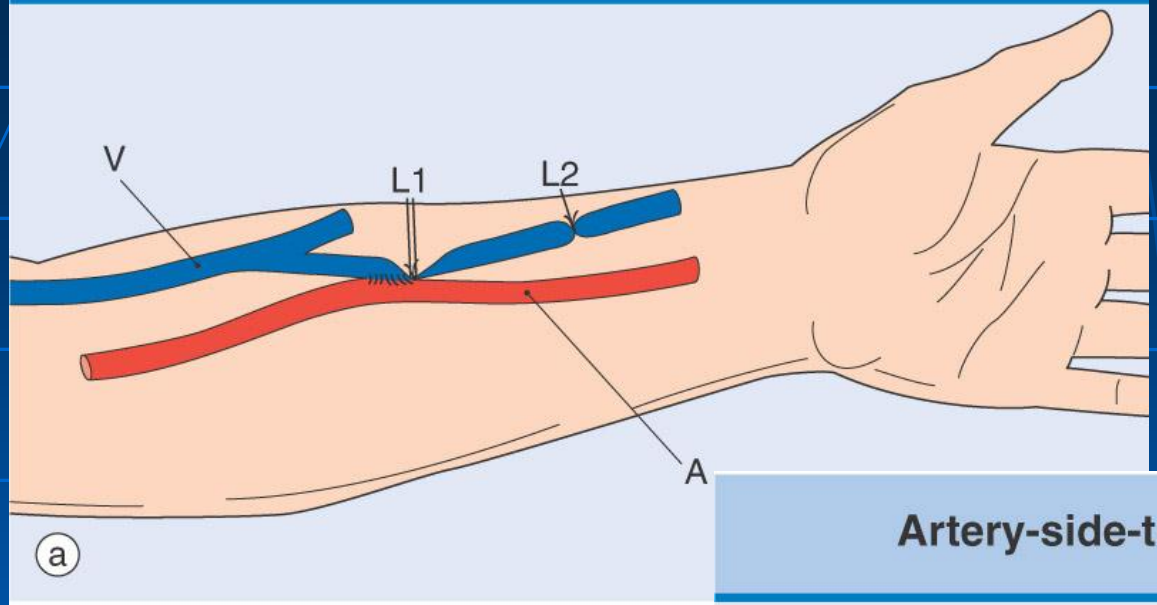
- Hemodialysis requires access to the pts circulation to provide continuous blood flow to the extracorporeal dialysis circuit

- For ongoing HD an autologous arteriovenous fistula is the most reliable type of vascular access

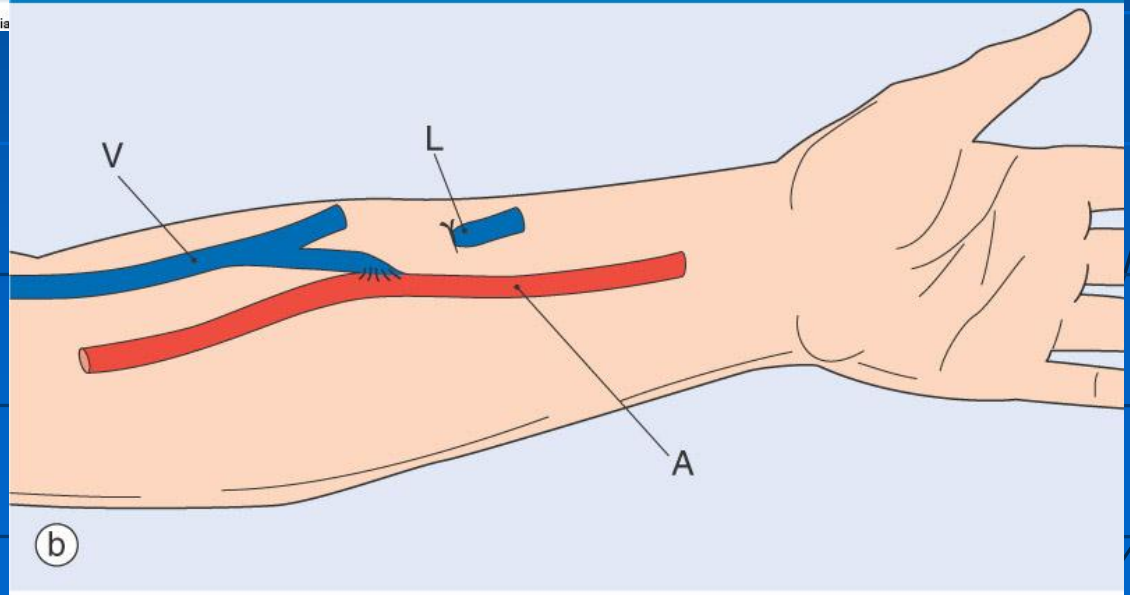
Long term patentcy is greatest with A-V fistulas, and the incidence rates of thrombosis and infection are low

A-V graft (synthetics) are often used in elderly and DM pts

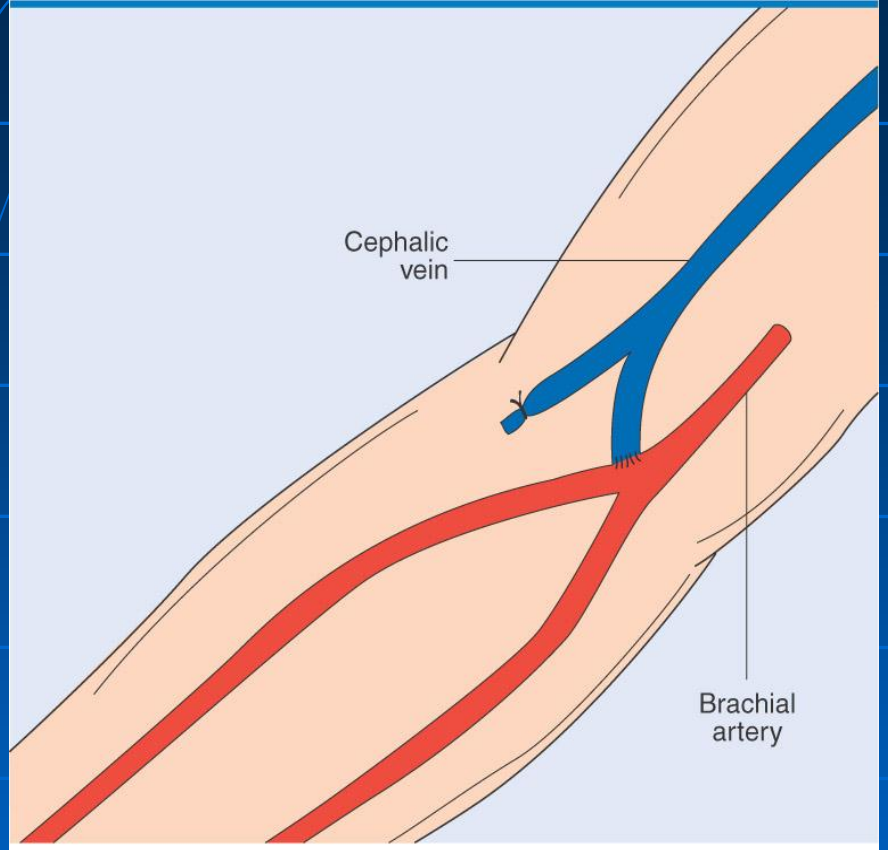
Side-to-side anastomosis



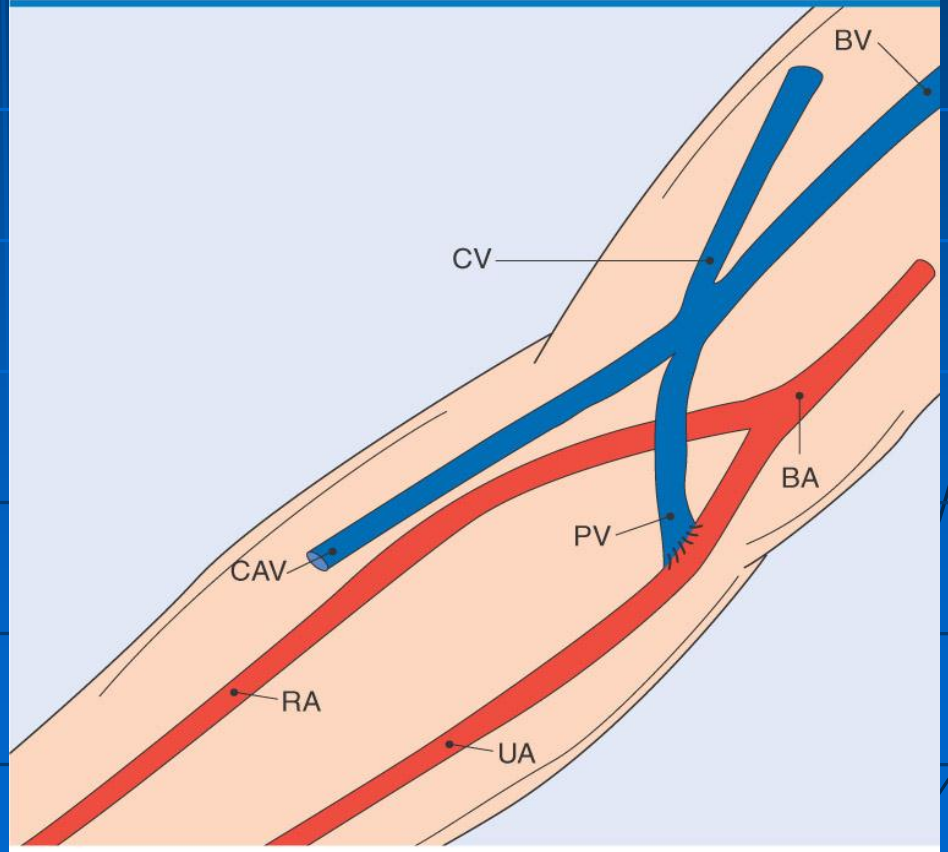
Artery-side-to-vein-end anastomosis



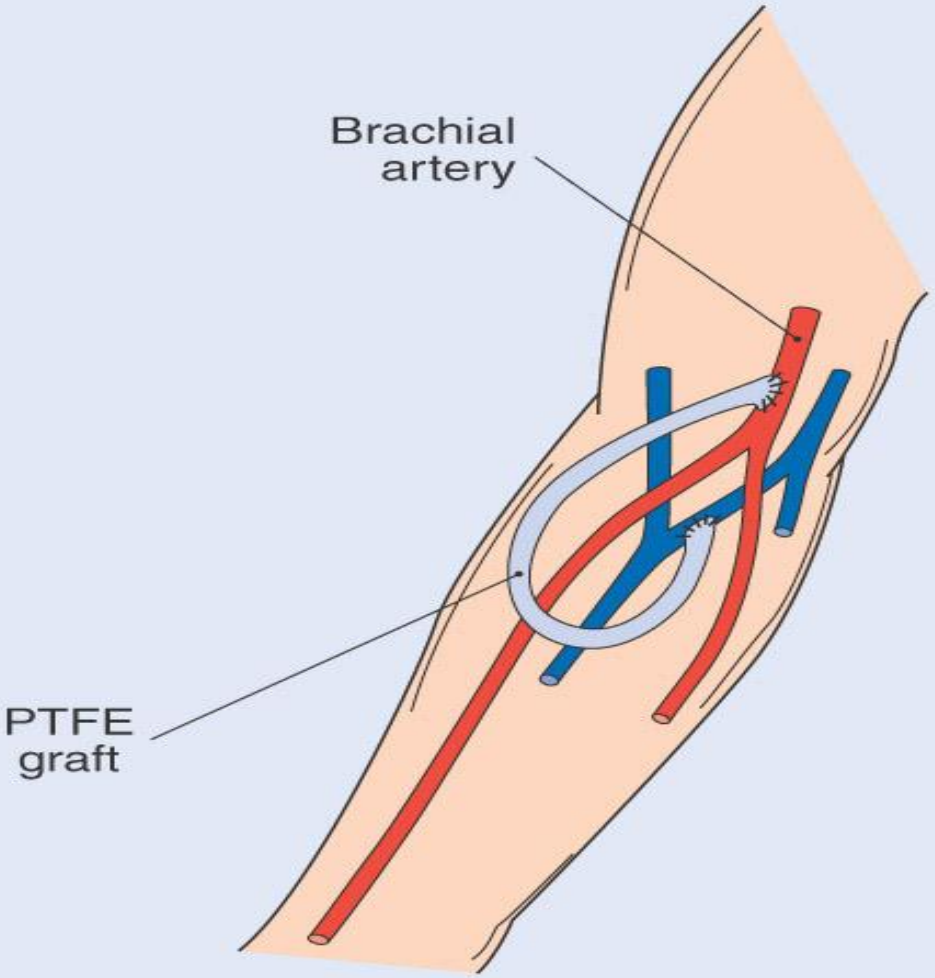
Upper-arm primary arteriovenous fistula



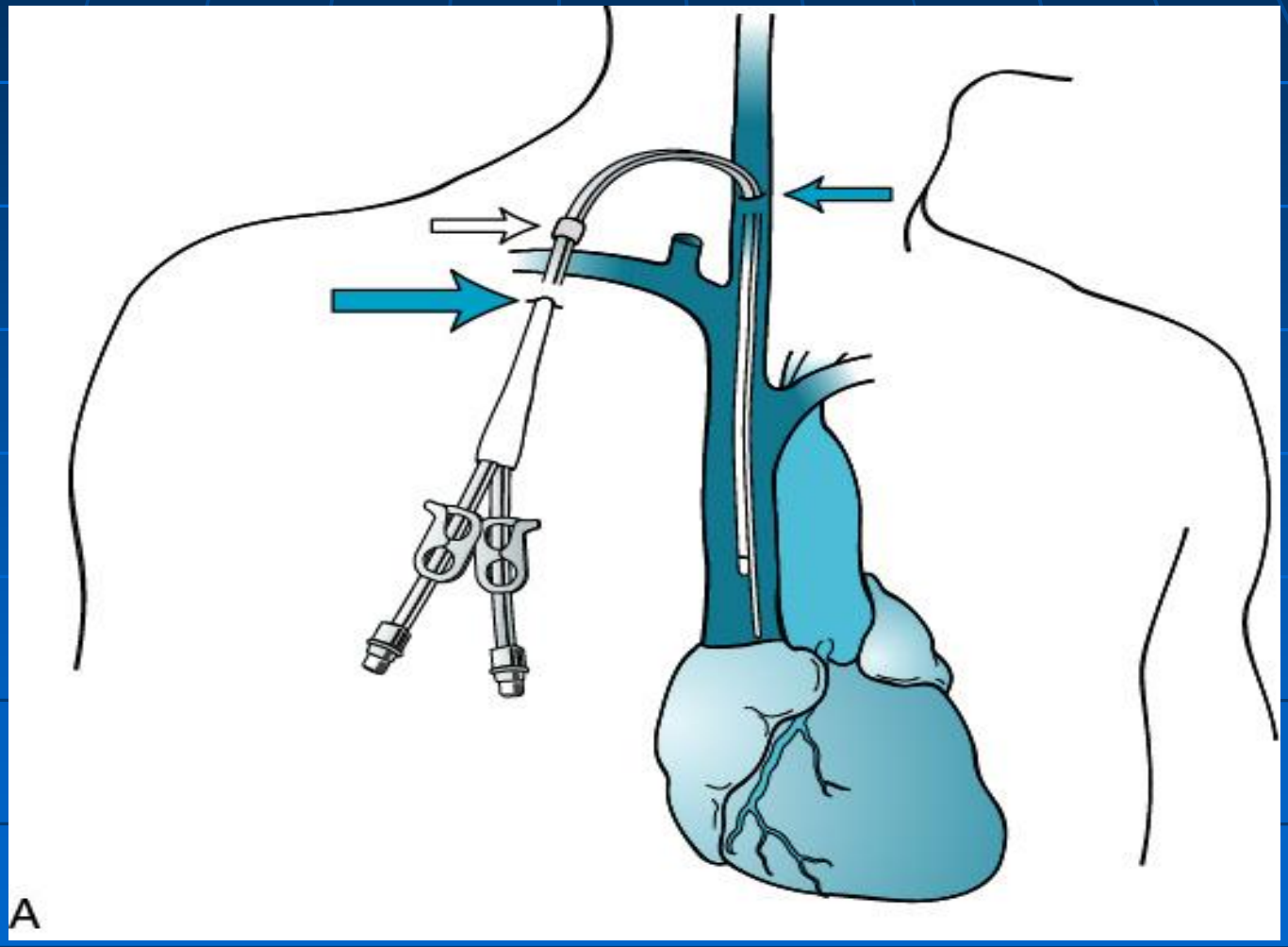
Upper-arm primary arteriovenous fistula using the perforating vein



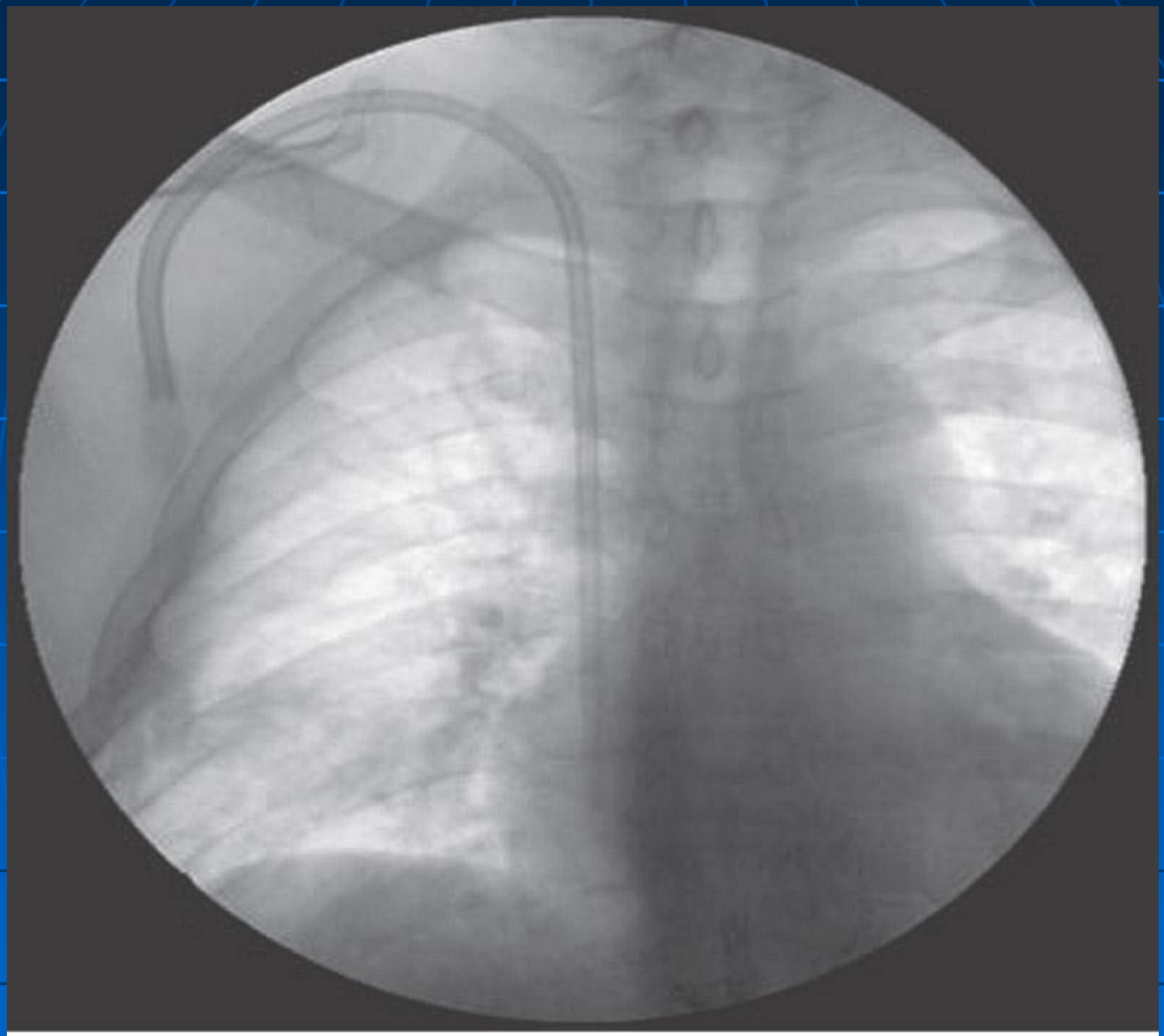
Arteriovenous polytetrafluoroethylene grafts in the arm



Temporary venous catheters are used to establish vascular access when HD must be started urgently.



Toros Kapoian, Jeffrey L. Kaufman, John Nosher & Richard A. Sherman



The tip of the catheter is at the junction of the superior vena cava and the right atrium

Hemodialysis (HD)

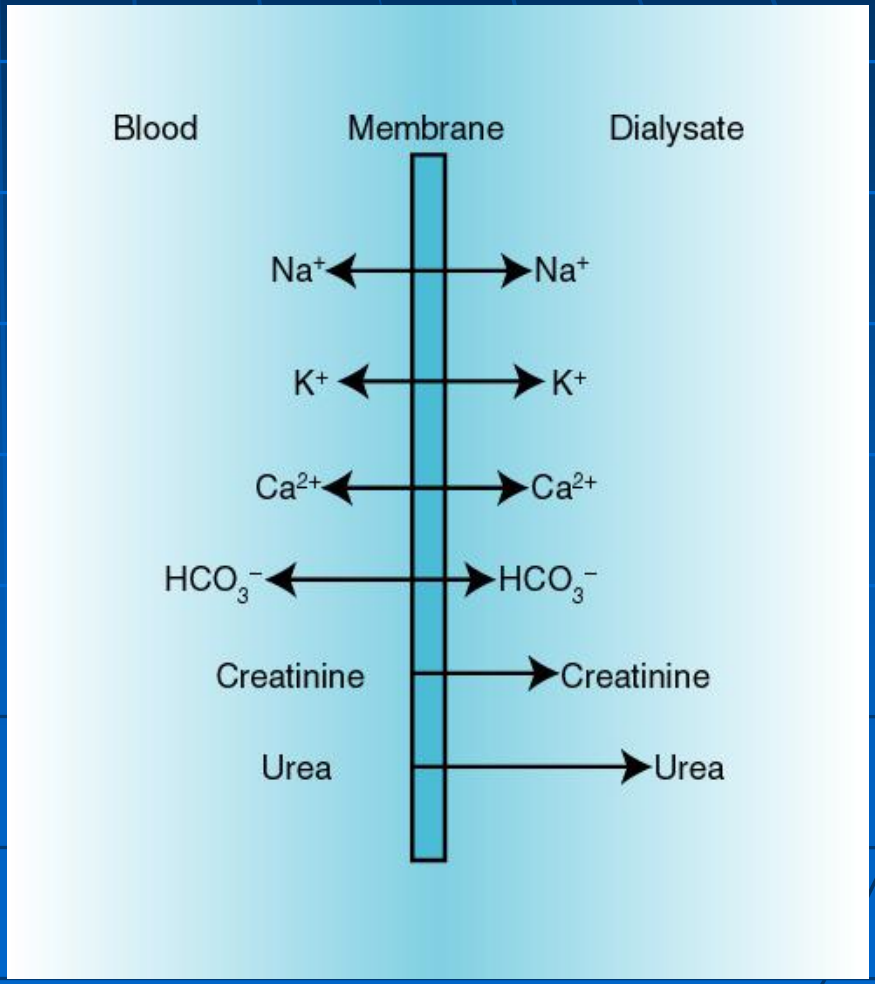
- Predominant technique
- Treatments typically range in lenght 3-5 hours three times a week

- HD refers to the transport process by which a solute passively diffuses down its concentration gradient from one fluid compartment (either blood or dialysate) into the other

- Solutes are removed by diffusion across a semipermeable membrane within a dialyzer, from a blood circulated through an extracorporeal circuit

Hemodialysis (HD)

During HD, urea, creatinine, and potassium move from blood to dialysate, while other solutes, such as calcium and bicarbonate, move from dialysate to blood



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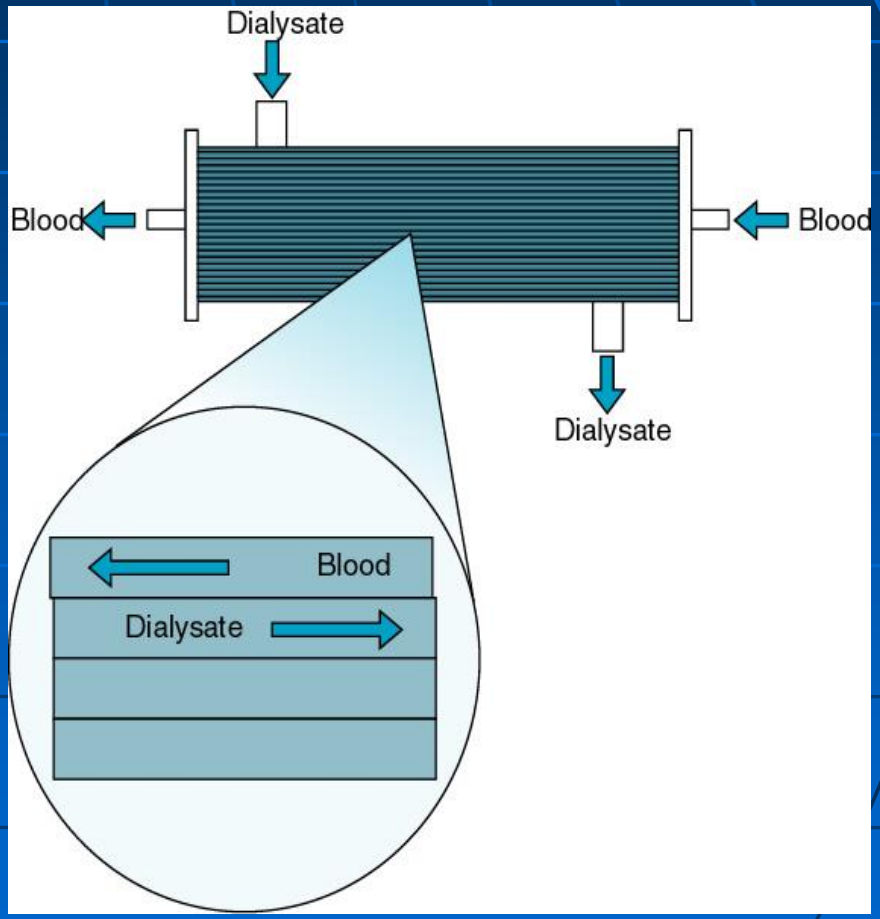
Hemodialysis (HD)

The dialysate flows countercurrent to blood flow through the dialyzer to maximize the concentration gradient between the compartments and therefore to maximize the rate of solute removal. The net effect is the production of desired changes in the plasma concentrations of these solutes: a reduction in the blood urea nitrogen and plasma creatinine concentration; and an elevation in the plasma calcium and bicarbonate concentrations



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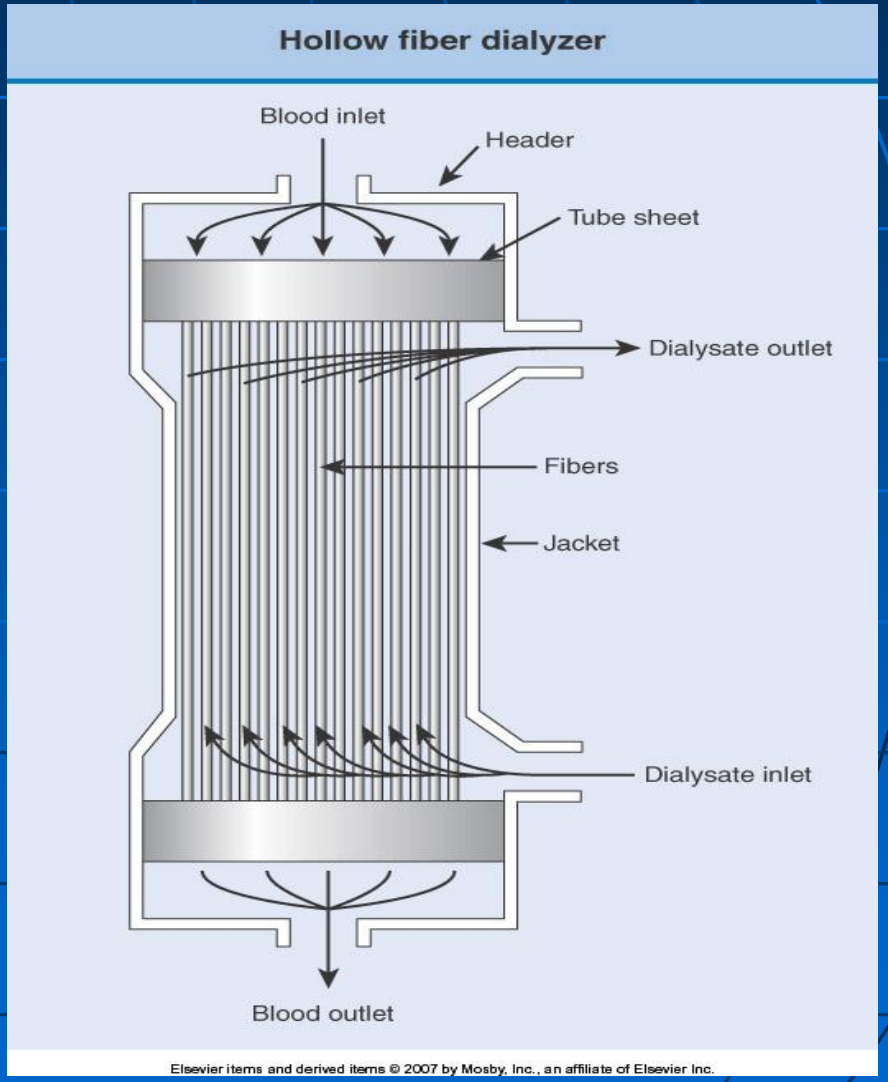
DIALYZERS


F60
HF80


Hollow fiber dialyzer
Blood inlet
Header
Tube sheet
Dialysate outlet
Fibers
Jacket
Dialysate inlet
Blood outlet
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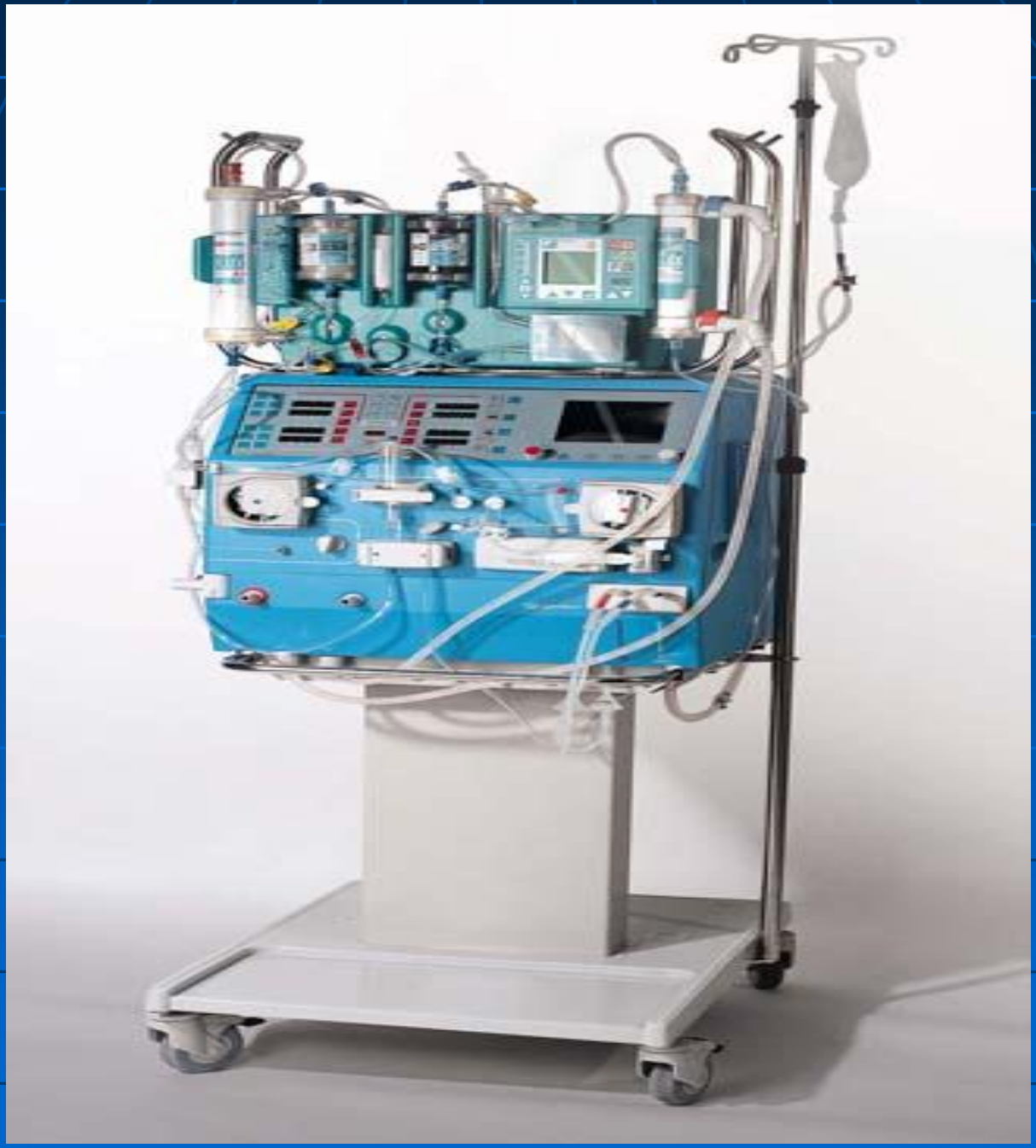
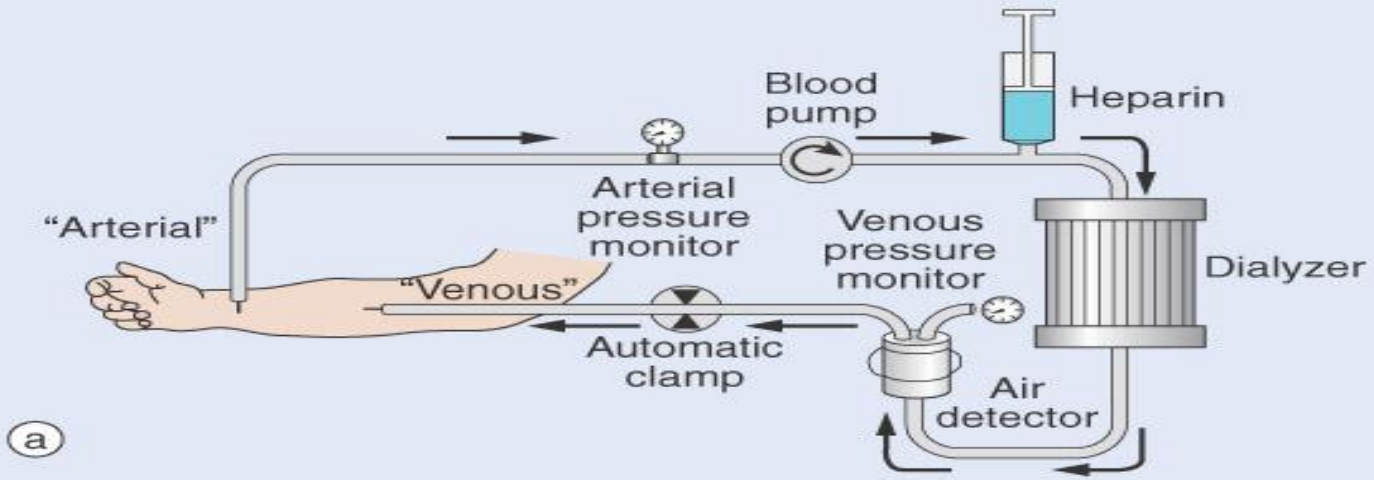
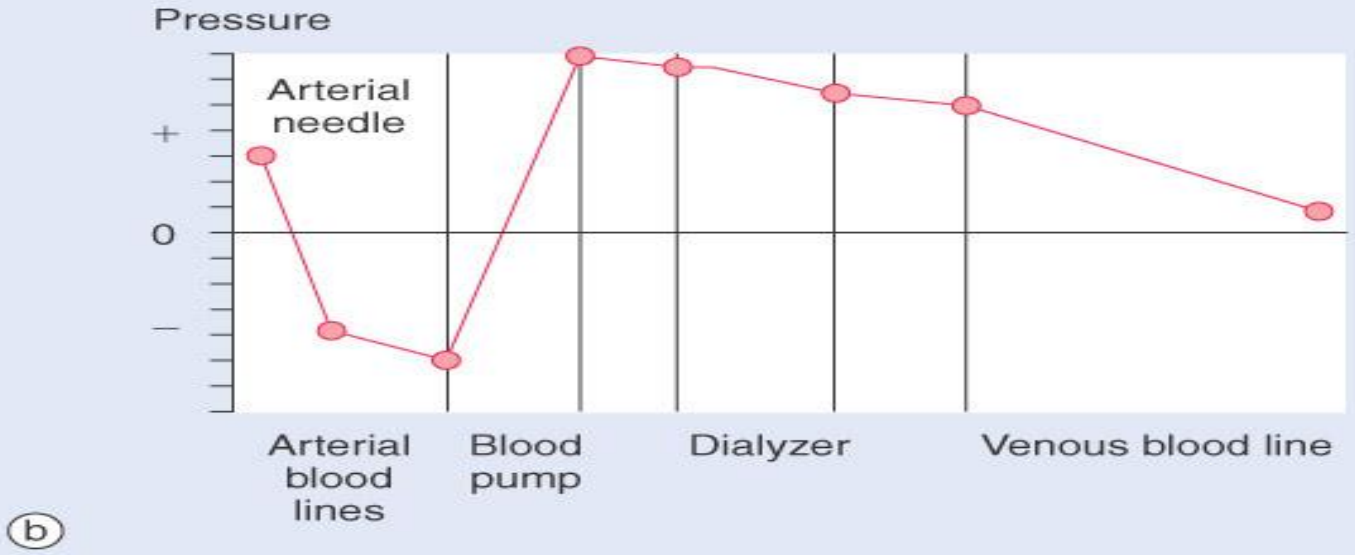
Dialysis membrane properties

Membrane	Membrane Name (example)	High or Low Flux	Biocompatibility
Cellulose semisynthetic cellulose			
Cellulose diacetate	Cellulose acetate	High and low	Intermediate
Cellulose triacetate	Cellulose triacetate	High	Good
Diethylaminoethyl-substituted cellulose	Hemophane	High	Intermediate
Synthetic polymers			
Polymethylmethacrylate	PMMA	High	Good
Polyacrylonitrile methacrylate copolymer	PAN	High	Good
Polyacrylonitrile methallyl sulfonate copolymer	PAN/AN-69	High	Good
Polyamide	Polyflux	High	Good
Polycarbonate/Polyether	Gambrane	High	Good
Polyethylene/Vinyl alcohol	EVAL	High	Good
Polysulfone	Polysulfone	High	Good

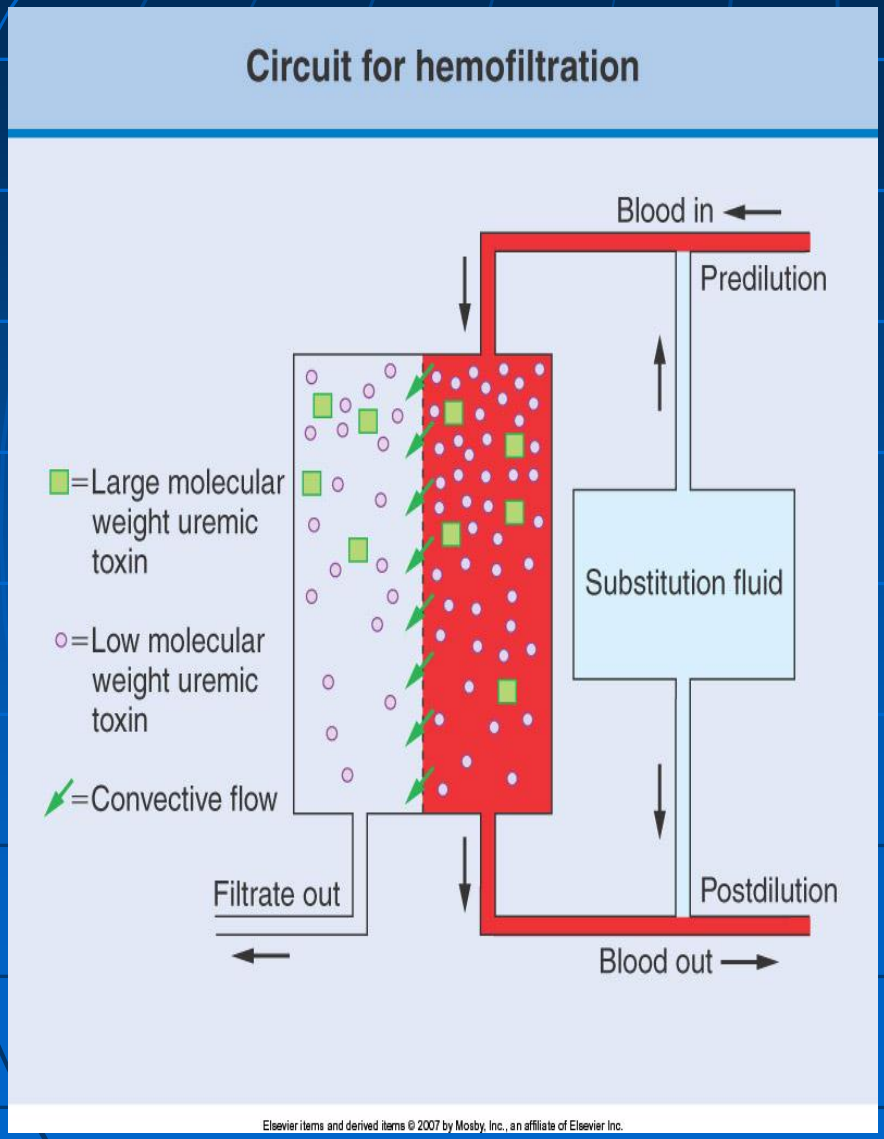


Blood circuit for hemodialysis





HEMOFILTRATION – high convective transport of substances



Blood under pressure passes down one side of a highly permeable membrane allowing both water and substances up to molecular weight of about 20kd to pass across the membrane by convective flow.

Pts receives a substitution fluid either before(predilution) or after (postdilution) the dialyzer.

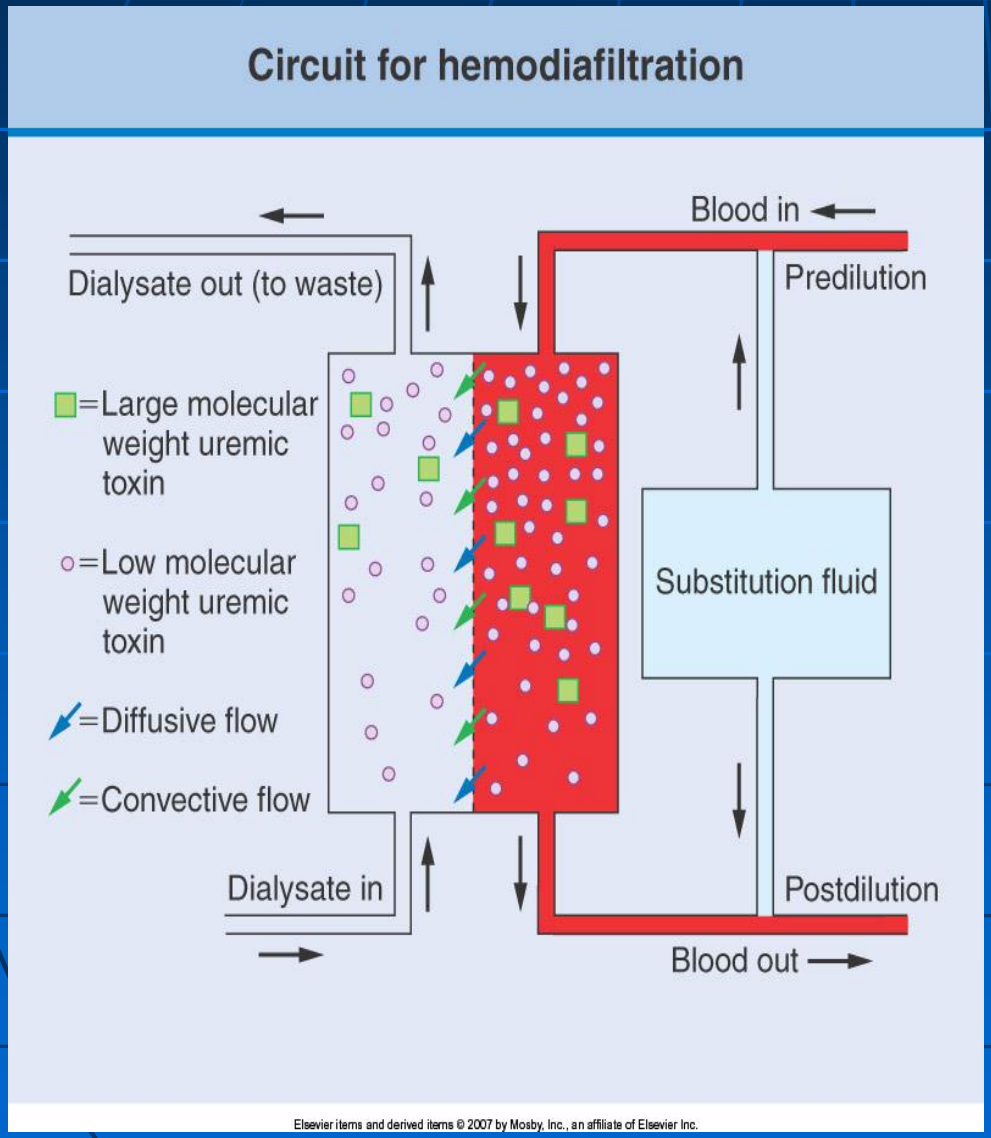
In pts with fluid overload, a negative fluid balance can be obtained by replacing less fluid through infusion that is removed.

Hemofiltration

- Hemofiltration (HF) refers to the use of a hydrostatic pressure gradient to induce the filtration (or convection) of plasma water across the membrane of the hemofilter. The frictional forces between water and solutes (called solvent drag) results in the convective transport of small and middle molecular weight solutes (less than 5000 Daltons) in the same direction as water. Substitution fluid is usually required to prevent excessive fluid removal

- The process of HF itself removes smaller solutes (such as urea and electrolytes) in roughly the same concentration as the plasma. There is therefore no change in the plasma concentrations of these solutes by HF, in contrast to those achieved by HD. However, the administration of substitution fluid will lower by dilution the plasma concentrations of those solutes (such as urea and creatinine) not present in the substitution fluid

HEMODIAFILTRATION = HD (high transport rate of low molecular weight solutes by diffusion) + HF(high convective transport of substances)



Anemia correction, ↓inflammation, oxidative stress, lipid profiles, calcium-phosphate product

Prevention of long-term complications; ex;amyloidosis

Adequacy of hemodialysis - assessment of dialysis dose

Computation of dialysis dose: results derived from different model equations

Formula	Result	Comment
$URR = (1 - C_t / C_0) \times 100\%$	67%	Urea rebound, urea generation, and ultrafiltration not taken into account
$Kt/V = \ln (C_0 / C_t)$	1.10	Urea rebound, urea generation, and ultrafiltration not taken into account
$spKt/V = -\ln (R - 0.008 \times t) + (4 - 3.5\ R) \times UF/W$	1.33	Single pool model; urea rebound not taken into account
$eKt/V = spKt/V - 0.6 \times spKt/V/t + 0.03$	1.16	Equilibrated double pool model for arteriovenous access
$eKt/V = spKt/V - 0.47 \times spKt/V/t + 0.02$	1.20	Equilibrated double pool model for central venous access

Patient's complaints during HD

1. Hypotension — 25 to 55 percent of treatments
2. Cramps — 5 to 20 percent
3. Nausea and vomiting — 5 to 15 percent
4. Headache — 5 percent
5. Chest pain — 2 to 5 percent
   may be associated with hypotension or dialysis disequilibrium syndrome*, angina, hemolysis, and (rarely) air embolism.
6. Back pain — 2 to 5 percent
7. Itching — 5 percent
8. Fever and chills — Less than 1 percent

Acute complications during HD

1.Dialysis reactions

Anaphylactic reactions

- first-use dialyzer syndrome (ethylen oxide acts as an allergen when conjugated to human serum albumin)

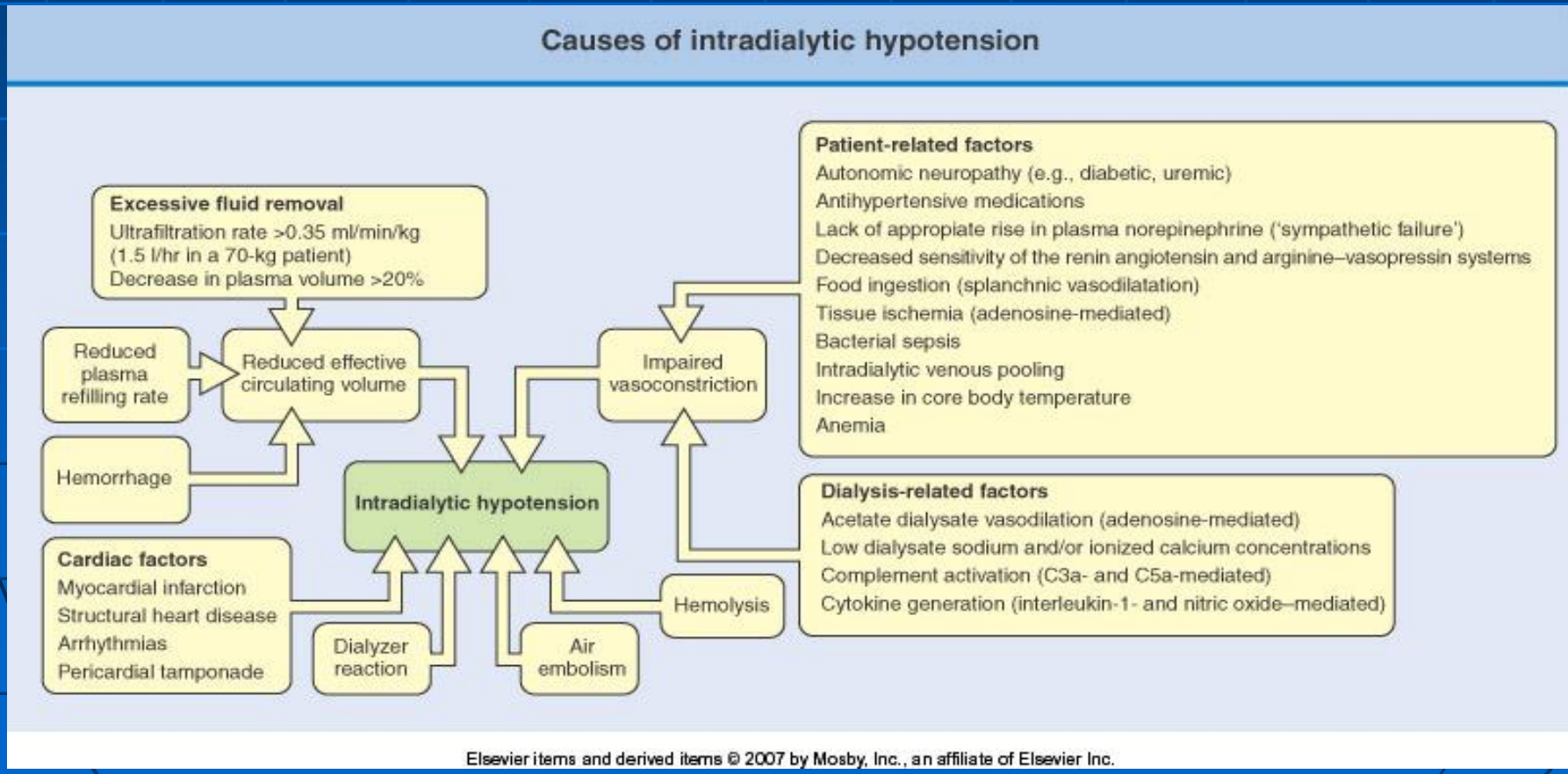
- bradykinin-mediated reactions (binding of factor XII to sulfonate-containing, negatively charged membrane results in the release of bradykinin).

- drug induced reactions

- microbial contamination

Acute complications during HD

2. Cardiovascular complications
   - hypotension
   - hypertension (primarily volumne dependent)



Acute complications during HD

2. Cardiovascular complications
   - cardiac arrhytmias
   - sudden death

Electrocardiographic abnormalities in renal failure

Function	Abnormality Seen in Renal Failure
P-R interval	Usually normal; prolongation in long-term hemodialysis Calcification of mitral valve annulus may involve His bundle, giving complete heart block
QRS interval	
Amplitude	Increases during ultrafiltration (correlates with reduction in left ventricular [LV] dimensions) LV hypertrophy (LVH) on voltage criteria found in up to 50%
Duration	Prolonged (within normal range) by hemodialysis Late potentials increased only in patients with pre-existing ischemic heart disease Prolonged in hyperkalemia
ST segment	Depression during hemodialysis does not predict coronary artery disease Depression or elevation may occur in hyperkalemia Depression during ambulatory monitoring poorly predictive of coronary artery disease
Q-T_c interval	Increases during hemodialysis (correlates with reduction in $[K^+]$ and $[Mg^{2+}]$) Increased Q-T dispersion reported in patients on dialysis
T wave	Peaking or inversion may occur in hyperkalemia Inversion in anterolateral leads in LVH with strain pattern
Rhythm	High incidence of atrial and ventricular arrhythmias during hemodialysis

Acute complications during HD

3.Neuromuscular complications

- muscle cramps

- in 33 to 86 percent of patients. Etiology is unknown - tend to occur most frequently near the end of hemodialysis treatments, changes in plasma osmolality and/or extracellular fluid volume have been implicated. Following factors may contribute: Plasma volume contraction, Hyponatremia, Tissue hypoxia, Hypomagnesemia.
- **TREATMENT** — the minimization of interdialytic weight gains, the prevention of dialysis-associated hypotension, the use of high concentrations of sodium in the dialysate.
- **Treatment of cramps during hemodialysis** — Hypertonic saline or Mannitol infusions.

- restless legs syndrome

Acute complications during HD

3.Neuromuscular complications

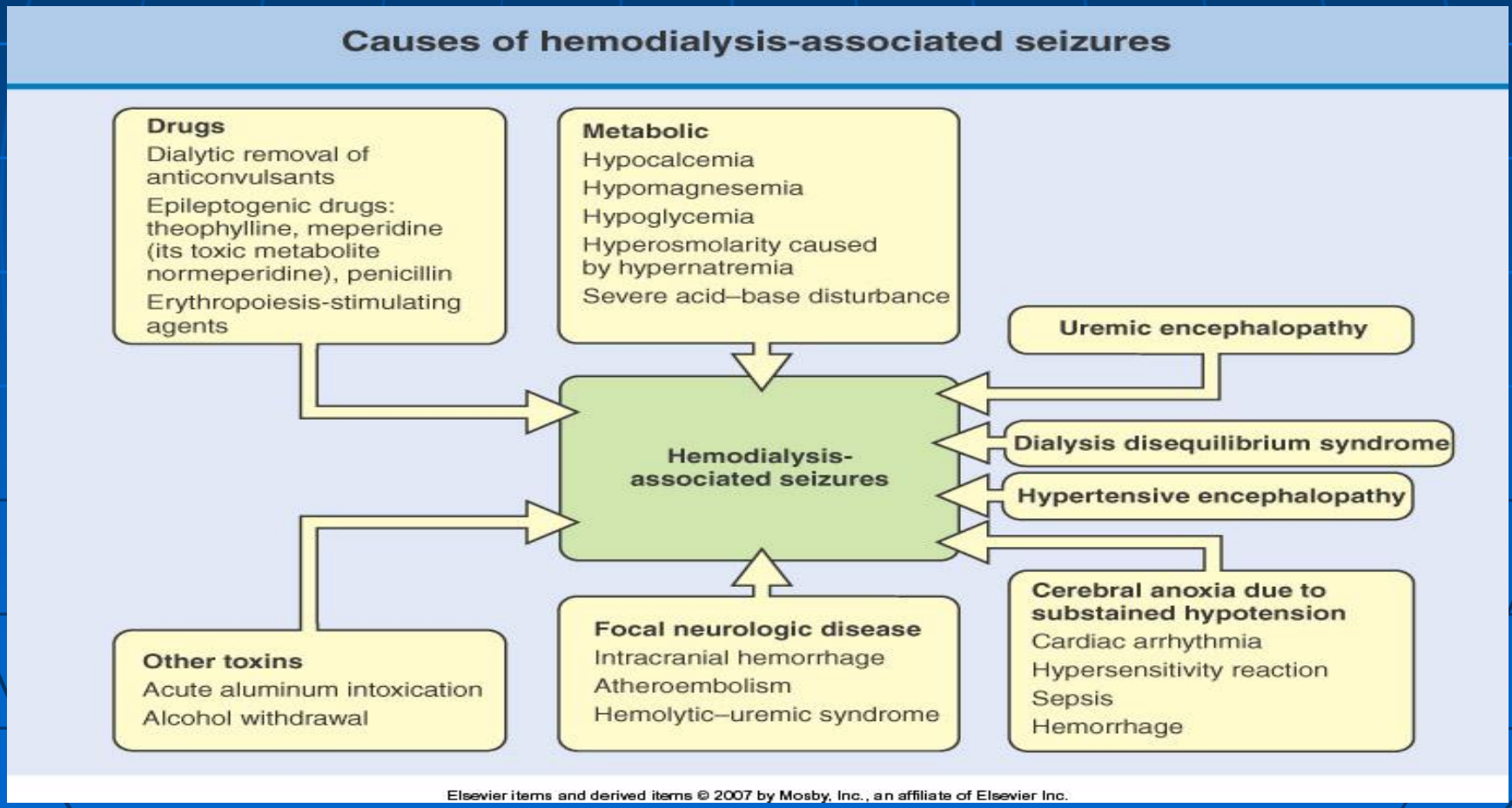
- dialysis disequilibrium syndrome is caused by water movement into the brain, leading to cerebral edema

CLINICAL MANIFESTATIONS —acute symptoms developing during or immediately after hemodialysis. Early findings include headache, nausea, disorientation, restlessness, blurred vision. More severely affected patients progress to confusion, seizures, coma, and even death. However, that many milder signs and symptoms associated with dialysis — such as muscle cramps, anorexia, and dizziness developing near the end of a dialysis treatment — are also part of this syndrome.

- **DIFFERENTIAL DIAGNOSIS** — uremia itself, subdural hematoma, cerebral infarction, intracerebral hemorrhage, meningitis, metabolic disturbances (hyponatremia, hypoglycemia), and drug-induced encephalopathy
- **PREVENTION** — The initial dialyses should be gentle, but repeated frequently. The aim is a gradual reduction in BUN
- **TREATMENT** —symptoms are self-limited and usually dissipate within several hours. The management of mild DDS is symptomatic; the blood flow rate should be slowed and consideration should be given to stopping the dialysis session. Dialysis is stopped in the patient with seizures, coma. Severe DDS with seizures can be reversed more rapidly by raising the plasma osmolality with infusion of hypertonic fluid.

Acute complications during HD

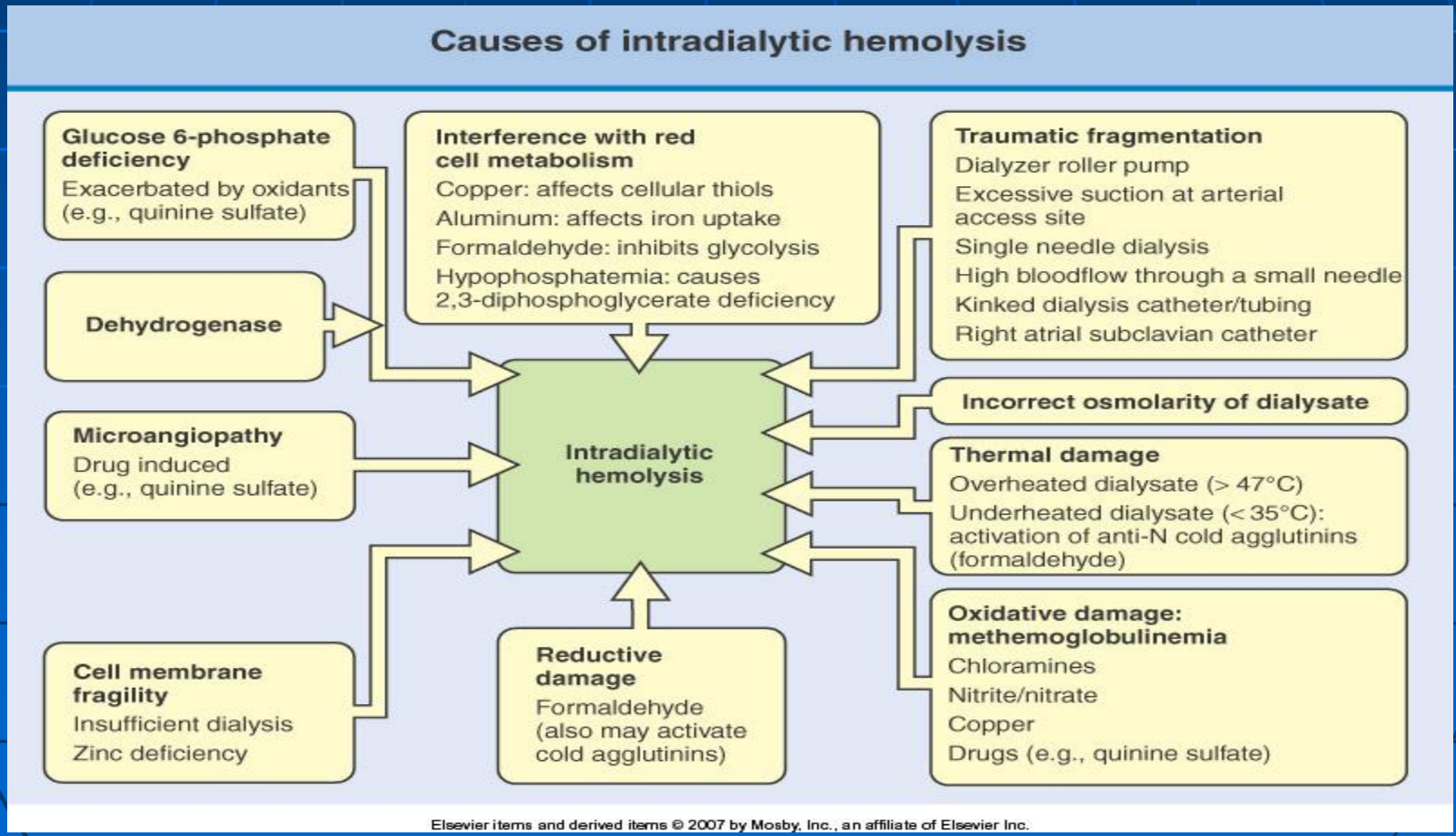
3.Neuromuscular complications
- seizures
- headache



Acute complications during HD

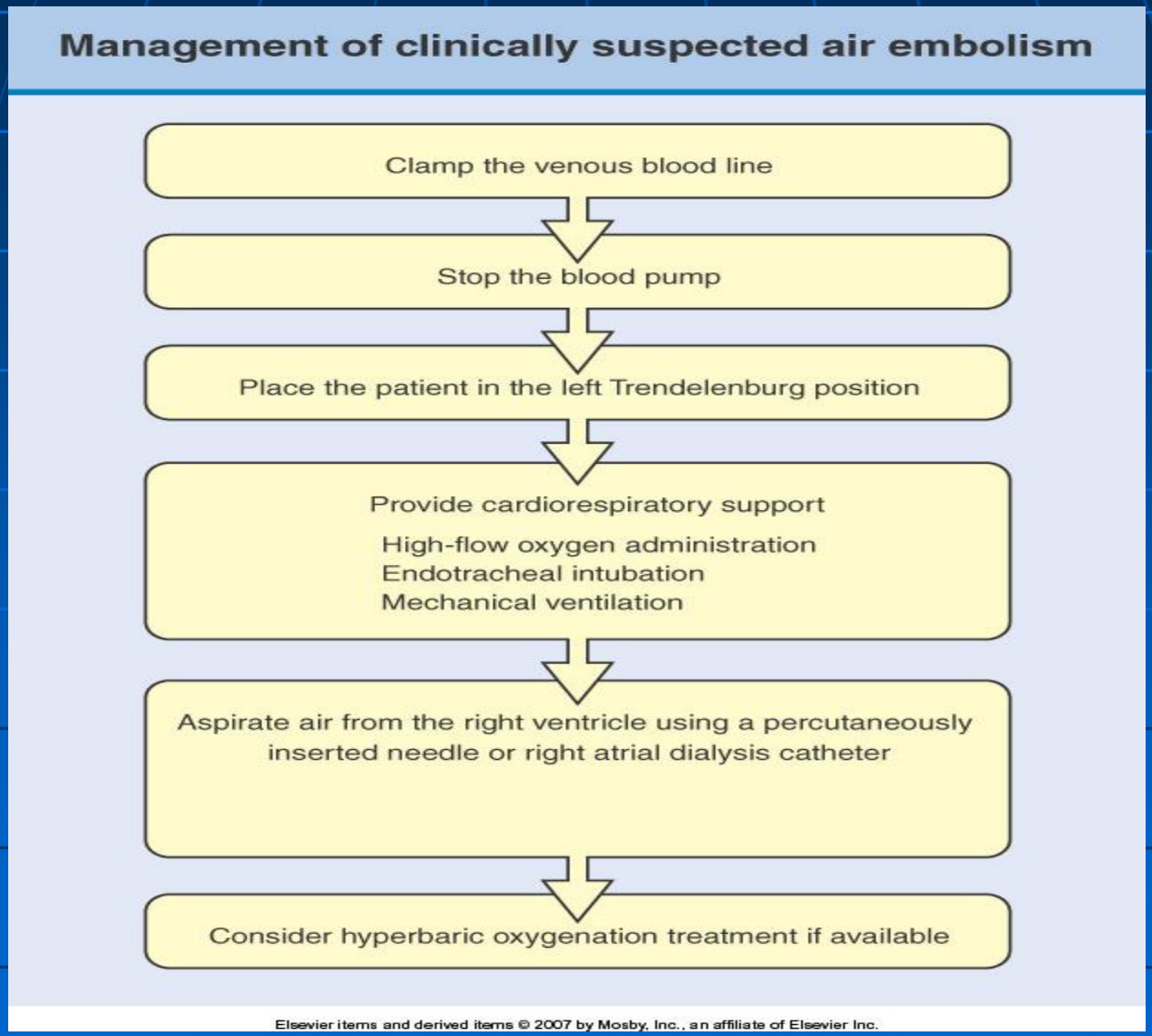
4. Hematologic complications

- complement activation and dialysis-associated neutropenia
- hemorrhage (intradialytic anticoagulation).
- intradialytic hemolysis (may present as chest pain, chest tightness, or back pain).



Acute complications during HD

5. Others; air embolism



Acute complications during HD

5. Others

- hypernatremia
- hyponatremia
- matabolic acidosis
- matabolic alkalosis
- temperature monitor malfunction
- blood loss

Long term complications of dialysis

Dialysis-related amyloidosis

- Dialysis-related amyloidosis (DRA) develops in long-term dialysis patients. Tissue deposition of amyloid occurs much earlier than any clinical or radiographic manifestations of the illness. Joint amyloid deposition in 100 percent of patients hemodialysed for more than thirteen years.

CLINICAL MANIFESTATIONS —carpal tunnel syndrome, bone cysts, spondoylarthopathy, pathologic fractures, and swollen painful joints, especially in the form of scapulohumeral periarthritis, effusive arthropathy, spondyloarthropathy. Consequence of preferential amyloid deposition in the bones, joints, and synovium.

Continuous renal replacement therapies:

- Continuous renal replacement therapies (CRRTs) involve either dialysis (diffusion-based solute removal) or filtration (convection-based solute and water removal) treatments that operate in a continuous mode.
- Variations of CRRT might run 12 to 20 hours, especially during daytime periods of full staffing. This regimen has become more prevalent in Europe and has been called "go slow dialysis". The longer duration of CRRT makes it quite different from conventional intermittent hemodialysis in which each treatment lasts four to six hours or less.

Continuous renal replacement therapies

- The major advantage of continuous therapy is the slower rate of solute or fluid removal per unit of time. Thus, CRRT is generally better tolerated than conventional therapy, since many of the complications of intermittent hemodialysis are related to the rapid rate of solute and fluid loss

Continuous renal replacement therapies

- Blood access:
- Arteriovenous
  Continuous arteriovenous hemofiltration
  Continuous arteriovenous hemodialysis
  Continuous arteriovenous hemodiafiltration
- Venovenous
  Continuous venovenous hemofiltration
  Continuous venovenous hemodialysis
  Continuous venovenous hemodiafiltration
- Slow continuous ultrafiltration
  Slow low efficiency dialysis or diafiltration
  Slow low efficiency daily dialysis
  Extended daily dialysis
- Peritoneal access
  Continuous equilibrium peritoneal dialysis

Renal replacement therapy options

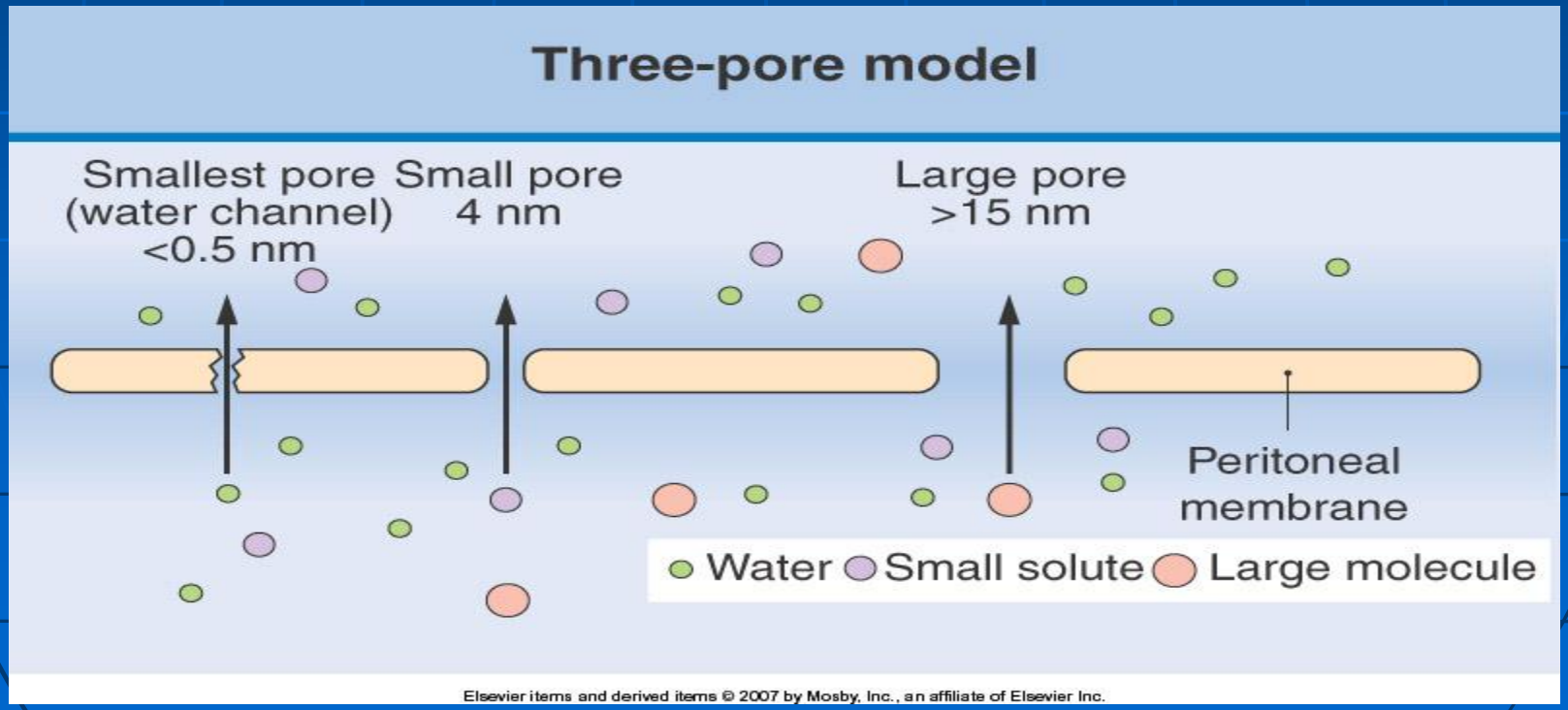
- Hemodialysis,hemofiltration, hemodiafiltration and hybrid treatments

- Peritoneal dialysis
  - continuous ambulatory peritoneal dialysis (CAPD)
  - automated peritoneal dialysis (APD)

- Kidney transplant
  - DD
  - LD

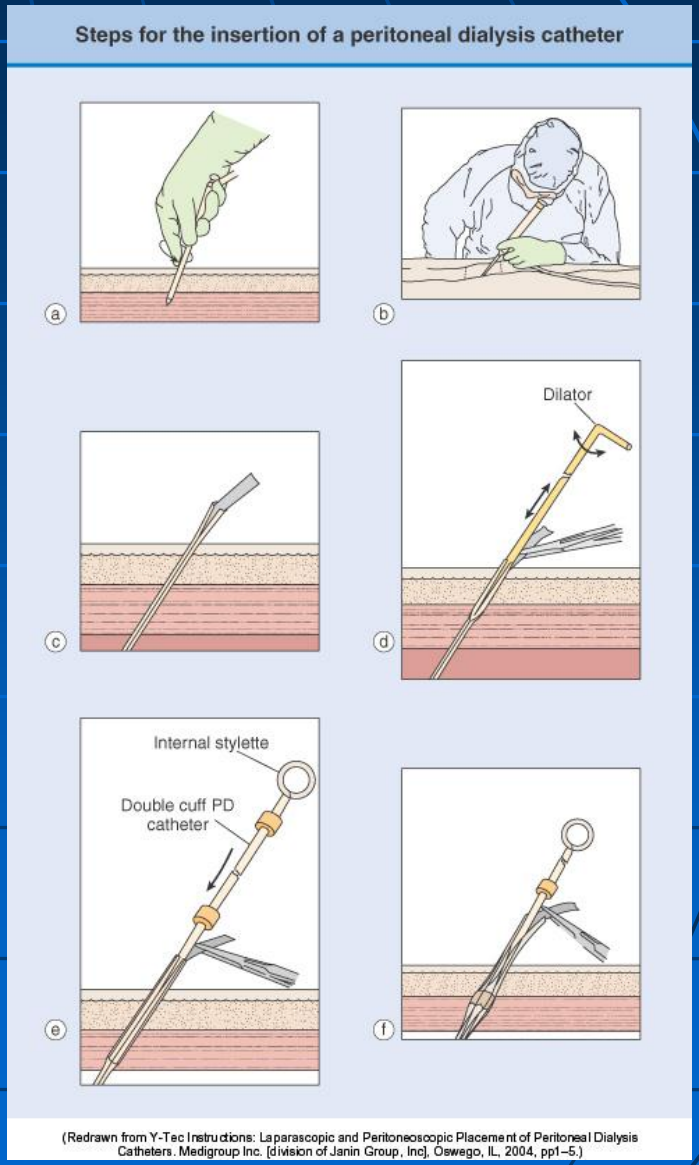
Peritoneal dialysis (PD)

- Alternative to HD –
  exploits the peritoneum as an endogenous dialysis membrane



Peritoneal dialysis (PD)

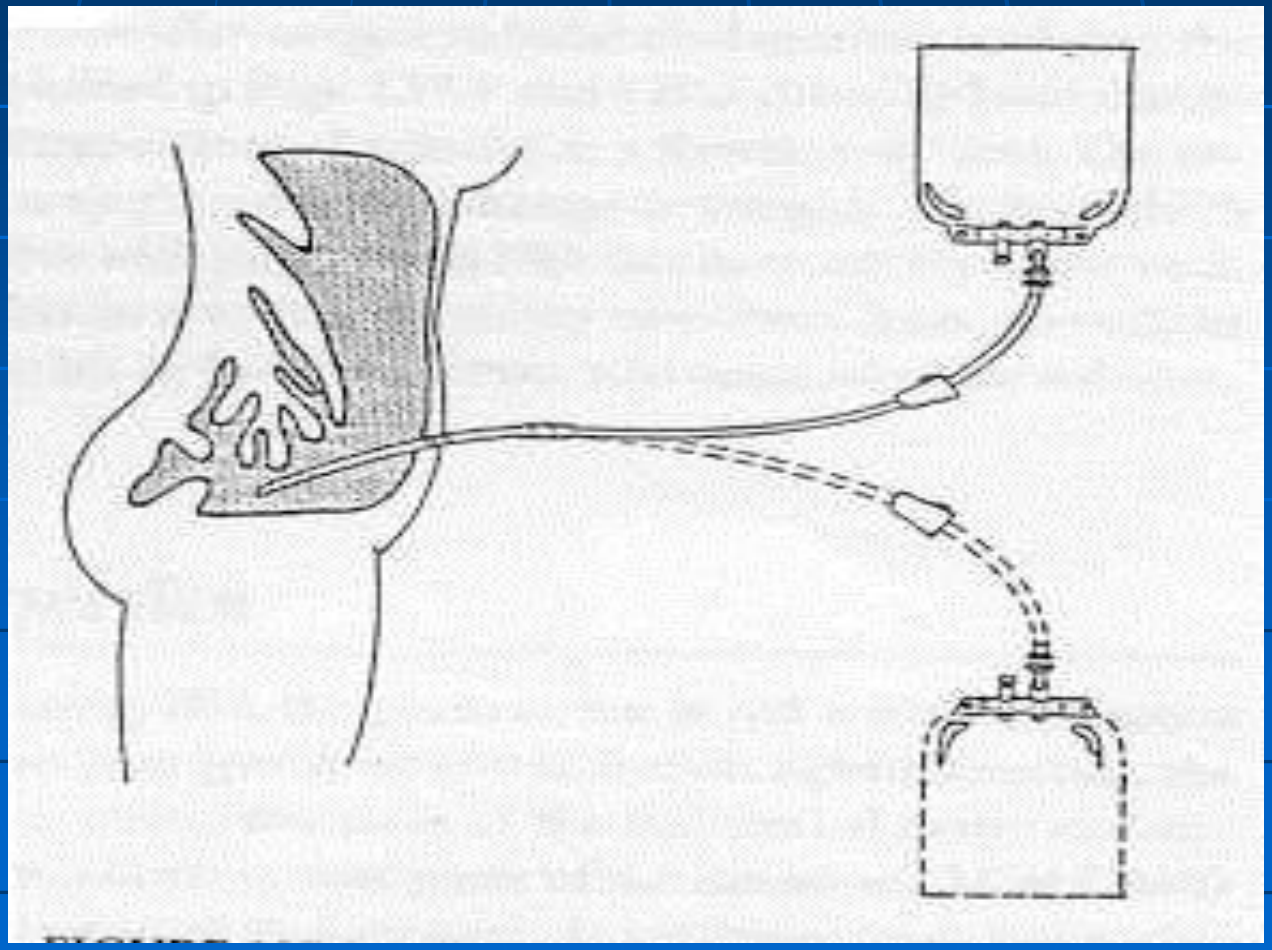
- Acces to peritoneal cavity is achieved by surgically placing a Silastic catheter (Tenckhoff catheter) through abdominal wall a few weeks before starting treatment, and pts are subsequently trained to perform their own dialysis procedures



Types of PD

- Continuous ambulatory peritoneal dialysis (CAPD) involves multiple exchanges during the day (usually 4-5)
- Automated peritoneal dialysis (APD) is similar to CAPD, but uses mechanical device to perform the fluid exchange during the night, leaving the patients free or with only a single exchange to perform during the day

PD is accomplished by introducing a specified volume of peritoneal dialysis fluid (1500-3000 mL), into the abdominal cavity by gravity-driven flow, allowing the fluid to remain in the abdomen for a defined period, then the fluid is drained and removed.



- During each dwell process, both solute removal and ultrafiltration are achieved. Solute removal occurs by diffusion down a concentration gradient from the extracellular fluid into peritoneal dialysate, with the peritoneal membrane acting as a functional semipermeable dialysis membrane.

- The efficiency of removal of small solutes is relatively low compared with HD, whereas the clearance of higher-molecular-weight solutes is somewhat greater.

- Ultrafiltration is accomplished by osmotic water movement from extracellular fluid compartment into hypertonic peritoneal dialysate that contains high concentration of dextrose (1.5-4.25 gram percent)
- The lower rates of solute removal are offset by prolonged treatment times
- For CAPD dialysis is done manually 4-5 times per day
- For APD automatic cycling device performs several automated exchanges nightly

Complications of PD

- Major complication of PD – bacterial peritonitis – average frequency one episode per patient per year
- When diagnosed promptly and treatment begun immediately, infection is not generally severe, and it resolves within a few days of appropriate antibiotic therapy
- Can lead to scarring of peritoneal cavity and to the loss of peritoneum as an effective dilalysis membrane

Diagnosis of peritonitis in peritoneal dialysis

Common and serious problem - the most frequent cause of peritoneal catheter loss and discontinuation of CAPD .

Also a significant cause of death in patients undergoing peritoneal dialysis.

CLINICAL PRESENTATION —often diagnosed on clinical grounds alone. Most patients present with cloudy abdominal fluid and abdominal pain

Fever (greater than 37.5ºC) — 53 %
Abdominal pain — 79 %

Nausea — 31 %

Diarrhea — 7 %

Laboratory findings — an increase in the white cell count in the peritoneal fluid to above 100 cells/mm3 (mostly neutrophils, usually greater than 50 percent); uninfected patients have less than 8 white blood cells/mm3 in the dialysate.

Noninfectious complications of peritoneal dialysis

Gastroesophageal reflux and delayed gastric emptying

Back and abdominal pain

Pleural effusion

Hemoperitoneum

Hypokalemia

Disorders of magnesium

Comparison of HD and PD

	Hemodialysis	Peritoneal Dialysis
Advantages	Short treatment time; highly efficient for small solute removal, socialization occurs in the dialysis center	Steady-state chemistries; higher hematocrit; better blood pressure control; dialysate source of nutrition; intraperitoneal insuline administration; self-care form of therapy; highly efficient for large solute removal; liberalization of diet
Disadvanta-ges	Need for heparin; need for vascular access; hypotension with fluid removal; poor blood pressure control; need to follow diet and treatment schedule	Peritonitis; Obesity; hypertriglicerydemia; malnutrition; hernia formation; back pain

Renal replacement therapy options

- Hemodialysis,hemofiltration, hemodiafiltration and hybrid treatments

- Peritoneal dialysis
  - continuous ambulatory peritoneal dialysis (CAPD)
  - continuous cycling peritoneal dialysis (CCPD)

- Kidney transplantation
  - DD - deceased
  - LD – related or unrelated

Kidney transplantation

- Organ sharing and procurement – DD or LD
- Possibility of resolving normal kidney function and correcting metabolic abnormalities of CKD
- ABO compatibility, HLA matching
- IS regimen
- 10 years of graft survival

Kidney transplantation

- Immunosupresive treatment increases risk of infectious complication, risk of malignancy (skin and lymphoma) and cardio-vascular and metabolic (steroids!!) complications
- Tx is the best treatment and cost-effective options for pts with CKD

Major contraindications to ktx

- Recent or metastatic malignancy
- Untreated current infection
- Severe irreversible extrarenal disease
- Psychiatric illness impairing consent and adherence
- Current recreational drug abuse
- Recurrent native kidney disease?

Assessment for transplantation

- A set of detailed investigations and lab test
- Then application is reported to the national waiting list

THE END