PRINCIPLES OF CHRONIC HD

F. Paglialonga

Pediatric Nephrology, Dialysis and Transplant Unit

Fondazione IRCCS Ca' Granda

Ospedale Maggiore Policlinico, Milan, Italy

21.10.2021

Aims of HD

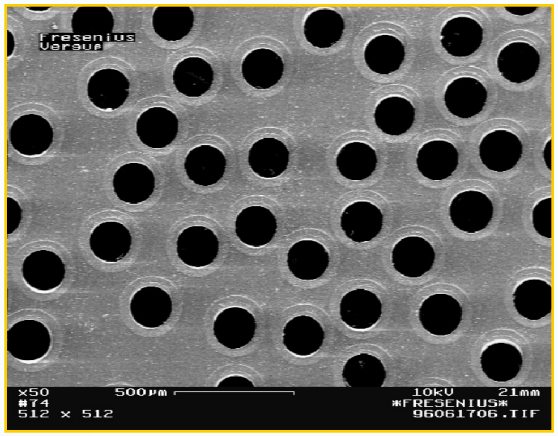
- To remove uremic toxins and restore metabolic equilibrium
- To remove fluids

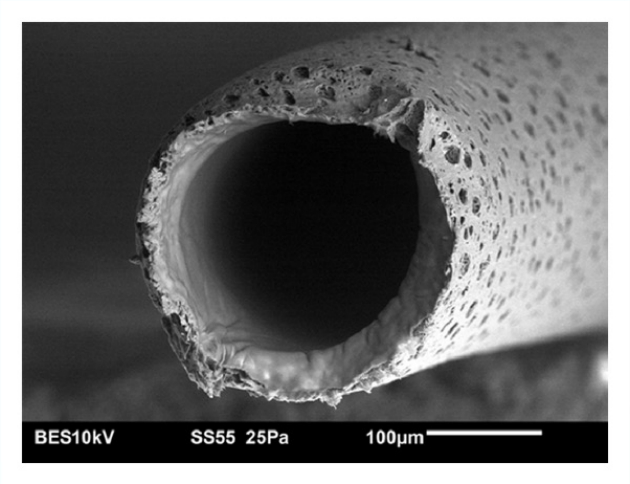
Uremic Toxins

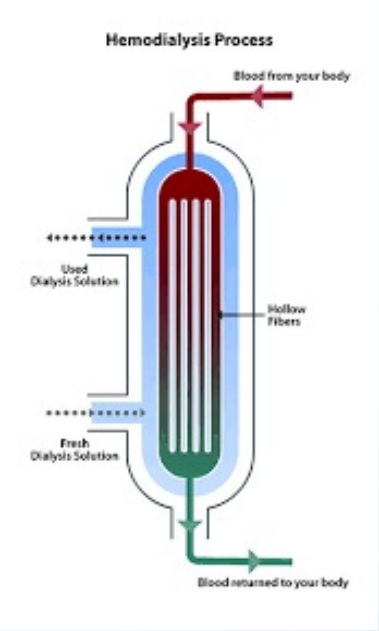
Compound	MW	Compound	MW
ADMA/SDMA	202	Adrenomedullin	5729
ANF	3080	Benzylalcohol	108
β-Endorphin	3465	β-Guanidinopropionic acid	131
β_2-Microglobulin	11,818	CGRP	3789
Cholecystokinin	3866	CIP	8500
Clara cell protein	15,800	CML	188
CMPF	240	Complement factor D	23,750
Creatine	131	Creatinine	113
Cystatin C	13,300	Cytidine	234
DIP I	14,400	DIP II	24,000
3-Deoxyglucosone	162	Dimethylarginine	202
Endothelin	4283	γ-guanidinobutyric acid	145
Glomerulopressin	500	GIP I	28,000
GIP II	25,000	Guanidine	59
Guanidinoacetic acid	117	Guanidinosuccinic acid	175
Hippuric acid	179	Homoarginine	188
Homocysteine	135	Hyaluronic acid	25,000
Hypoxanthine	136	Imidazolone	203
Indole-3-acetic acid	175	Indoxyl sulfate	251
Leptin	16,000	Melatonin	126
Methylguanidine	73	Myoinositol	180
Neuropeptide Y	4272	Orotic acid	156
Orotidine	288	o-OH-hippuric acid	195
Oxalate	90	p-Cresol	108
p-OH-hippuric acid	195	Parathyroid hormone	9225
Pentosidine	135	Phenylacetylglutamine	264
Phenol	94	Phosphate	96
Pseudouridine	244	Putrescine	88
Retinol binding protein	21,200	Spermine	202
Spermidine	145	Thymine	126
Trichloromethane	119	Tryptophan	202
Urea	60	Uric acid	168
Uridine	244	Xanthine	152

Small Water-Soluble Compounds (<500 Da)	**Middle Molecule ($\geq$500 Da)**	**Protein Bound Compounds (Mostly < 500 Da)**
ADMA	ANP	AGEs
Carbamylated compounds	β_2-microglobulin	Homocysteine
Creatinine	Endothelin	Indoxyl sulfate
SDMA	FGF23	Indole acetic acid
TMAO	Ghrelin	Kynurenines
Urea	Immunoglobulin light chains	p-cresylsulfate
Uric acid	Interleukin-6	Phenyl acetic acid
	Interleukin-8	
	Interleukin-18	
	Lipids and lipoproteins	
	Neuropeptide Y	
	PTH	
	Retinol binding protein	
	TNF-α	

The semipermeable membrane



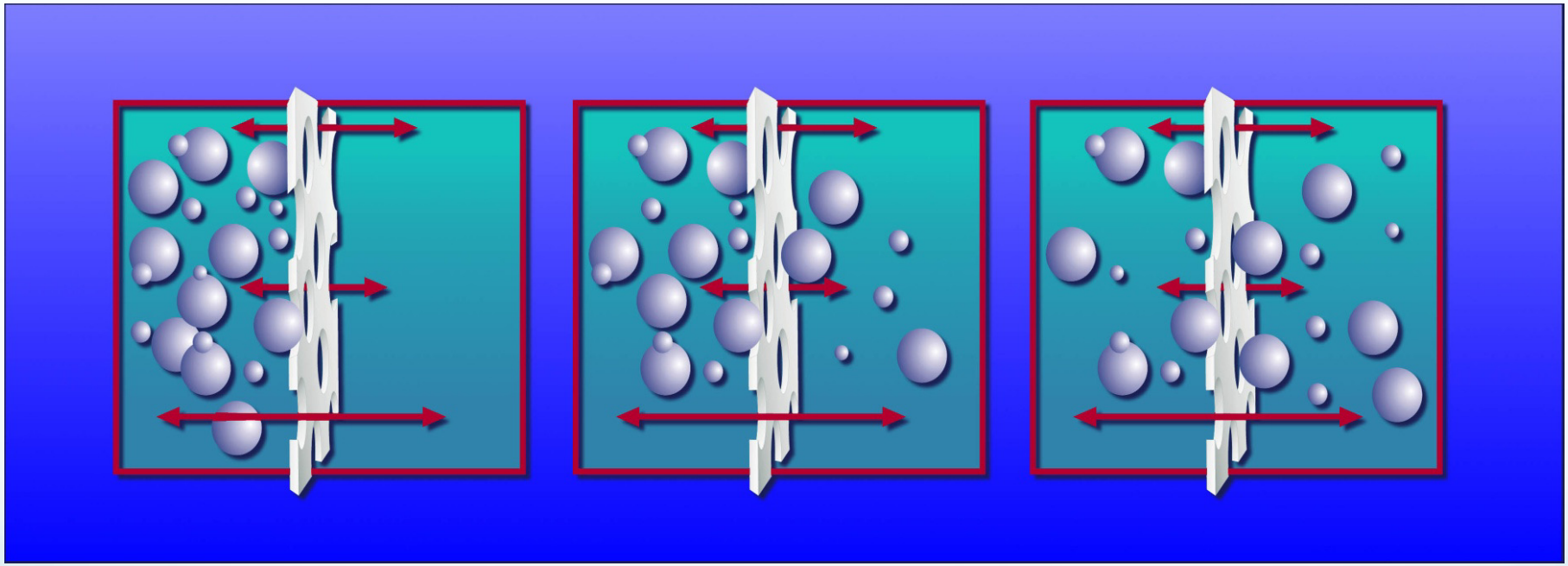




Mechanisms of solutes removal:

- Diffusion
- Convection
- Adsorption

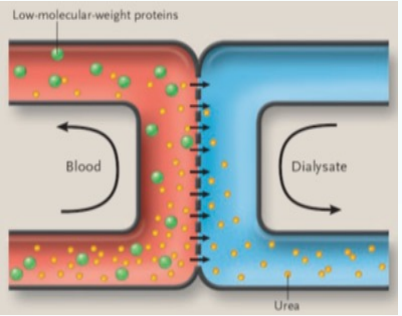
Diffusion

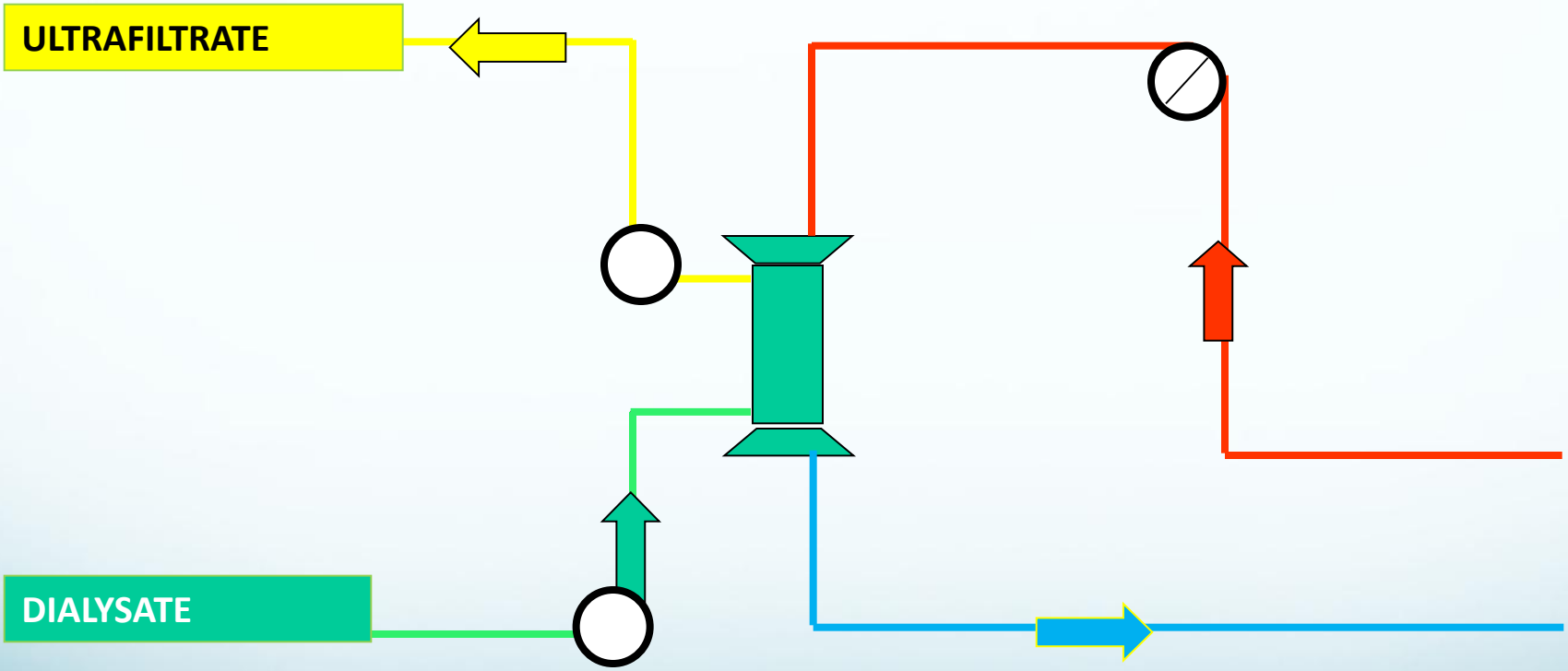


Mainly dependent on: MW, concentration gradient, charge, temperature

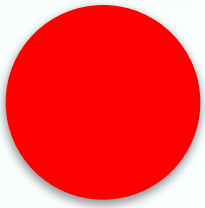
Conventional Hemodialysis (HD) (Bicarbonate HD)

DIFFUSION





Toxin removal by conventional HD
(with standard cut-off membranes)



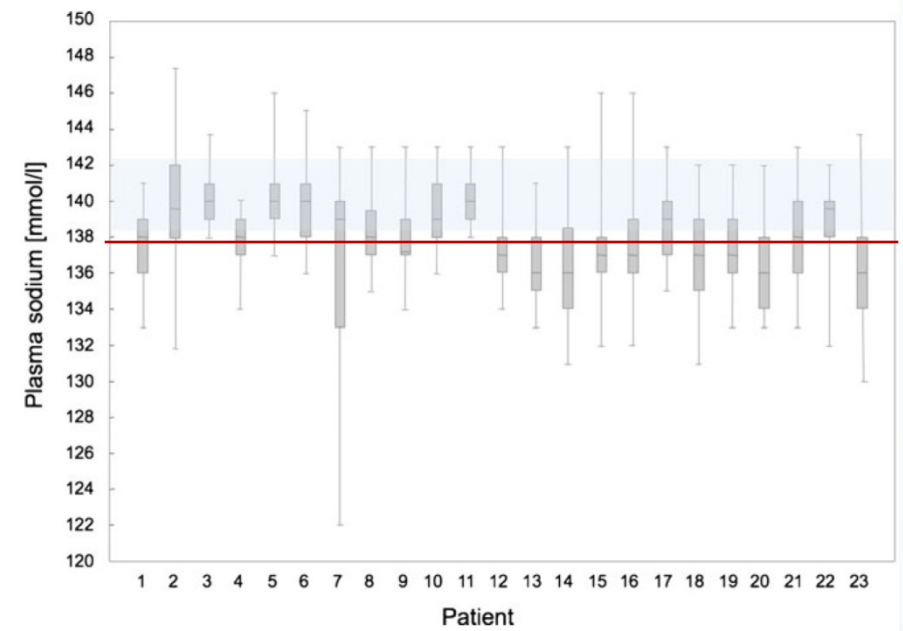
Albumin	60000
Beta2microglobulin	11800

Vancomycin	1500
B12 Vitamin	1355

Glucose	180
Uric Acid	168
Creatinine	113
Bicarbonate	61
Urea	60
Potassium	35
Phosphorus	31
Sodium	23

Diffusive clerance of a toxin

- Concentration gradient
- Blood flow (Qb)
- Dialysate flow (Qd)
- Membrane KoA
  - Ko
  - Area



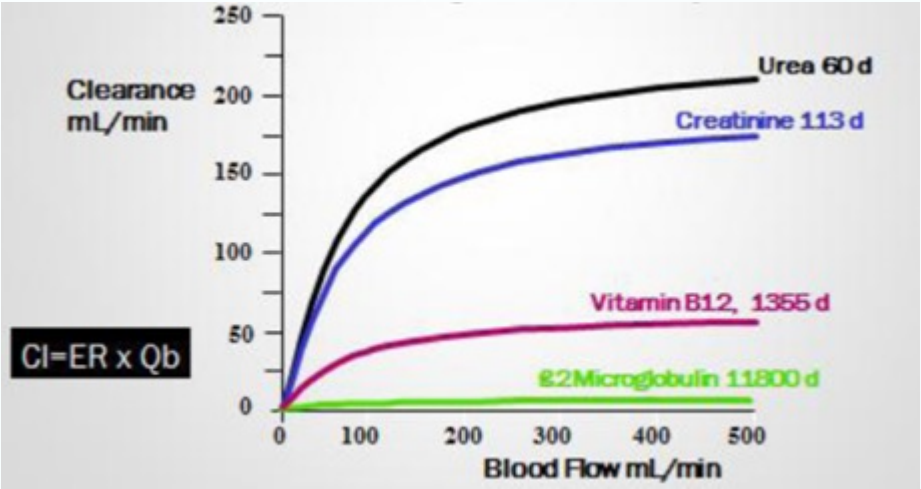
dNa:
usually 138-140 mEq/L

Positive Na balance in most of the sessions

Zaloszyc, Pediatr Nephrol 2013

Diffusive clerance of a toxin

- Concentration gradient
- Blood flow (Qb)
- Dialysate flow (Qd)
- Membrane KoA
  - Ko
  - Area



Diffusive clerance of a toxin

- Concentration gradient
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- Membrane KoA
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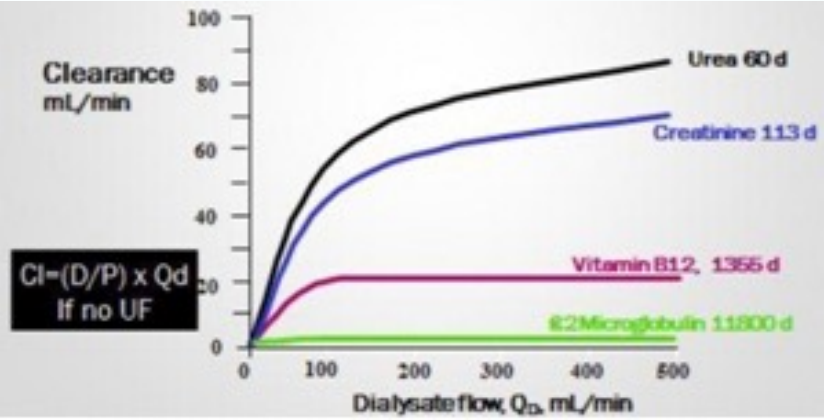
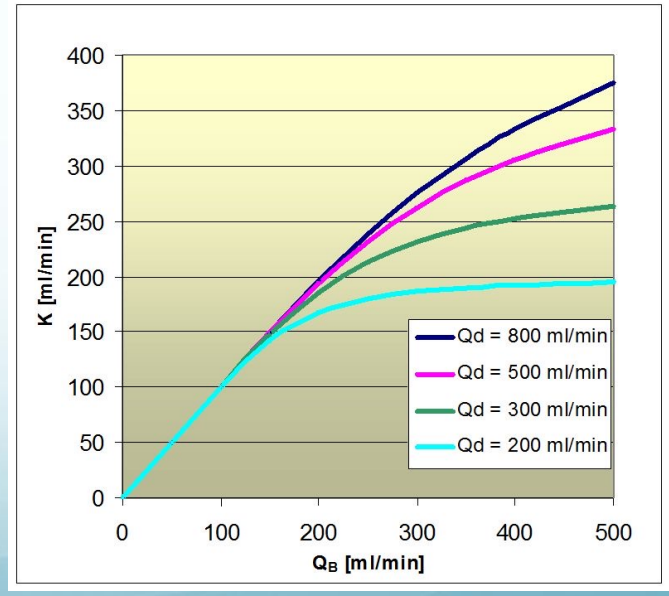
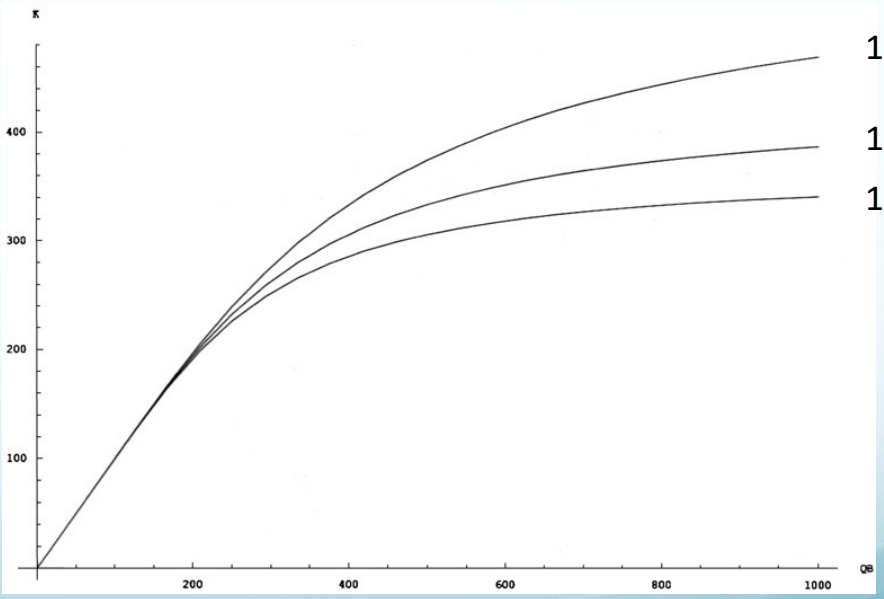




Diffusive clerance of a toxin

- Concentration gradient
- Blood flow (Qb)
- Dialysate flow (Qd)
- Membrane KoA
  - Ko
  - Area

Membrane surface



1.7 sqm

1.4 sqm

1.0 sqm

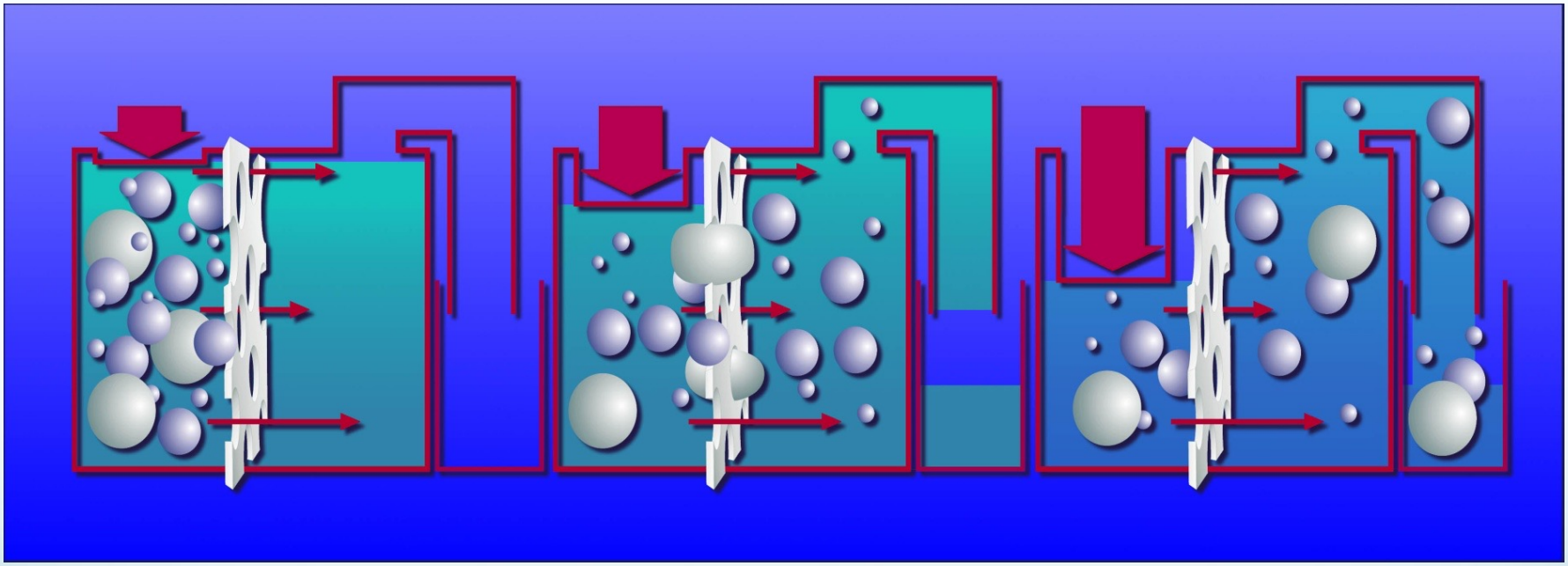
Diffusive clerance of a toxin

- Concentration gradient
- Blood flow (Qb)
- Dialysate flow (Qd)
- Membrane KoA
  - Ko
  - Area

	FX paed	FX 40
Ultrafiltration coeff. (mL/h x mmHg)	7	20
Clearance Q_B = 100 mL/min, Q_D = 300 mL/min		
Urea	76	–
Creatinine	64	–
Phosphate	57	–
Vitamin B_{12}	34	–
Inulin	20	–
Clearance Q_B = 200 mL/min Q_D = 500 mL/min		
Urea	–	170
Creatinine	–	144
Phosphate	–	138
Vitamin B_{12}	–	84
Inulin	–	54

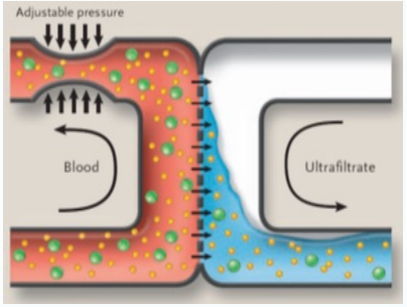
In vitro performance: Q_F = 0 mL/min, T = 37 °C (EN 1283, ISO 8637).

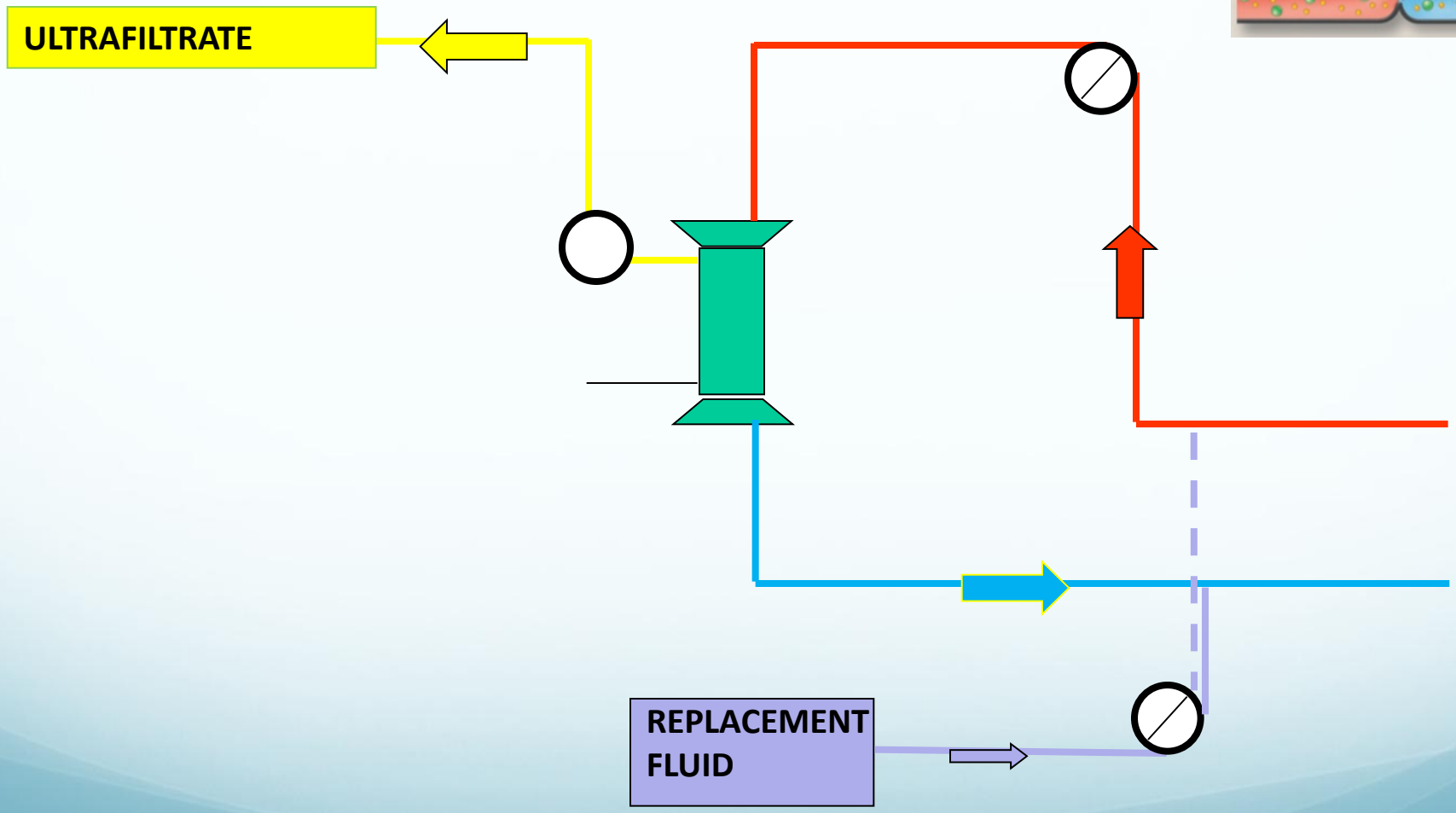
Convection



Hemofiltration (HF)

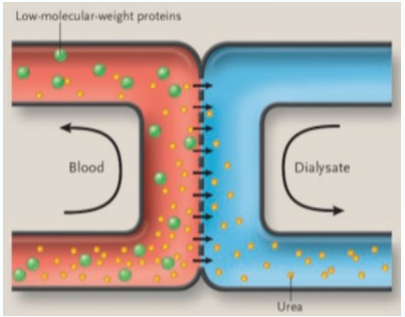
CONVECTION



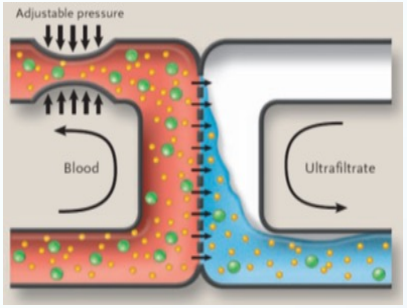


Hemodiafiltration (HDF)

DIFFUSION



CONVECTION



ULTRAFILTRATE

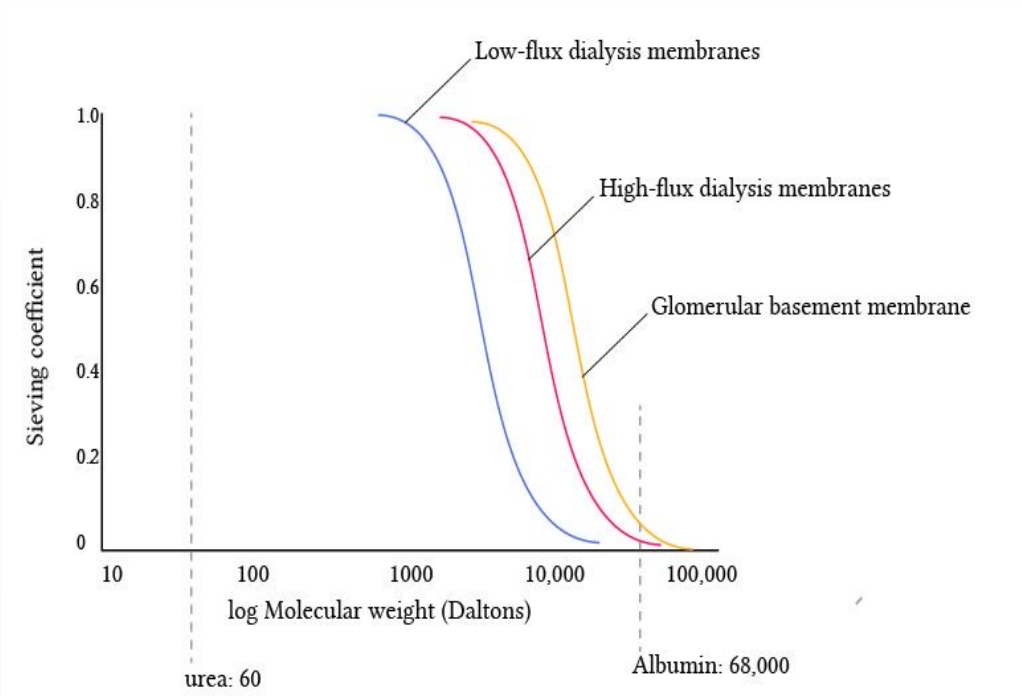
DIALYSATE

Ultrapure replacement fluid

REPLACEMENT FLUID

Convective clerance of a toxin (= S x Quf)

- Sieving coefficient
- Convective volume (Quf)



Convective clerance of a toxin (= S x Quf)

- Sieving coefficient

- Convective volume (Quf)

Target 12-15 L/m^2 in postdil.

- TMP (mmHg)
- Kuf (ml/h/mmHg)

High flux :
Kuf > 20 ml/h/mmHg

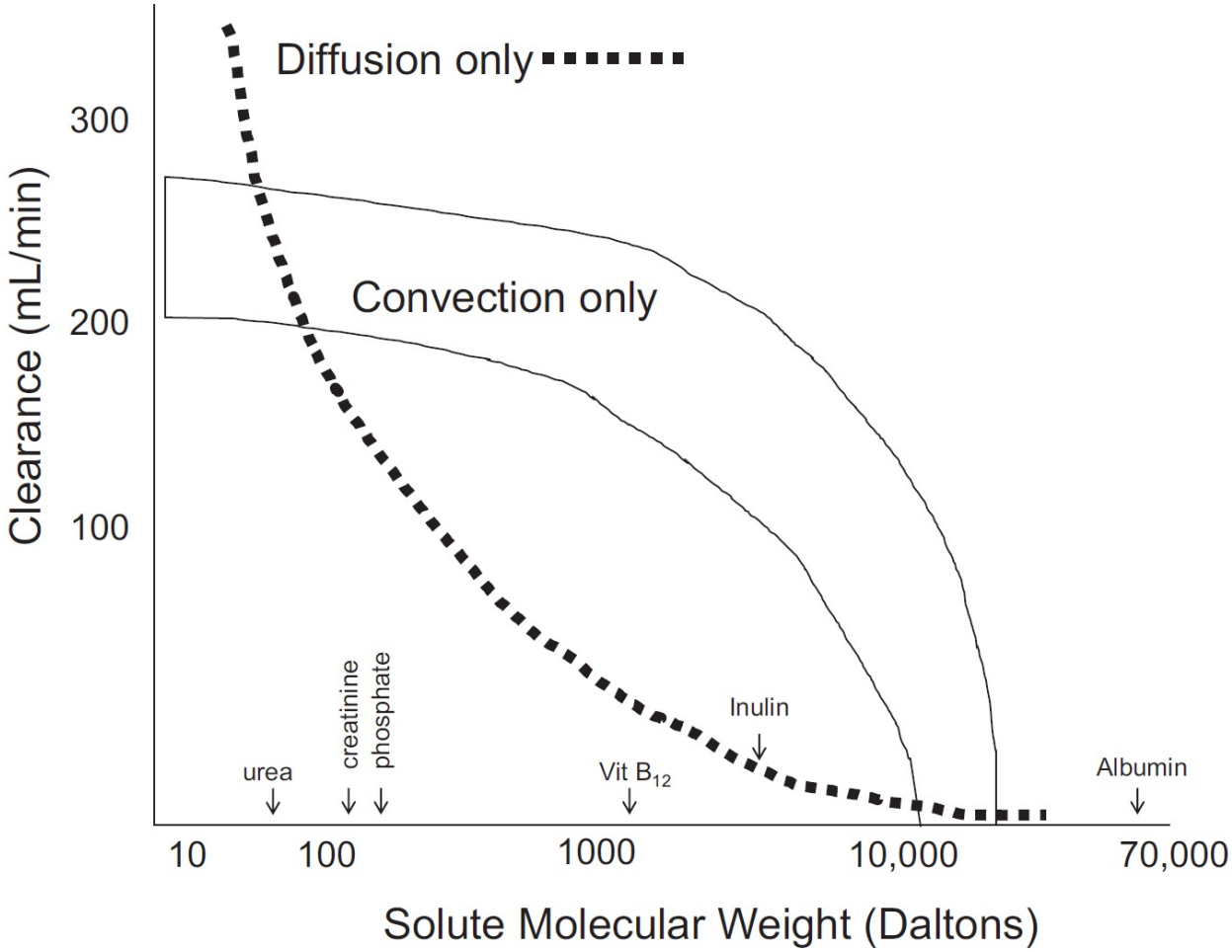
- Qb
- Ht
- Serum protein

		FX 40	FX 50	FX 60	FX 80
Coefficiente di ultrafiltrazione (ml/h • mmHg)		20	33	46	59
Clearance: Q_s 200 (ml/min)					
	Urea	170	189	193	197
	Creatinina	144	170	182	189
	Fosfati	138	165	177	185
	Vitamina B_{12}	84	115	135	148
	Inulina	54	76	95	112
Clearance: Q_s 300 (ml/min)					
	Urea	209	250	261	276
	Creatinina	168	210	230	250
	Fosfati	160	201	220	239
	Vitamina B_{12}	91	130	155	175
	Inulina	56	81	104	125
Clearance: Q_s 400 (ml/min)					
	Urea	233	286	303	326
	Creatinina	182	233	262	287
	Fosfati	173	222	248	272
	Vitamina B_{12}	94	137	167	190
	Inulina	57	84	109	133

I dati in vitro sono stati ottenuti con Q_b = 500 ml/min, Q_f = 0 ml/min et T = 37 °C (EN 1283).
Il coefficiente di ultrafiltrazione è stato misurato usando sangue umano, Hct 32%, proteine totali 6%.

Sieving coefficient Q_s = 300 ml/mn, u_F = 60 ml/mn					
	Inulina		**1**		
	β_2 microglobulina		**0,8**		
	Albumina		**0,001**		
Superficie effettiva	(m^2)	0,6	1,0	1,4	1,8

Convection vs diffusion



Effects of Hemodiafiltration versus Conventional Hemodialysis in Children with ESKD: The HDF, Heart and Height Study

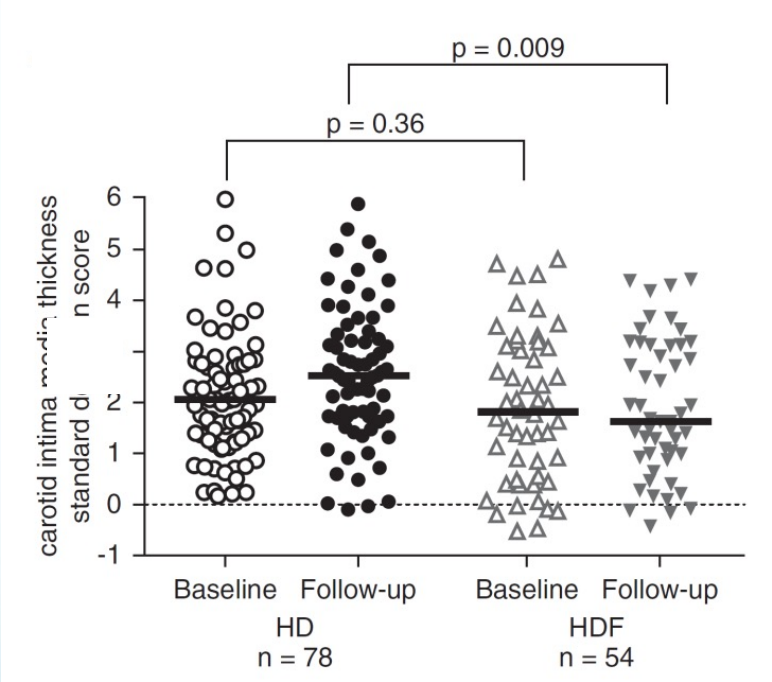
Rukshana Shroff,[1,2] Colette Smith,[3] Bruno Ranchin,[4] Aysun K. Bayazit,[5] Constantinos J. Stefanidis,[6] Varvara Askiti,[6] Karolis Azukaitis,[7] Nur Canpolat,[8] Ayşe Ağbaş,[8] Helen Aitkenhead,[1] Ali Anarat,[5] Bilal Aoun,[9] Daley Aofolaju,[1] Sevcan Azime Bakkaloglu,[10] Devina Bhowruth,[2] Dagmara Borzych-Dużałka,[11] Ipek Kaplan Bulut,[12] Rainer Büscher,[13] John Deanfield,[2] Claire Dempster,[1] Ali Duzova,[14] Sandra Habbig,[15] Wesley Hayes,[1] Shivram Hegde,[16] Saoussen Krid,[17] Christoph Licht,[18] Mieczyslaw Litwin,[19] Mark Mayes,[1] Sevgi Mir,[12] Rose Nemec,[18] Lukasz Obrycki,[19] Fabio Paglialonga,[20] Stefano Picca,[21] Charlotte Samaille,[22] Mohan Shenoy,[23] Manish D. Sinha,[24] Brankica Spasojevic,[25] Lynsey Stronach,[1] Enrico Vidal,[26] Karel Vondrák,[27] Alev Yilmaz,[28] Ariane Zaloszyc,[29] Michel Fischbach,[29] Claus Peter Schmitt,[30] and Franz Schaefer[30]

- Non-randomized observational study in pediatric patients
- **Conventional hemodialysis (HD)** *versus* **high volume postdilution online HDF** (12-15 l/sqm/session, ultrapure water)
- 190 children from 28 centers:
  78 on HD and 55 on HDF completed 1-year follow-up

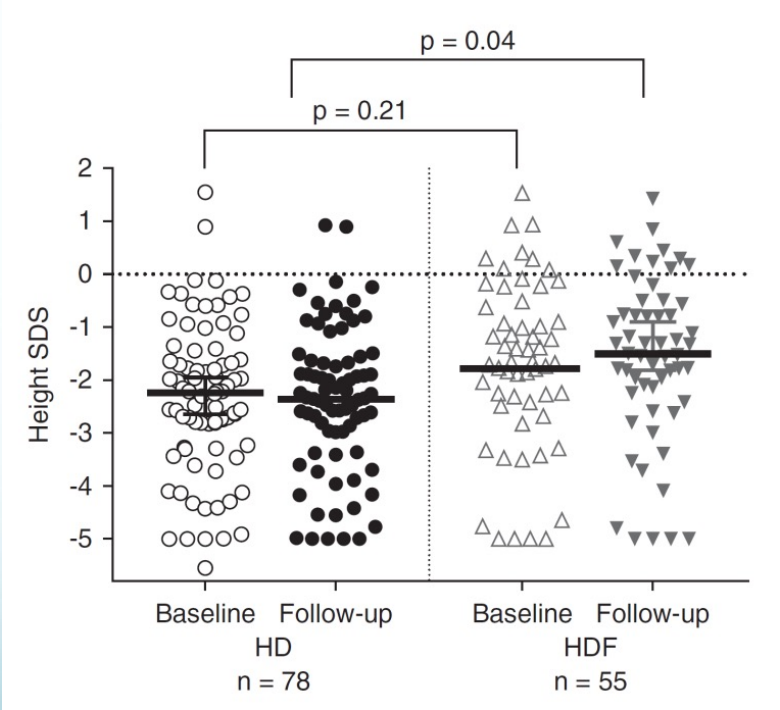
Shroff, JASN 2019

The 3H study: primary end-points

Carotid Intima Media Thickness



Height SDS



Shroff, JASN 2019

3H study: secondary endpoints

Patients treated with HDF had

- lower pulse wave velocity and left ventricular mass index
- better blood pressure control
- lower interdialytic weight gain
- fewer episodes of headaches, dizziness, or cramps, and shorter postdialysis recovery time
- lower b2-microglobulin
- lower inflammatory markers: IL-6, TNFα, hs-CRP
- higher BAP/TRAP5b ratio; lower FGF-23

Shroff, JASN 2019
De Zan, Pediatr Nephrol 2021
Fischer, KI reports 2021

Nephrol Dial Transplant (2019) 1–9
doi: 10.1093/ndt/gfz132

ndt
Nephrology Dialysis Transplantation

Haemodiafiltration does not lower protein-bound uraemic toxin levels compared with haemodialysis in a paediatric population

Evelien Snauwaert [1], Wim Van Biesen[1], Ann Raes[1], Griet Glorieux[1], Johan Vande Walle[1], Sanne Roels[2], Raymond Vanholder[1], Varvara Askiti[3], Karolis Azukaitis[4], Aysun Bayazit[5], Nur Canpolat[6], Michel Fischbach[7], Krid Saoussen[8], Mieczyslaw Litwin[9], Lukasz Obrycki[9], Fabio Paglialonga[10], Bruno Ranchin[11], Charlotte Samaille[12], Franz Schaefer[13], Claus Peter Schmitt[13], Brankica Spasojevic[14,15], Constantinos J. Stefanidis[3], Rukshana Shroff[16,*] and Sunny Eloot[1,*]

toxins

MDPI

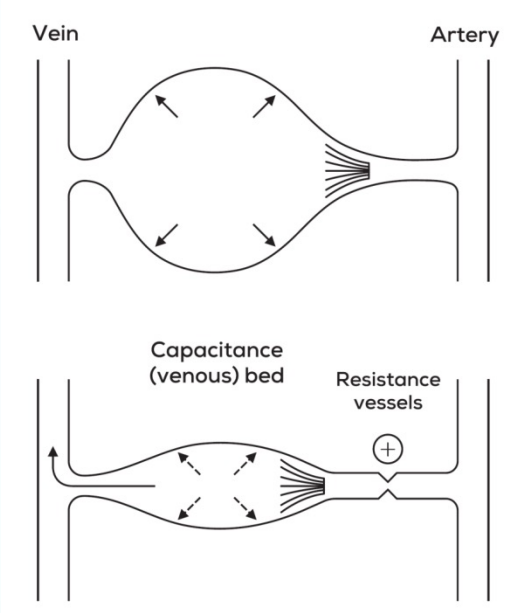
Article

Uremic Toxin Concentrations are Related to Residual Kidney Function in the Pediatric Hemodialysis Population

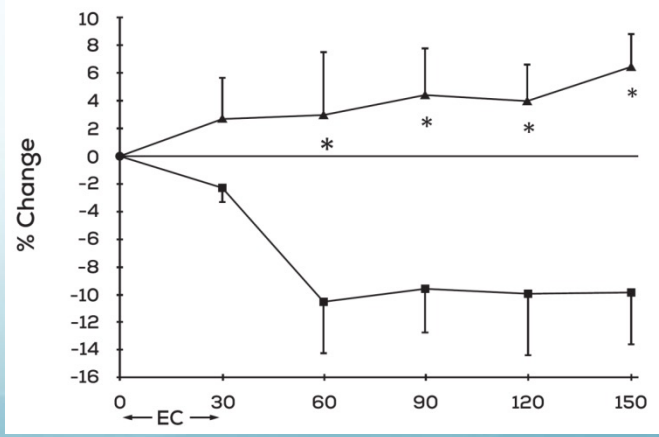
Evelien Snauwaert [1,*], Els Holvoet [1], Wim Van Biesen [1], Ann Raes [1], Griet Glorieux [1], Johan Vande Walle [1], Sanne Roels [2], Raymond Vanholder [1], Varvara Askiti [3], Karolis Azukaitis [4], Aysun Bayazit [5], Nur Canpolat [6], Michel Fischbach [7], Nathalie Godefroid [8], Saoussen Krid [9], Mieczyslaw Litwin [10], Lukasz Obrycki [10], Fabio Paglialonga [11], Bruno Ranchin [12], Charlotte Samaille [13], Franz Schaefer [14], Claus Peter Schmitt [14], Brankica Spasojevic [15], Constantinos J. Stefanidis [3], Maria Van Dyck [16], Koen Van Hoeck [17], Laure Collard [18], Sunny Eloot [1,†] and Rukshana Shroff [19,†]

Fluid removal during HD

- Vascular refill
- Splanchnic shift
- Vasoconstriction? ✗
- Increased cardiac frequency?

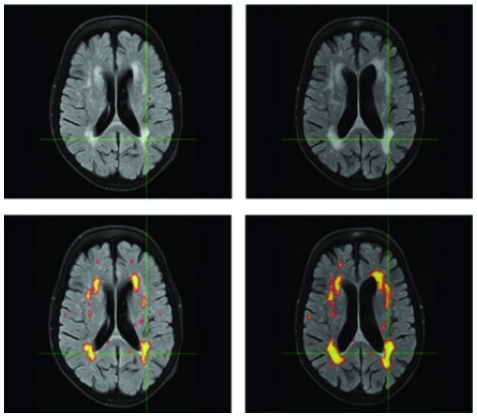


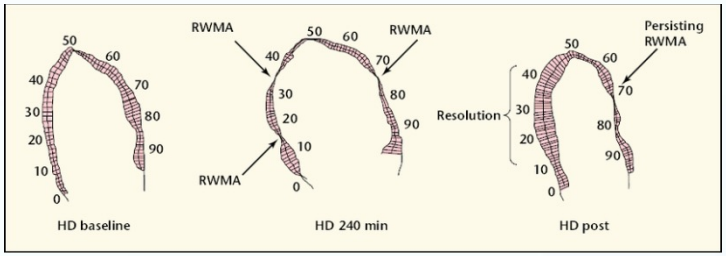
- Reduced venous return
- Reduced cardiac output

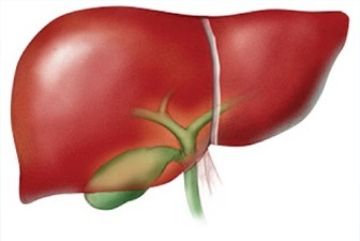


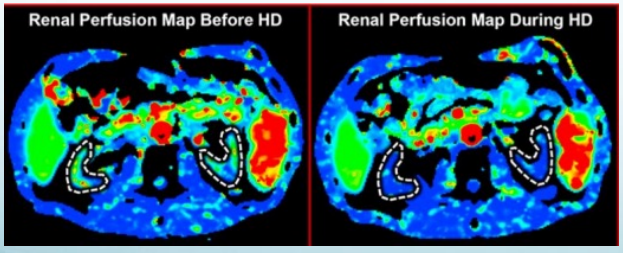
- Hypoperfusion
- Symptoms/hypotension

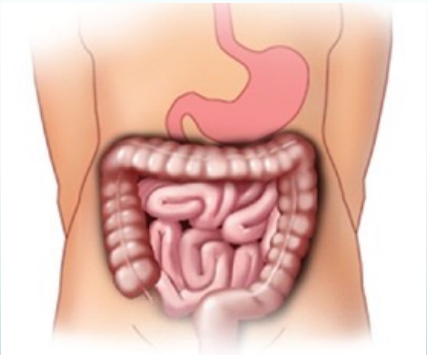
Excessive/aggressive fluid depletion





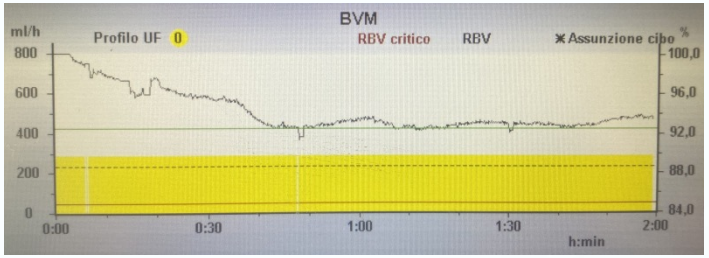


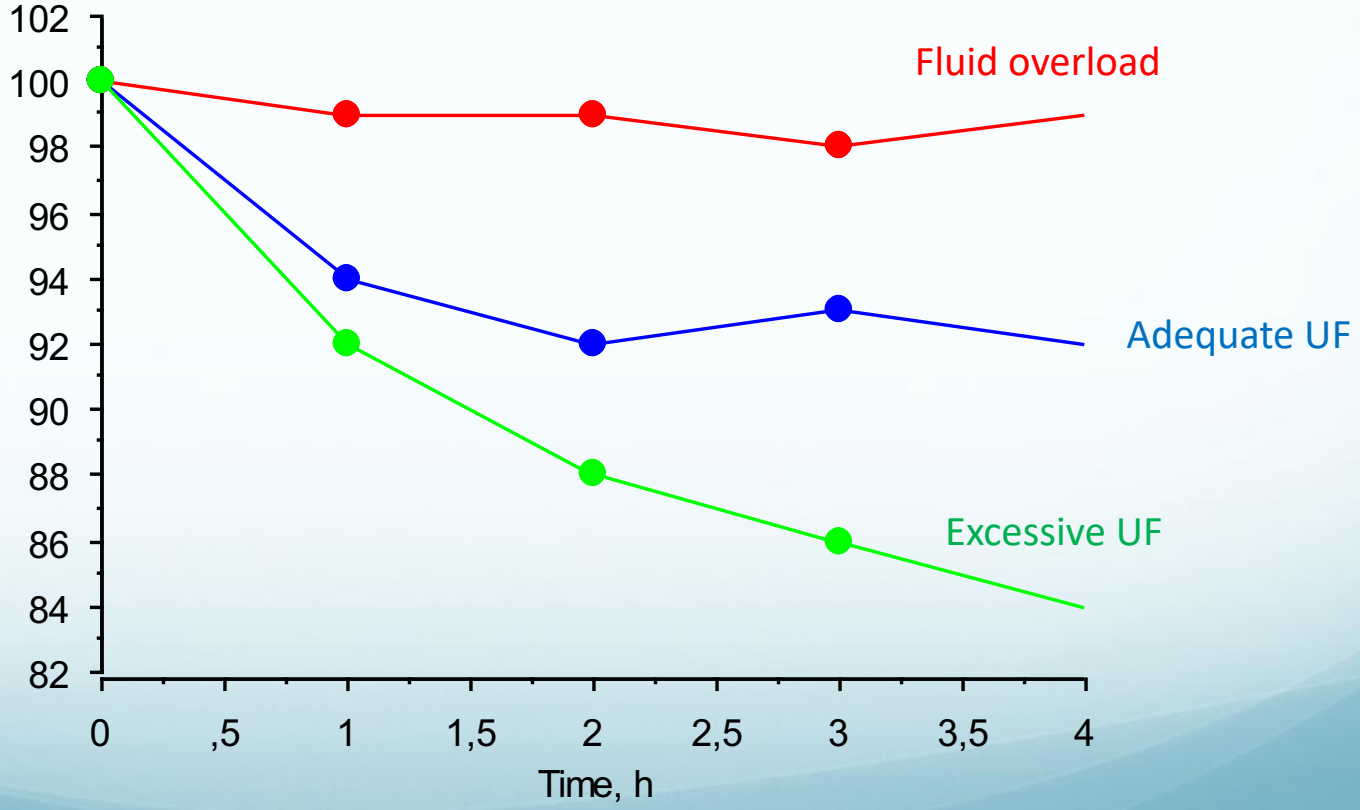




…even during asymptomatic sessions !!

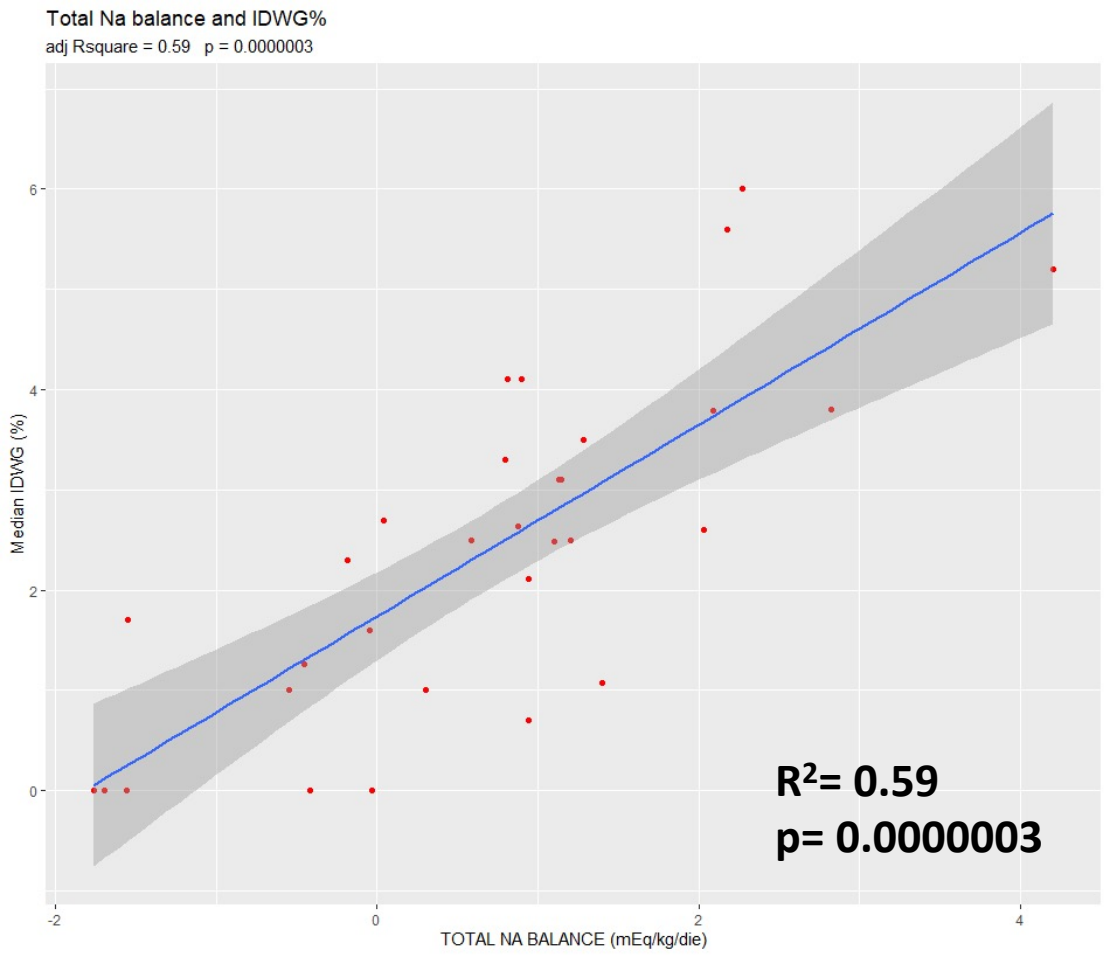
Blood Volume Monitoring (BVM)





IDWG and sodium balance in pediatric patients on HD

Target:
IDWG < 4% BW
(UF< 10 ml/kg/h)



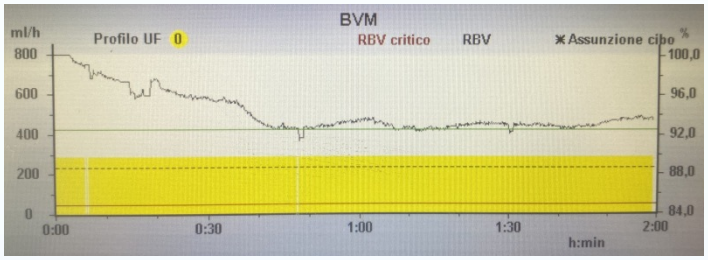
VOLUME = WATER + SODIUM

Paglialonga, Pediatr Nephrol 2016
Multicenter EPDWG study 2021

The basics of extracorporeal dialysis in 2021

- **Access**

- **BVM**



- **Convection + Diffusion**