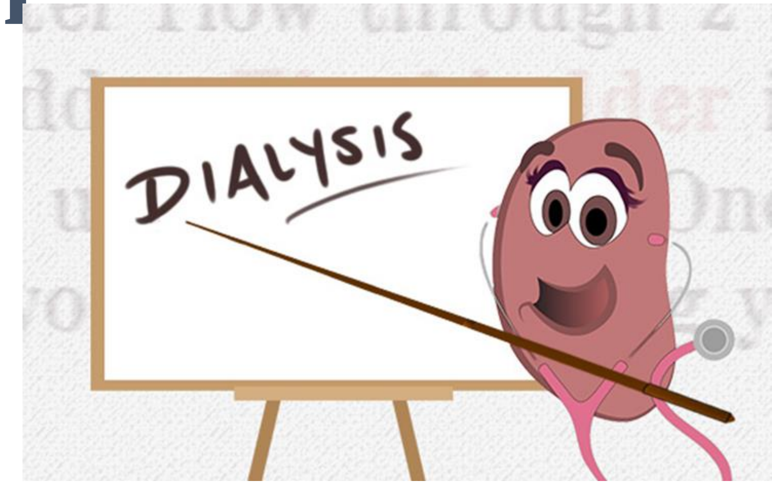
Hemodialysis vs. Hemodiafiltration in Pediatric Patients

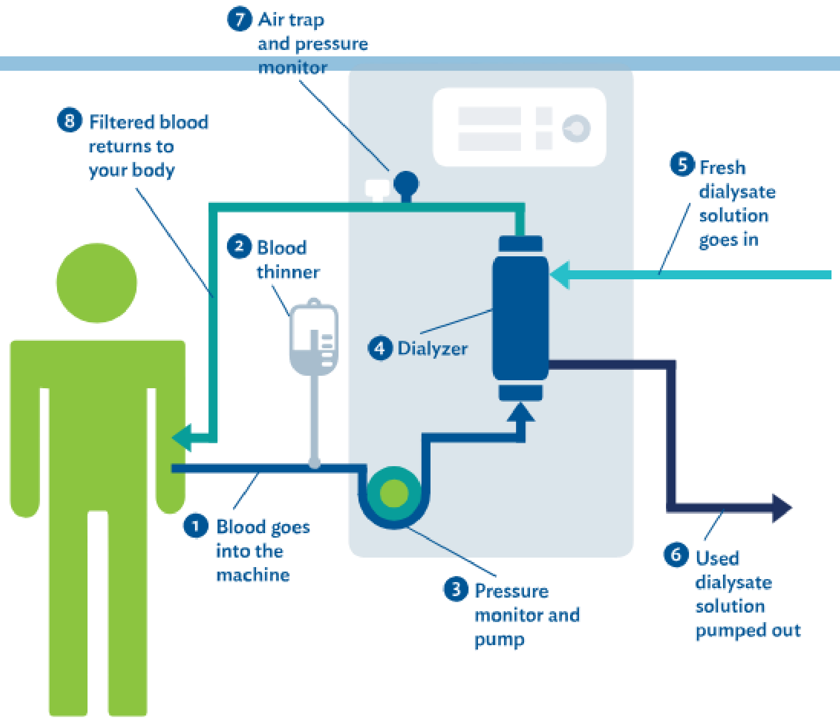


Alaleh Gheissari. MD
Professor of Pediatrics
Pediatric Nephrologist
IUMS

TEHRAN 2023

Part Ⅰ

Conventional Hemodialysis



The 19th International Congress of Nephrology, Dialysis and Transplantation (ICNDT)
12-15 December 2023
Homa Hotel, Tehran
TEHRAN 2023

Mechanisms of Solute Removal

✓ I - Diffusion:

✓Solute removal according to concentration difference between plasma water and the dialysate.

- It is greatest for small molecules removal •
- Increase with increasing the small solute concentration.
- Depends on **membrane factors**: Sieving coefficient, porosity of the membrane, diffusivity & thickness of the membrane •
- Decreases with increasing molecular size of a solute.

Mechanisms of Solute Removal

✓ II - Convection: :

✓Solute clearance occurs as a result of water flow through the membrane in response to hydrostatic pressure difference between the two sides of the membrane (solvent drag)•

- The driving force is a pressure gradient rather than a concentration gradient •
- The major impact comes from the solute size relative to the membrane pores size (radius).

Determinants of Convective Transport Across Membranes

i. Water flux across the membrane
ii. Pore size
iii. Pore size distribution of the membrane
iv. Molecular size (molecular mass)
v. Hydrostatic pressure difference
vi. Viscosity of the fluid in the membrane pores
vii. Molecular shape and configuration
viii. Charges(solutes and membranes)

TEHRAN 2023

Important Dialyzer character relevant to its Convective Function

- ✓**Ultrafiltration co-efficient or KUF (mL/h/mm Hg):**
- ✓An intrinsic characteristic of dialysers, reported by the manufacturer as a single value, which drives and limits fluid removal.
- ✓ High-flux dialysers have been introduced with the appearance of convective techniques, aiming to increase fluid and solute removal.
- ✓ It characterizes the membrane's permeability to water.
  - **The higher KUF is the greater the permeability to water**

TEHRAN 2023

Mechanisms of Solute Removal

✓Ⅲ- Adsorption:

✓Plasma proteins being adsorbed to the surface of the membrane. (So, effect is limited to LMW Proteins clearance) •

- Difficult estimation.
- High flux membranes has more protein adsorption than Low Flux membranes (Larger pores).

Hemodialysis & Its Principle

✓Extracorporeal removal of waste products

- Such as urea and creatinine and excess water

✓Principle:

- Diffusion of solutes across a semipermeable membrane
- Utilizes counter current flow:
  - Counter-current flow maintains the concentration gradient across the membrane at a maximum.
  - Fluid removal (ultrafiltration) is achieved by altering the hydrostatic pressure of the dialysate compartment.
  - Conventional HD prescription provides only about 10% of the clearance power of the natural kidneys

Incapabilities of Conventional HD

✓Removing ***middle and large size molecules*** (>500 Dalton).

- Such as β -microglobulin (β -M), which is strongly associated with carpal tunnel syndrome and dialysis-related amyloidosis (G, spine and cardiac problem).

✓Removing ***protein-bound toxic molecules***.

✓Removing ***pro-inflammatory cytokines.***

✓ Removing ***severe vasoactive molecules*** such as p-cresol and uridine adenosine tetraphosphate.

- **Skipping at least one dialysis session is associated with a 25%-30% increase in the risk of death.**

Examples of types and sizes of different uremic toxic molecules

Protein-Bound Molecules (MW >500 Daltons)	Middle Molecules (MW >500 Daltons	Small Water Soluble Molecules (MW <500 Daltons)
Hippuric acid (insulin resistance and glucose intolerance)	**Adrenomedullin** (potent hypotensive peptide)	**Sodium**
Homocystein (atherogenecity and thrombogenecity	**AGE**	**Phosphorus**
Indoxyl sulfate pro-inflammatory effect & endothelial dysfunction	**AOP**	**potassium**
p-cresyl sulfate/ p-cresol Endothelial and pro-inflammatory	**Vitamin B12**	**urea**
Polyamines inhibit erythroid colony growth in a dose dependent way	**Endothelin** strong vasoconstrictor	**Creatinine**

Examples of types and sizes of different uremic toxic molecules

Protein-Bound Molecules (MW >500 Daltons)	Middle Molecules (MW >500 Daltons
Uric acid	PTH
Glucose	Beta 2- M
	Leptin
	Cytokines
	Immunoglobulin LC

It has been reported that only 32% to 33% of patients on conventional HD survive to the fifth year of treatment.

The mortality rate in conventional HD ranges between 14-26% in Europe and 24% in USA.

Dialyzer Membranes (PROS & CONS)

✓**Made primarily of cellulose:**

- Derived from cotton linter
- The surface of such membranes was not very biocompatible
  - Because exposed hydroxyl groups would activate complement in the blood passing by the membrane.

✓**More recently, made from synthetic materials:**

- These synthetic membranes activate complement to a lesser degree than unsubstituted cellulose membranes.
  - Using polymers such as polyarylethersulfone, polyamide, polyvinylpyrrolidone, polycarbonate, and polyacrylonitrile.
  - Made in either low- or high-flux
  - Nanotechnology (high-flux)

Advantages of Innovations in the Technology of Dialysis Membranes

✓Improvement of:

- Biocompatibility,
- Anti-thrombotic effect,
- Hydraulic properties,
- Perm-selective properties.

High-Flux Vs Low-Flux Dialyzers

✓High-Flux

- Ultrafiltration Coefficient (KUF): > 15 ml/h/mmHg
- β -M clearance > 20 ml/min

✓Low-flux

- Ultrafiltration Coefficient (KUF): <15 ml/h/mmHg
- β -M clearance < 10 ml/min

- ***Larger pore size semipermeable membranes in compact cartridges***

TEHRAN 2023

High-Flux Vs Low-Flux Dialyzers (continue)

✓High-Flux

- Enhanced ability to remove small solutes and middle molecules.
- Allow the passage and removal of retained solutes of higher molecular weight (than do low-flux membranes).
- Superior to peritoneal dialysis in clearing β –M.
- Superior to peritoneal dialysis in clearing the protein-bound middle molecule p-cresol.

TEHRAN 2023

'Super high-flux' Membranes

✓ **A high cut-on pore size**

- Efficient in removal of middle and large size uremic toxin molecules
- **A new generation of hemodialysis membranes with M.W cut-points closer to that of the native kidney (65000 Dalton)**
  - Efficient in removal of myoglobin in patients with rhabdomyolysis.
  - Efficient in direct removal of free light chains and other plasma components.
  - Greater clearance of inflammatory cytokines than conventional high-flux membranes.
  - A positive impact on restoration of immune cell function.
  - Attenuation of hemodynamic instability and decrease in plasma interleukin-6 levels in septic patients with AKI.
    - **More Albumin Loss**

Anticoagulants Used in the Blood Circuit

- ✓**Unfractionated heparin,**
- ✓**Low molecular-weight heparin,**
- ✓**Natural and synthetic heparinoids,**
- ✓**Direct thrombin inhibitors,**
- ✓**Prostanoids,**
- ✓**Saline flushes**
- ✓**Citrate infusion**
- ✓**Citrate- based dialysate.**
  - ✓**Long-term use of heparin side-effects:**
    - thrombocytopenia, hypertriglyceridemia, osteoporosis, hypersensitivity, alopecia, metabolic disturbances, and hypotension.

TEHRAN 2023

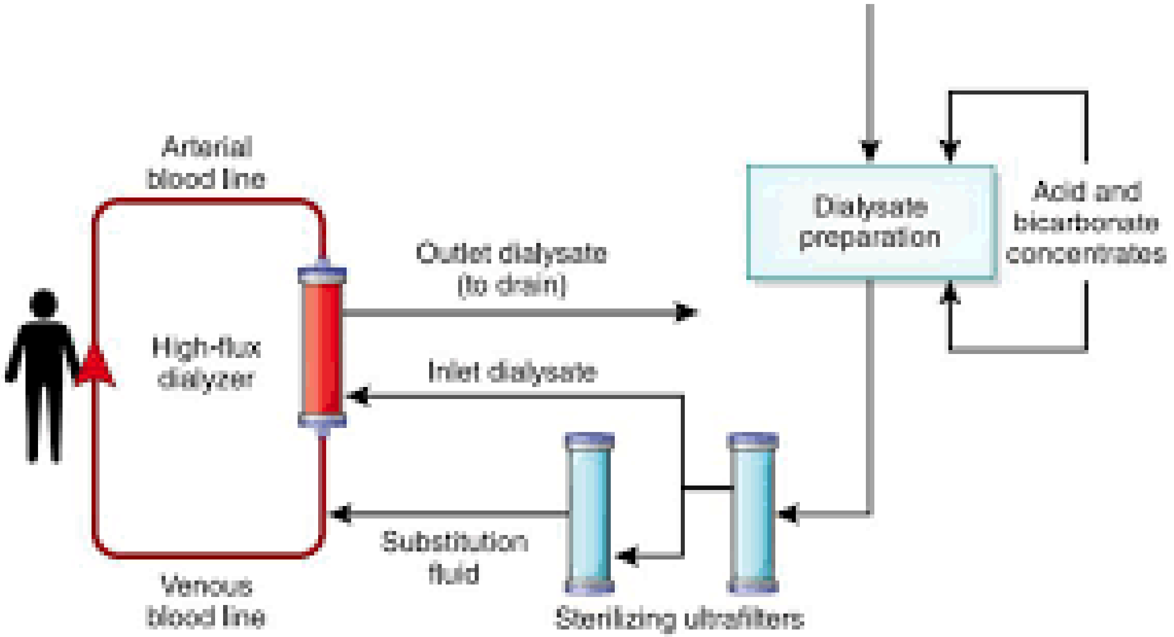
Blood	Dialysate
Na = 140 mEq/L	Na= 140 mEq/L
K = 4.5 mEq/L	K= 2 mEq/L
Cl =100 mEq/L	Cl= 100 mEq/L
CO2 = 24 mEq/L	HCO3=35 mEq/L
BUN = 30 mg/dL	Urea=0 mg/dL
Cr = 5 mg/dL	Cr=0 mg/dL
Glucose = 100 mg/dL	Dextrose= 200 mg/dL
Calcium=1.2 mmole/L	Calcium=2.5 mEq/L
Phosphorus=4 mg/dL	Phosphorus = 0 mg/dL
Magnesium=2 mg/dL	Magnesium=1.2 mg/dL
Vit B12 = 500 pg/mL	Vit B12= 0
Albumin = 4 g/dL	Albumin =0

TEHRAN 2023

Part Ⅱ

Hemodiafiltration

Henderson 1967



The 19th International Congress of Nephrology, Dialysis and Transplantation (ICNDT)

12-15 December 2023
Homa Hotel, Tehran

What was the problem with HD after improving membranes???

- ✓ **Failure to improve outcome**:

↓

- ➢Reconsider the implementation of the other physiologic principle of "convection"
  - ➢Larger size uremic toxins can be dragged and removed from blood by filtering large volume of fluid pushed under high hydrostatic pressure through a larger pore size membrane (high cut-on membrane/high-flux dialyzer).
- ➢**This technique is known as "*hemofiltration*".**

TEHRAN 2023

Fluid Balance in Hemodiafiltration

✓**Infusion of replacement solutions**

- To replace the large volume of filtered fluids (***convection volume or substitution fluid***):
- **Pre-dilution:** fluid administration before the filter
- **Post-dilution**: fluid administration after the filter
  - Combination of the two physiologic principles of **diffusion** (hemodialysis) and **convection** (hemofiltration) in the management of patients with ESRD is known as "**hemodiafiltration**" (since 1974).

TEHRAN 2023

Fluid Balance in Hemodiafiltration

✓**Predilution on demand consists in:**

- An automatic feedback of the machine,
- Diverting part of the filtered dialysate into a predilution mode:
  - with an infusion of 200 ml in 30 s
  - while the ultrafiltration pump stops.

Fluid Balance in Hemodiafiltration

✓**Backflush on demand consists in:**

- An automatic feedback of the machine
- Triggered by the TMP control:
  - Producing a positive pressure in the dialysate compartment due to a stop of filtration
  - Rapid infusion of at least 100 ml of ultrapure dialysate into the hollow fiber.

Online Hemodiafiltration(HDF)

✓The main problem in applying HDF:

- Supplying a large quantities of replacement solutions.
- Needed autoclaved expensive plastic bags.

➡

- Improvement in the performance of water treatment plants:
  - producing ultrapure water (almost nil bacterial growth and endotoxin free)

Microbiological Standards for Water and Dialysis Fluid Purity

	Standard Water	Standard Dialysate	Ultrapure Water	Ultrapure Dialysate	Sterile Dialysate
Bacterial limits , CFU/mL	< 100-200	< 100-200	**< 0.1**	< 0.1	< 10-6
Endotoxin limits , EU/mL	< 0.25-2	< 0.25	**< 0.03**	< 0.03	< 0.03

Online Hemodiafiltration(HDF) Continue

- ✓The most physiologic clearance profile for:
  - Small, medium-sized and large toxic molecules
- ✓Performed three times per week/4 hour.
- ✓Effective online HDF should ensure:
  - Higher blood and dialysate flow rates
- ✓Ultrafiltration not less than 20% depending on the mode of HDF.
- ✓ Substitution/replacement fluids 5-25 liters/session

Online Hemodiafiltration(HDF) Continue

✓The data from randomized controlled studies (CONTRAST and Turkish studies):

- **A convection volume higher than 15 liters** in the **post-dilution mode** should be targeted in order to achieve successful HDF.

TEHRAN 2023

Online Hemodiafiltration(HDF) Continue

✓**HDF (*in particular online HDF*):**

- The implementation of both physiologic principles of diffusion and convection:
  - Achieving better adequacy of dialysis
  - Achieving better clearance of small and middle-size uremic toxins
  - Achieving higher values of Kt/V (averages of 1.37 and 1.44 versus 1.35 and 1.33 in conventional HD).

Online Hemodiafiltration(HDF) Continue

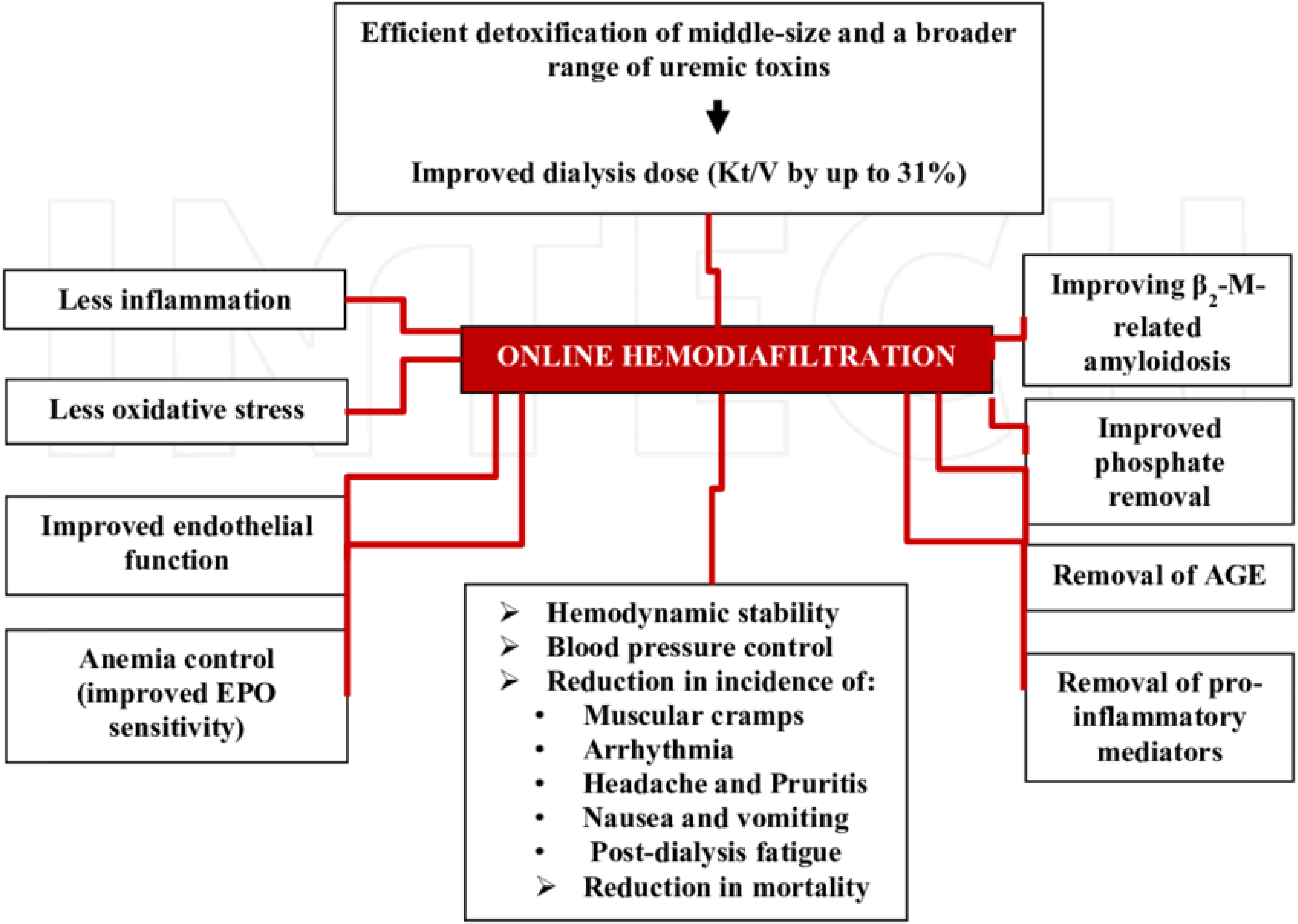
✓**HDF (*in particular online HDF*):**

- Achieving better levels of phosphate.
- Achieving higher removal of serum free light chain (MM).
- Achieving higher removal of larger solutes:
  - Myoglobin (16000 D), retinol-binding protein (25000 D) and the protein-bound p-cresol
- Achieving higher removal of pro-inflammatory stimuli
  - oxidative stress molecules, advanced glycation end-products, homocysteine, and pro-inflammatory cytokines.

Types of Hemodiafiltration

Hemodiafiltration Volume	Convection Volume, L	Convection Volume, L/1.73 m2	Source of Substitution Fluid
Low volume	2-12	2.5-14.5	Prepackaged bags, internal filtration/backfiltration
Medium volume	12-23	14.5-25.5	Online preparation
High volume	>23	>25.5	Online preparation

The convection volume is the total amount of fluid filtered during a hemodiafiltration treatment. It includes both the substitution fluid and the excess fluid removed to return the patient to his/her dry weight. Typically, the substitution fluid volume will be 2–4 L less than the convection volume


Efficient detoxification of middle-size and a broader range of uremic toxins
Improved dialysis dose (Kt/V by up to 31%)
ONLINE HEMODIAFILTRATION
Less inflammation
Less oxidative stress
Improved endothelial function
Anemia control (improved EPO sensitivity)
Improving β2-M-related amyloidosis
Improved phosphate removal
Removal of AGE
Removal of pro-inflammatory mediators
Hemodynamic stability
Blood pressure control
Reduction in incidence of:
Muscular cramps
Arrhythmia
Headache and Pruritis
Nausea and vomiting
Post-dialysis fatigue
Reduction in mortality

Haemodiafiltration

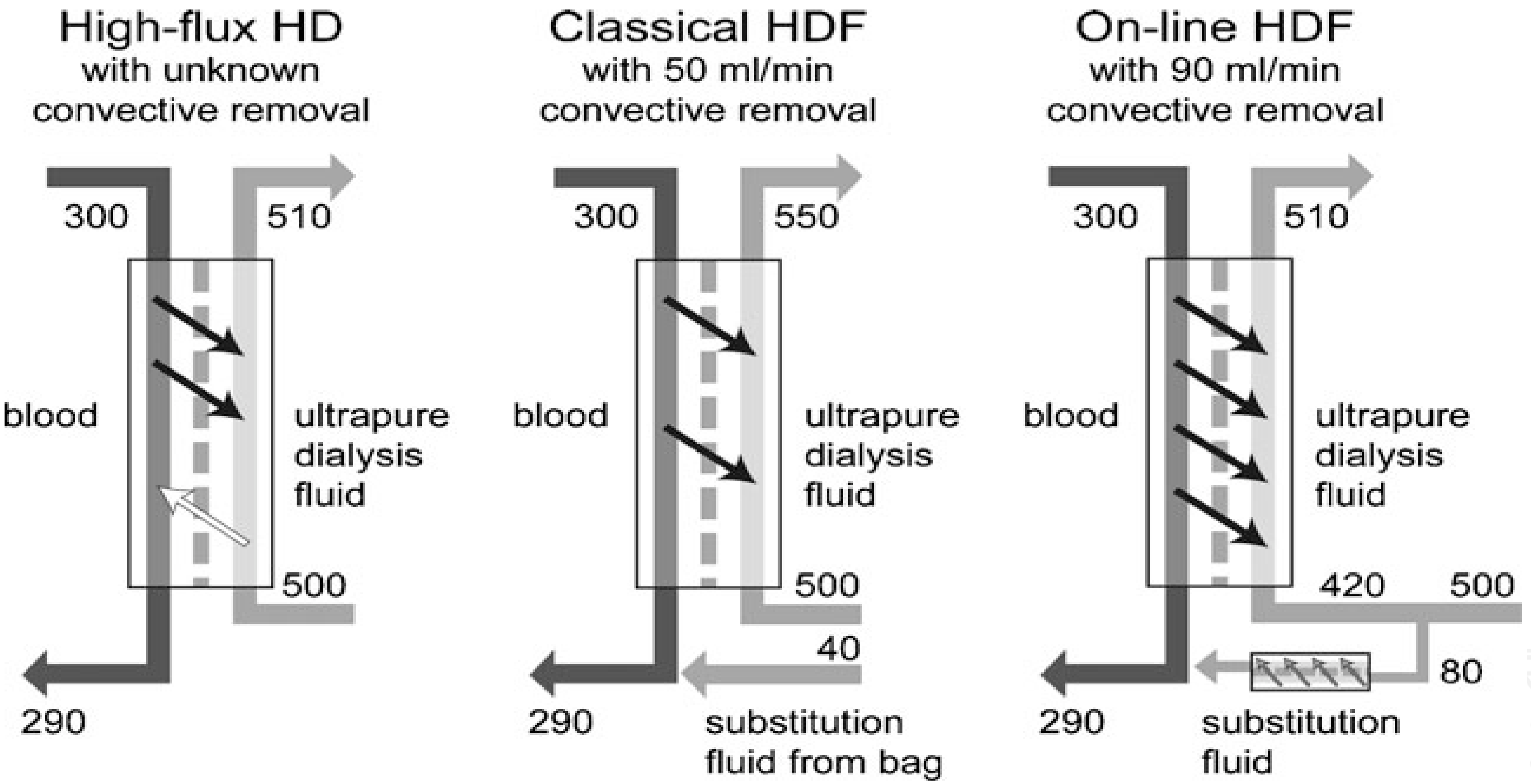
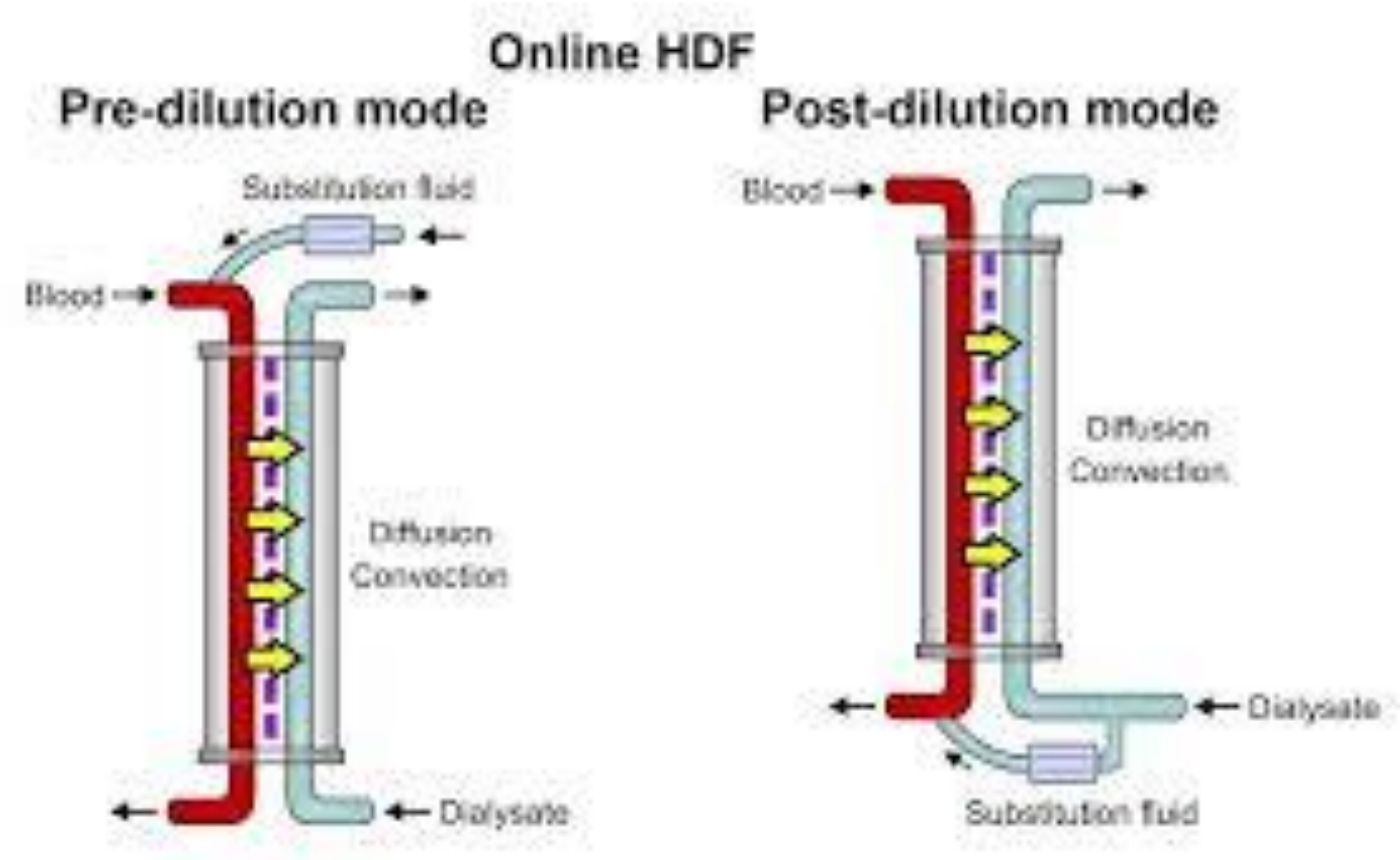
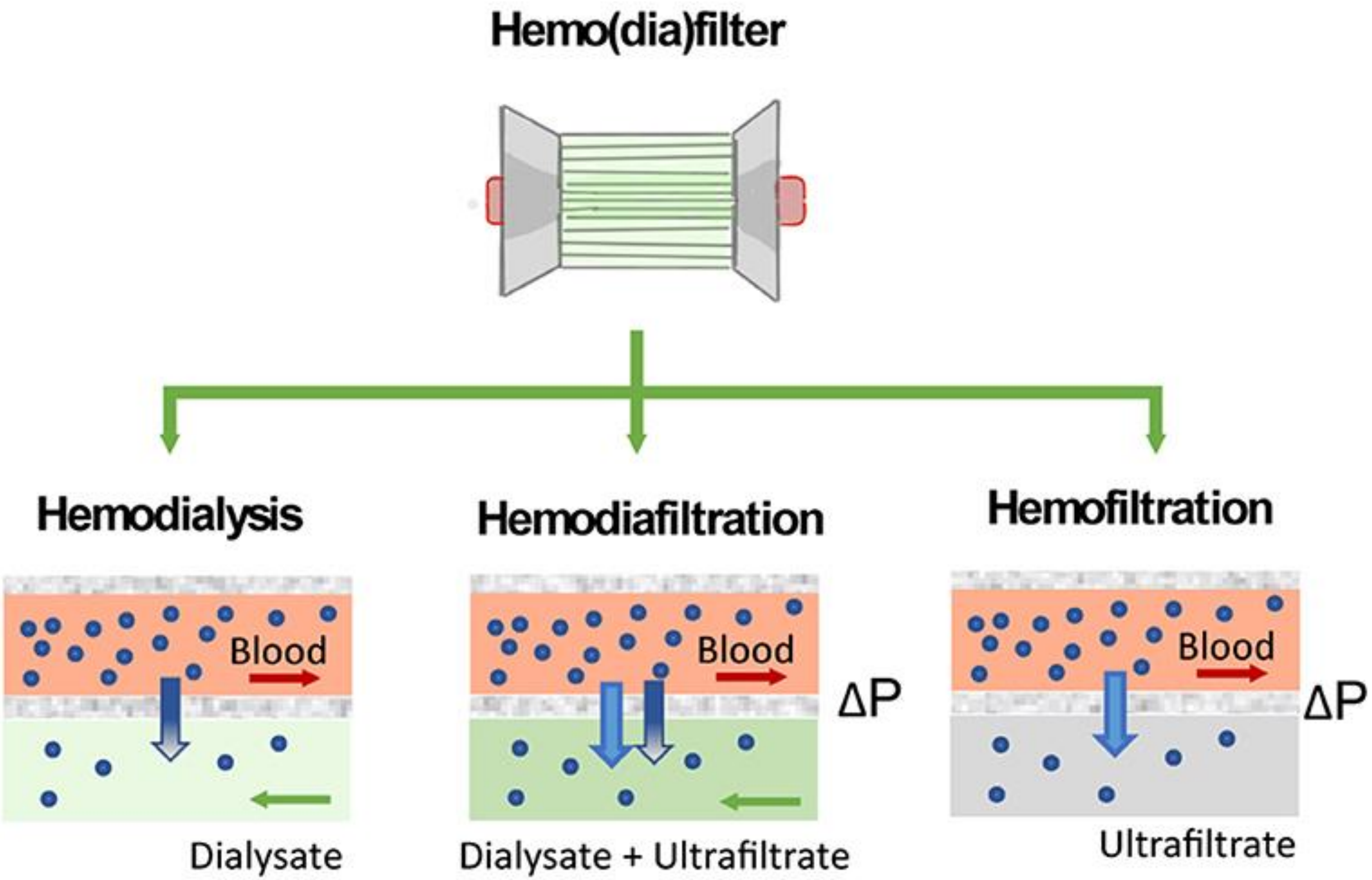
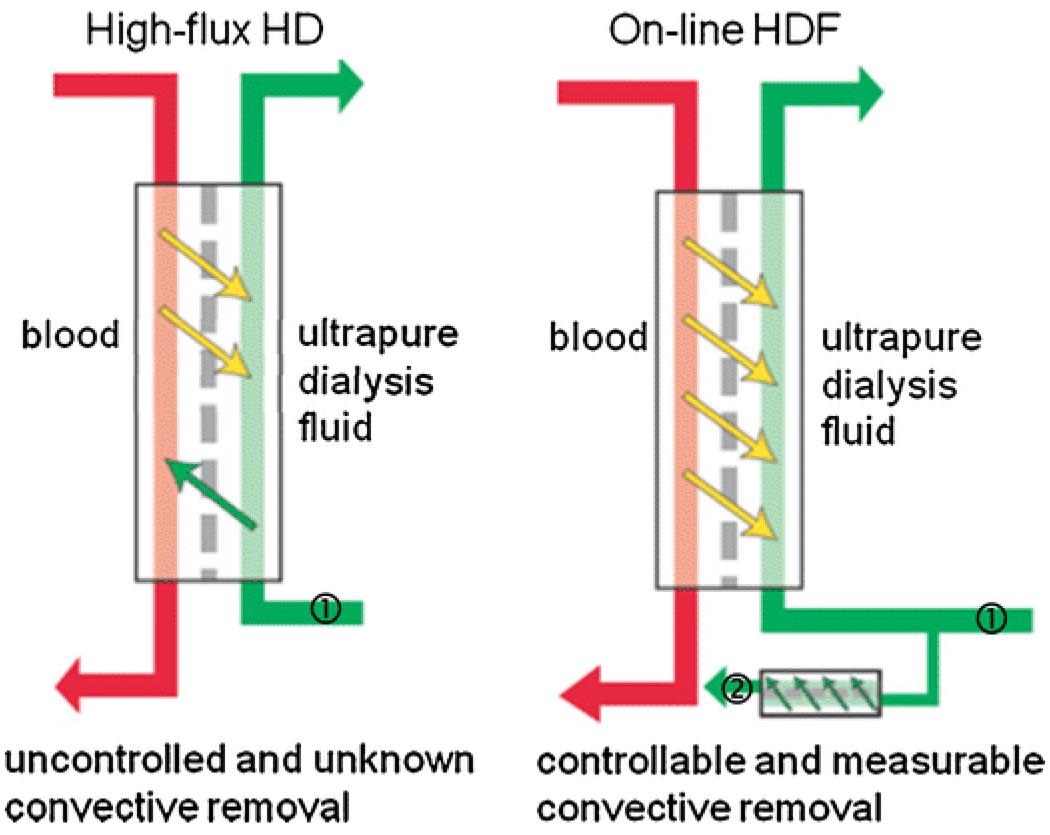


Fig. 3. Flow diagrams for different forms of haemodiafiltration (HDF)



Online HDF
Pre-dilution mode
Substitution fluid
Blood
Diffusion
Convection
Dialysate
Post-dilution mode
Blood
Diffusion
Convection
Dialysate
Substitution fluid


Hemo(dia)filter
Hemodialysis
Hemodiafiltration
Hemofiltration
Blood
Blood
Blood
ΔP
ΔP
Dialysate
Dialysate + Ultrafiltrate
Ultrafiltrate


High-flux HD
On-line HDF
blood
ultrapure dialysis fluid
blood
ultrapure dialysis fluid
①
①
②
uncontrolled and unknown convective removal
controllable and measurable convective removal

References

I. Hemodiafiltration: Technical and Clinical Issues. Claudio Ronco. Blood Purif 2015.

II. Hemodialysis. Ayman Karkar. Advances in Hemodialysis Techniques 2013

III. Beta-2 Microglobulin Amyloidosis: Past, Present, and Future. Castello e al. KIDNEY360 1: 1447–1455, 2020.

IV. Approach to new advances in dialysis. Middle East Medical Portal 2023

V. Calcium balance in pediatric online hemodiafiltration. Bacchetta et al. Néphrologie & Thérapeutique 2015

VI. Chronic intermittent high-volume hemodiafiltration. Grooteman et al. Up To Date 2023

VII. Fischbach Michel. Dialysis practice: how to write an HDF prescription.

VIII. Effects of Hemodiafiltration versus Conventional Hemodialysis in Children. Shroff et al. J Am Soc Nephrol 2019

IX. Hemodiafiltration in Children. Fischbach et al. Hemodiafi ltration: Theory, Technology

X. and Clinical Practice 2015


Thank
you