Dialysis practice:
how to write an HDF prescription
high efficiency HDF: convective volume OL-HDF (purity); membrane quality volume control (BCM, UF and Na_D)

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Pediatric Dialysis Unit

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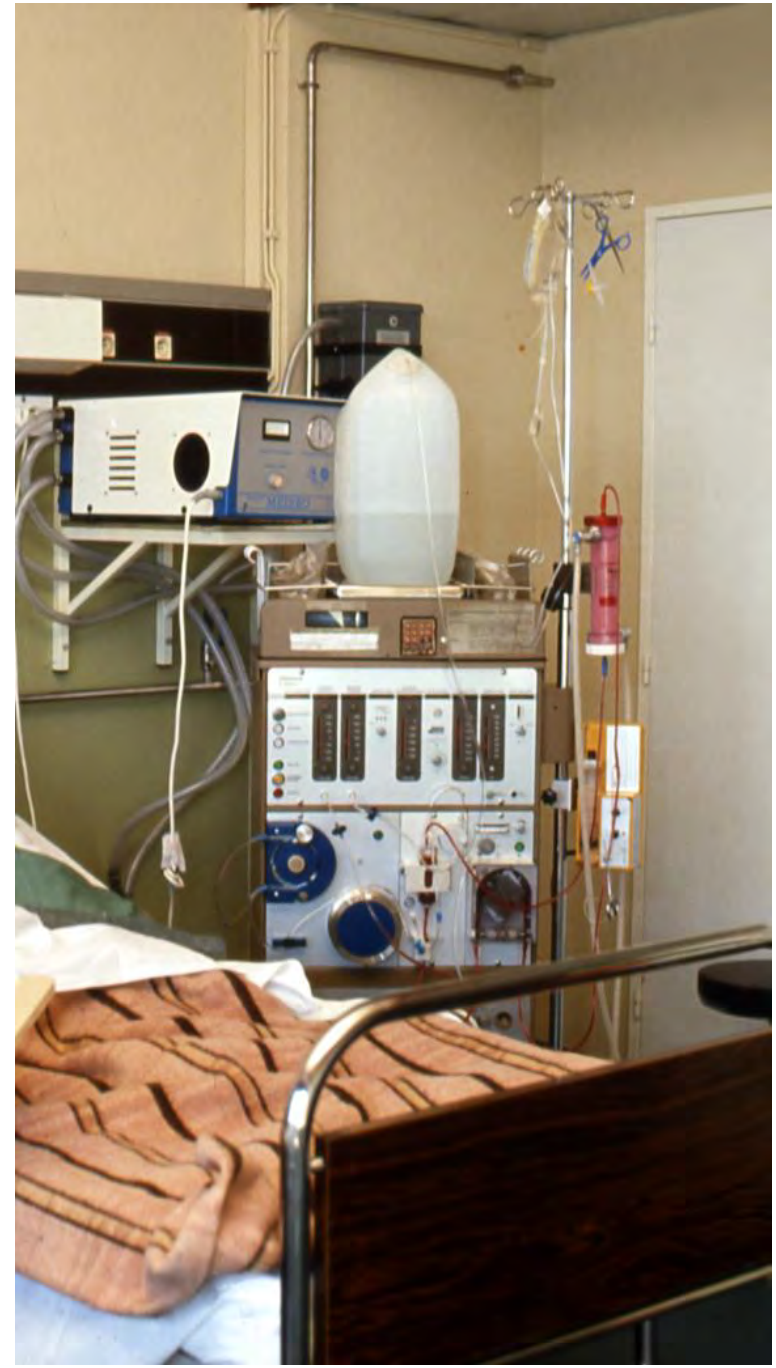
HDF started

1981 July
Strasbourg
France



High technollogy, and life

July 1981
Start of HDF
STRASBOURG

1) HDF with bags

2) water treatment: individual bedside reverse osmosis

3) Conventional heparin

4) heating of the substitution fluid

5) membranes, « water permeability for UF »

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Hemodiafiltration in children, a history

1) HDF with bags, July 1981: *tolerance, « a complete blood uremic detoxification, urea and more : Ph, beta2micro… »*

2) HDF on line, November 1989: *purity of the dialysis fluids (germ free; « no » endotoxins), less protein wasting/cachexia*

3) daily OL-HDF, Sept 2002: ***more dialysis time,*** *catch up growth*

4) high efficiency HDF *(autosub + technology=high convective volume, « tools not toys ») (BCM/BVM/BTM and on-line diffusive plasmatic sodium)* **and daily HDF** : *volume control (floating dry weight), cardiovascular preservation, normal growth*

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Writing a HDF prescription for children

- The dialysis prescription (blood flow, duration of the session and dialysate flow) should be individually adapted to achieve an urea dialysis dose of Kt/V≥1.4, which is a surrogate for predominantly diffusive clearance as well as the highest possible convective clearance (blood flow/convective flow: maximal UF <<<blood flow; <1/3 in postdilution).
- The following points should be considered when writing an HDF prescription for children and in first “line” the blood flow
- HDF requires an optimal arterial blood flow of 5 to 8 ml/min/kg body weight or 150 to 240 ml/min/m² body surface area. This can be achieved through either a fistula (+++) or a central venous line.

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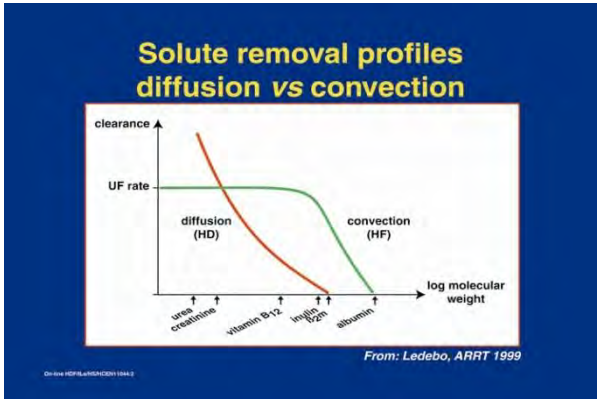
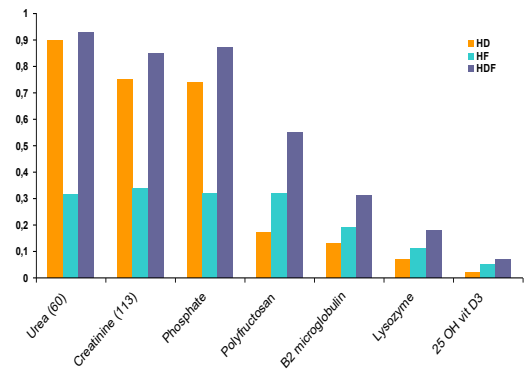
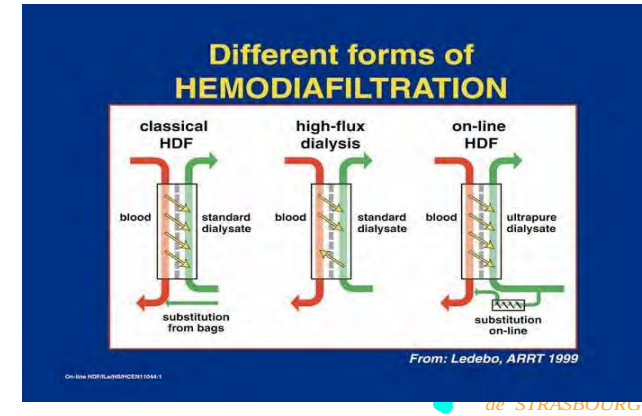
Principles of blood purification

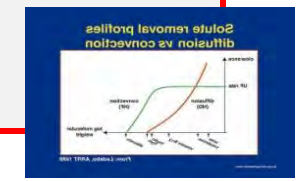
- Diffusive Process (HD) : low MW uremic toxins removal i.e.urea
- Convective mass transport (HF) : middle MW uremic toxins removal i.e.phosphate, beta2micro
- Membrane adsorption (+++/PMMA/Torray ?)







Blood purification dialysis modalities : diffusion versus convection



Diffusive Process (hemodialysis)

Small molecules
Membrane area
Mass transport coefficient
Concentration gradient
Blood flow x extraction coefficient (<1)

$$K_{HD} = Q_B \times \frac{c_i - c_o}{c_i}$$

i, o : in outlet solute concentrations

Convective mass transport (hemofiltration)

Ultrafiltrate flow (Q_{UF})
Hydraulic permeability
Transmembrane pressure (TMP ; mmHg)
Sieving coefficient (S)*
Molecular permeability (MW): <1

$$*S = \frac{2\,C_{UF}}{c_i + c_o}$$

C_{UF} : ultrafiltrate solute concentration

$K_{HF} = Q_{UF} \times S$ (postdilution)

$Q_{UF} < 1/3\ Q_B$ (in practice oftently lower)

Simultaneous purification: diffusion process and convection mass transport i.e. hemodiafiltration

one minute of dialysis « is equal» to two minutes of purification, one of HD and another one of HF

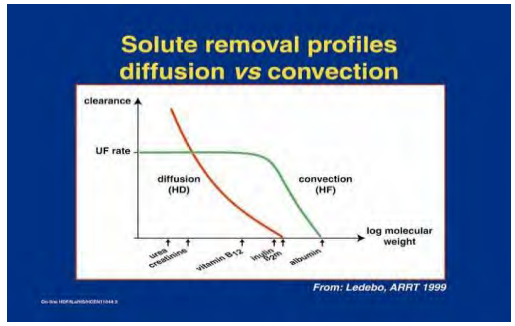
$K_{HDF} = K_{HD} + x\ Q_{UF} \times 0.46$

$K_{HDF} = K_{HD} (1 - Q_{UF} \times S/Q_B) + K_{HF}$ (Granger)

with $Q_{UF} \times S = K_{HF}$ and $Q_B = K_{max}$

$$K_{HDF} = K_{HD} + K_{HF} - \frac{K_{HD} \times K_{HF}}{K_{max}}$$

If K_{HD} is equal to K_{max} then $Q_{HDF} = K_{HD}$



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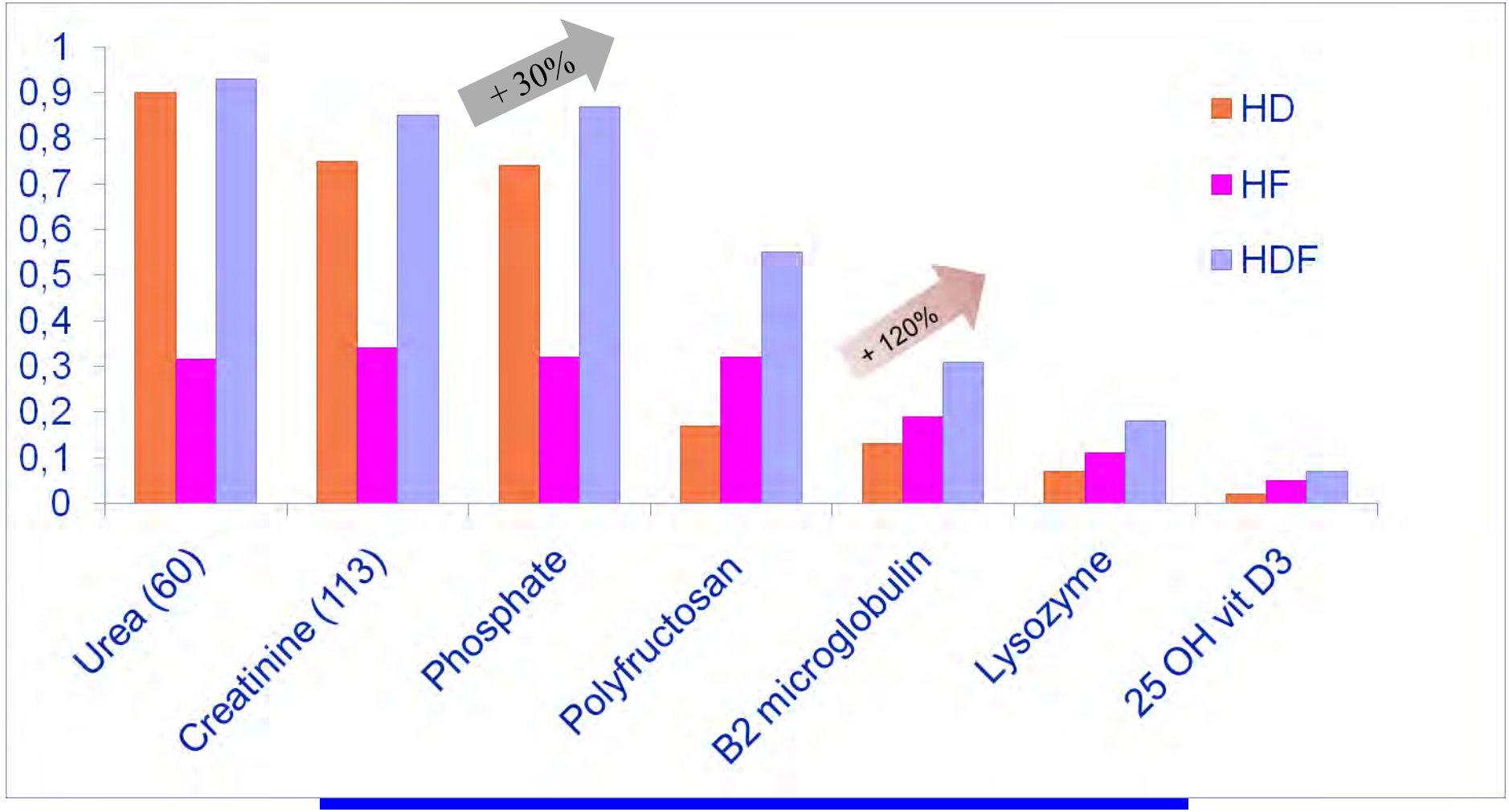


HDF allows an optimal blood purification not only for urea, but also for the middlemolecular weight compounds (Babb theory)

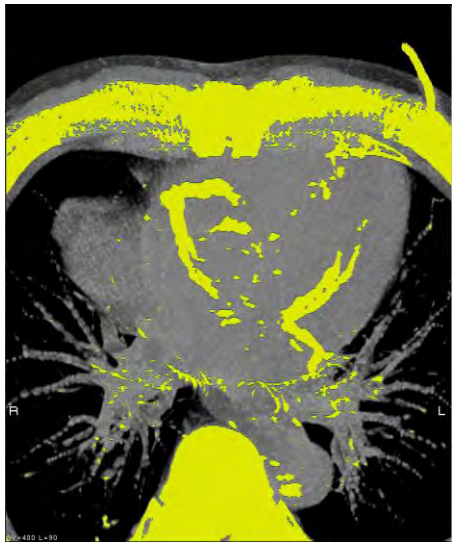
From M Fischbach et all .Contr Nephrol1985

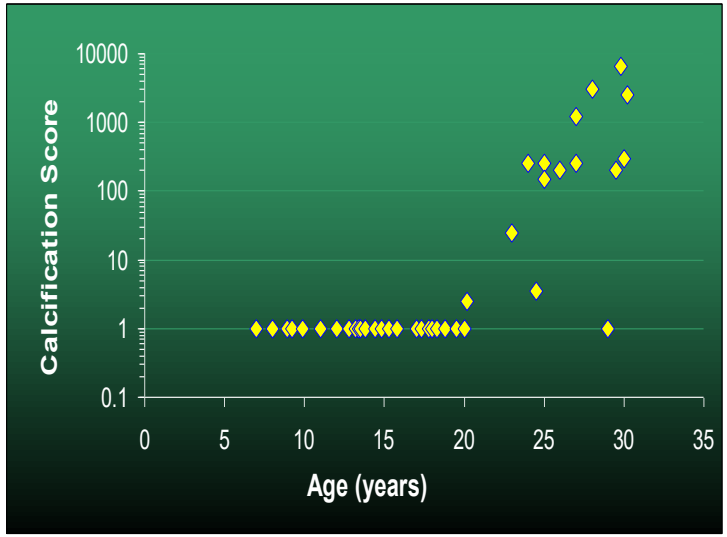
Hyperphosphatemia, a « silent killer »

(FGF23;Klotho) of patients with renal failure

K. Amann, M.C. Gross, G.M. Landon, E. Ritz Nephrol Dial Transplant 1999;14:2085-87

coronary calcification : Ca x P





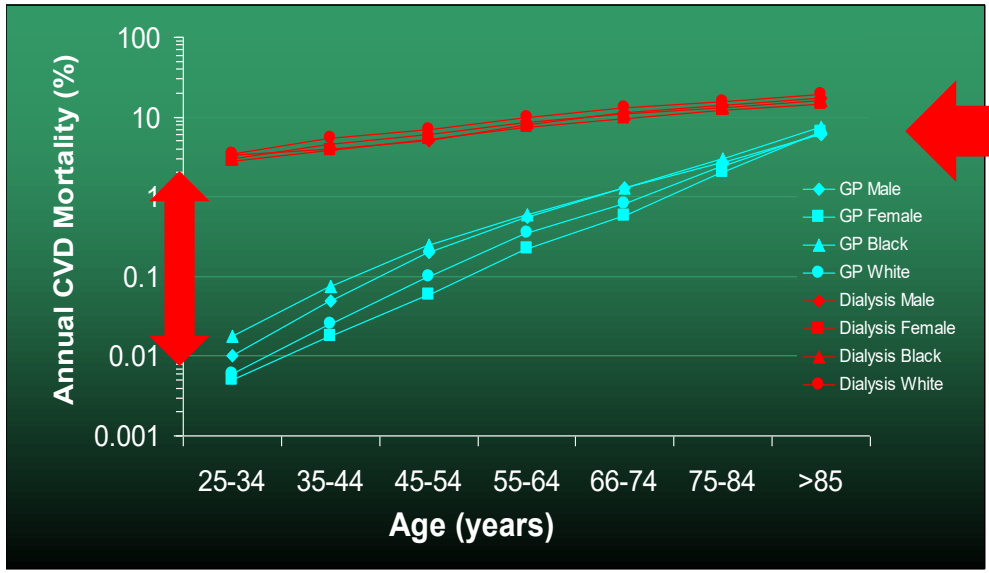
17 young adult patients with childhood onset of CRF (median 26 years at screening time): *coronary calcifications* were found in 7 out of 17 patients

Premature atherosclerosis in young adults and childhood onset chronic renal failure

OH J. et al. J Am Soc Nephrol 2000; 11:A857 and Circulation 2002; 106:100-105

Increased cardiovascular risk for children on ESRF : predialysis, dialysis, transplantation

- ***Conventional risks factors_:*** *BMI, cholesterol, sedentarity, BP, tabacco..*
- ***Specific ESRF factors :*** *CKD-MBD (calcium/phosphate/ PTH/vit D), volume control (BP and uremic cardiomyopathy), inflammation/protein wasting….*
- **All together conducting to atherosclerosis (cholesterol) and mediacalcosis (CaxP)**



At 25 years, the same cardiovascular death risk as elderly over 85 years

Foley RN, Parfrey PS, Sarnak MJ 1998 Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol 9:S16-23.

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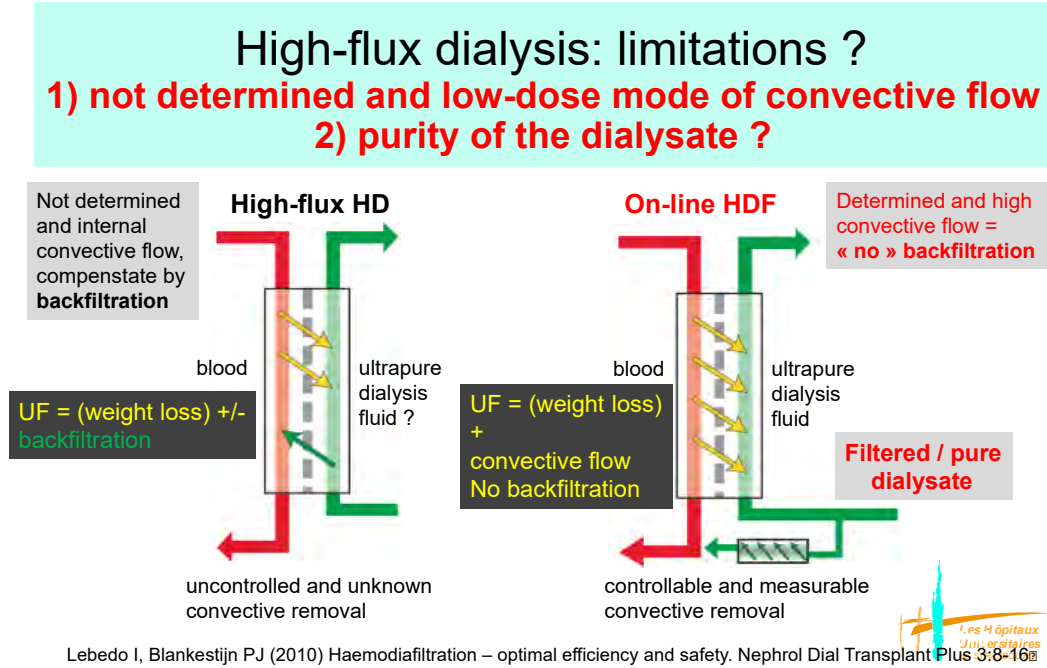
- A high flux membrane with surface area equal to the child's body surface area is used.
- Dialysate flow of 1.5 times the blood flow is sufficient and adequate to optimize the diffusive blood purification process using highly permeable membranes for HDF
- Convective flow is equal to total ultrafiltration flow i.e. the sum of the weight loss and the replacement fluid (convective dialysis dose per session; L/m^2/session or per week)

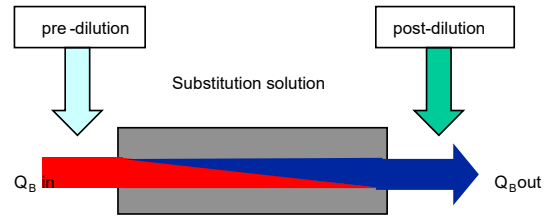


Lebedo I, Blankestijn PJ (2010) Haemodiafiltration – optimal efficiency and safety. Nephrol Dial Transplant Plus 3:8-16

- **Post-dilution HDF** - the convective flow is ≤1/3 of the blood flow, and limited by the risk of filter clotting. It typically decreases over the dialysis session (TMP should be limited less than 300 mm Hg)
- **Pre-dilution HDF** - the convective flow is set at ≥ 50% of blood flow, but optimally can be increased to 75 - 100% of blood flow ; despite the dilution of the blood potentially impacting negatively on urea clearance, β2 microglobulin and phosphate dialytic removal is optimized as is the clearance of uremic protein bounded toxins

Hemodiafiltration : pre/post dilution

The convective transport requires ultrafiltration (UF) of fluid, i.e. the convective flow. If the convective flow exceeds the desired weight loss, the fluid balance is maintained by an infusion of replacement fluid, as applied in HF.



In HDF addition of substitution solution can be made before the filter called *predilution* mode, after the filter, *postdilution* mode, or mixed

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Predilution HDF

To improve efficiency in the pre dilution mode, the convective flow should be high enough to ensure increased solute clearance despite blood dilution. In practice, this is *superior to 50 % of the blood flow, and "ideally" should be two thirds of or equal to the blood flow.*

In cases of high hematocrit levels or blood conditions that limit the filtration capacity e.g. elevated blood protein concentration, or in patients with low blood flow (as is often the case in children), ***predilution compared to postdilution modalities HDF***, have been proven to be of significant clinical benefit, especially ***less risk of membrane clotting***.

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Comparison of removal capacity of two consecutive generations of high flux dialysers during different treatment modalities

Meert N and Vanholder R. Nephrol Dial Transplant 2011; 26:2624-30

	Pre HDF	Post HDF
Qb eff (mL/min)	300	300
Q_D (mL/min)	800	800
Qinf (mL/min	145	70

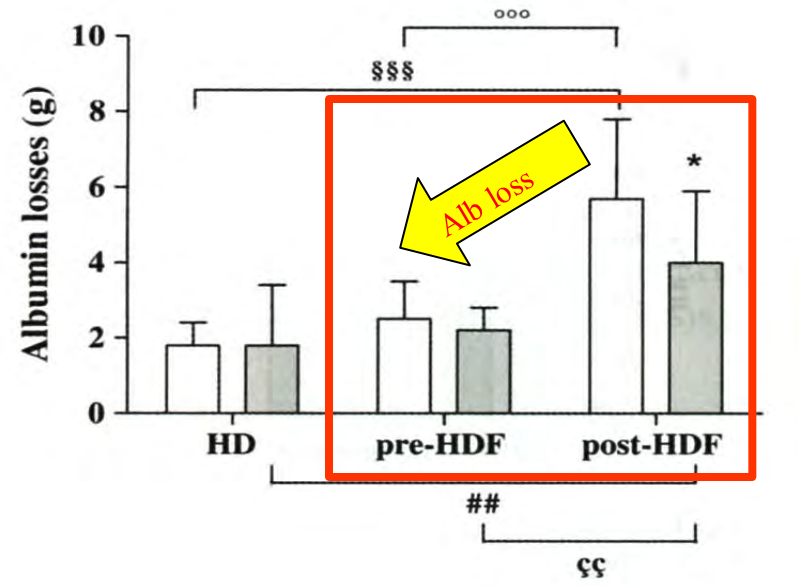

Fig. 3 : when comparing strategies, post dilution HDF induced more albumin losses (5.7±2.1 g/session) than the two other modalities (1.8±0.6 g/session)

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Uremic toxins: which to dose?

Urea Kt/V as surrogate for the diffusion process and β2 microglobulin or the convective volume as surrogate for the convective mass transport?

Focusing on middle molecules...Convective dialysis dose

diffusion

convection

Small water soluble solutes	Protein-bound solutes	Middle molecules
Asymmetric dimethylarginine	3-Deoxyglucosone	Adrenomedullin
Benzylalcohol	CMPF*	Atrial natriuretic peptide
ß-Guanidinopropionic acid	Fructoselysine	$ß_2$-Microglobulin
ß-Lipotropin	Glyoxal	ß-Endorphin
Creatinine	Hippuric acid	Cholecystokinin
Cytidine	Homocysteine	Clara cell protein
Guanidine	Hydroquinone	Complement factor D
Guanidinoacetic acid	Indole-3-acetic acid	
Guanidinosuccinic acid	Indoxyl sulfate	**Middle molecules**
Hypoxanthine	Kinurenine	**β2 - Microglobulin**
Malondialdehyde	Kynurenic acid	
Methylguanidine	Methylglyoxal	
Myoinositol	N-carboxymethyllysine	Interleukin 1ß
Orotic acid	P-cresol	Interleukin 6
Orotidine	Pentosidine	Kappa-Ig light chain
Oxalate	Phenol	Lambda-Ig light chain
Pseudouridine	P-OHhippuric acid	Leptin
Symmetric dimethylarginine	Quinolinic acid	Methionine-enkepahlin
Urea	Spermidine	Neuropeptide Y
Uric acid	Spermine	Parathyroid hormone
Xanthine		Retinol binding protein
*CMPF is carboxy-methyl-propyl-furanpropionic acid		Tumor necrosis factor alpha

?

EUTox European Uremic Toxin Work Group of the ESAO

Vanholder R. et al New insights in uremic toxins. *Kidney Int*, 2003, 63; 84: S6–S10

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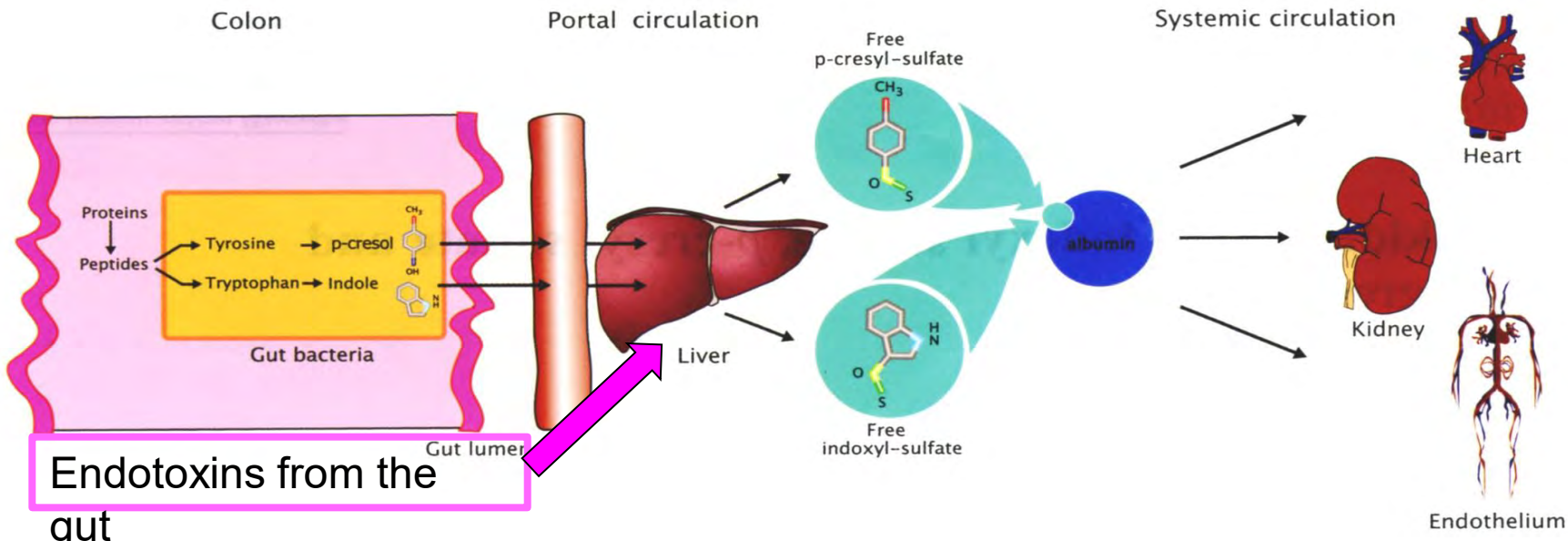
The gut-kidney axis:
indoxyl sulfate, *p-cresyl* sulfate, endotoxins and CKD progression

Björn KI Meijers and Pieter Evenepoel.
Nephrol Dial Transplant 2011; 26:759-761



CKD : a systemic disease with cross talk between the gut and the "body" (CKD-MBD-CardioVascular)

- ✓ Uremic toxins production
- ✓ "leaky" gut (endotoxins)

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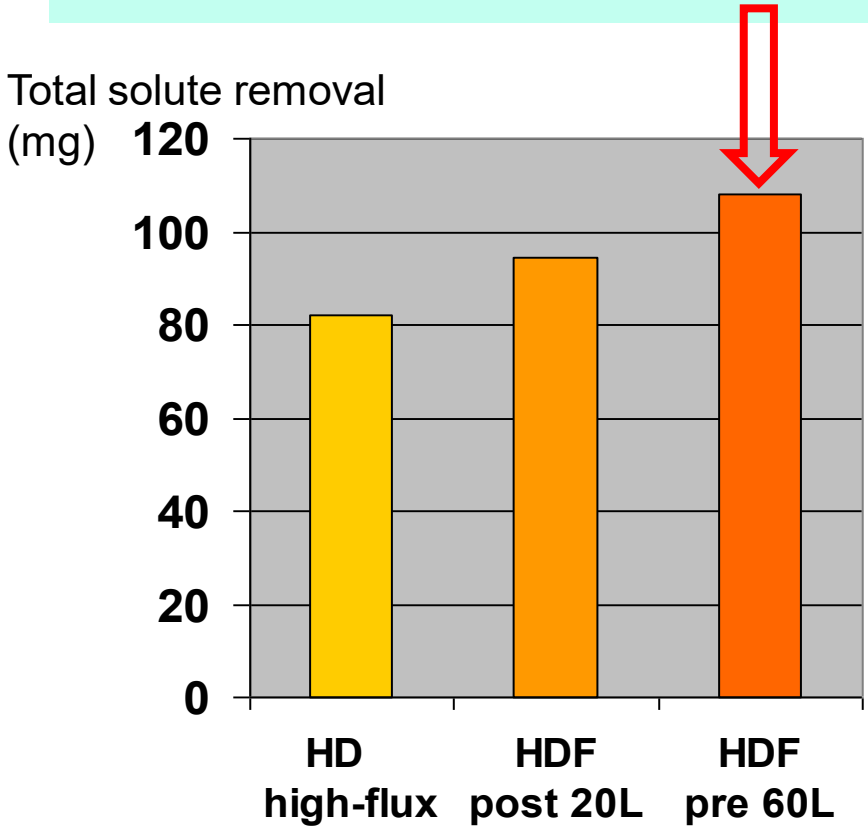
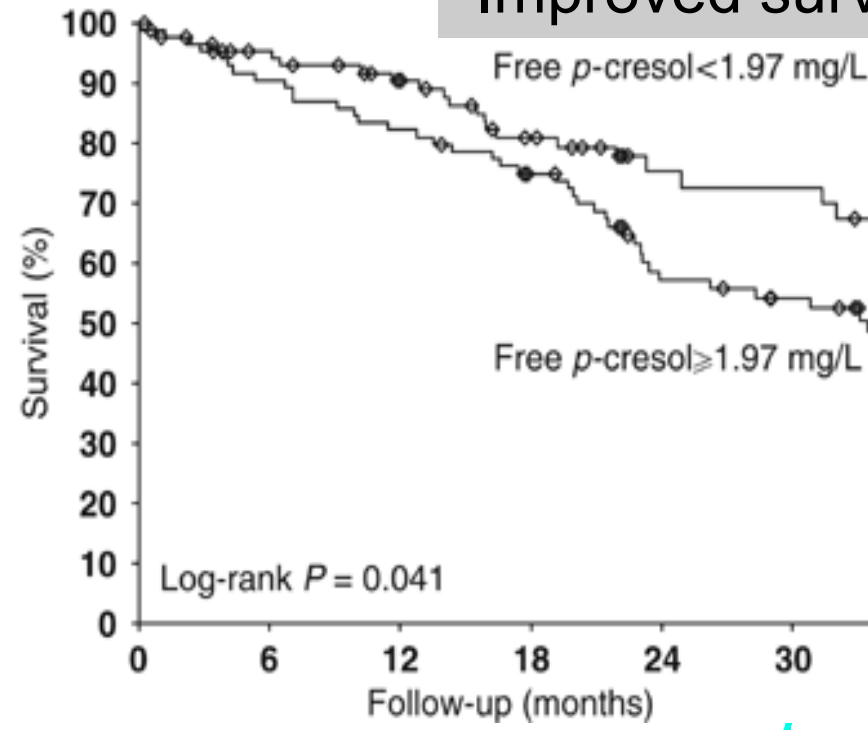
P-cresol , a protein-bound uremic toxin impact on survival

Bammens et al, AJKD 2004 and Kidney Int 2006



14 patients treated w the same high-flux filter 2 wks on each modality

Improved survival



N= 175 HD patients, prosp. obs. study

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Predilution HV-HDF with AutoSub plus

Q_{inf} / Q_b	Q_{inf} / Q_{pw}	Indoxyl-Sulfate free-fraction f_{pre}
0,0	0,0	10%
0,7	1,0	18%
1,0	1,5	22%
4,0	6,0	44%

Protein-bound uremic-toxins removal rises with increasing Qsub

Q_{inf} : Infusion rate
Q_b : blood flow rate
Q_{pw} : plasma flow rate

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How to prescribe hemodialysis or hemodiafiltraiton in order to ameliorate dialysis-related symptomes and complications

Ikuo Masakane. Kawanishita H, Yamashita AC, (eds):Hemodiafiltration – A new Era. In Contrib Nephrol. Basel, Karger; 2011, vol 168, pp 53-63.

Higher albumin loss was observed when HPM dialyzers were used for post dilution HDF. Thus, elevation of the efficiency of high molecular solutes removal while controlling albumin loss by employing pre dilution HDF has become actively performed.

The excessive plasma dilution in *pre dilution HDF could be* an important factor for *enhancing the efficacy of protein bound uremic toxins removal*

Pre dilution HDF using HPM dialyzer has become the main trend in Japan

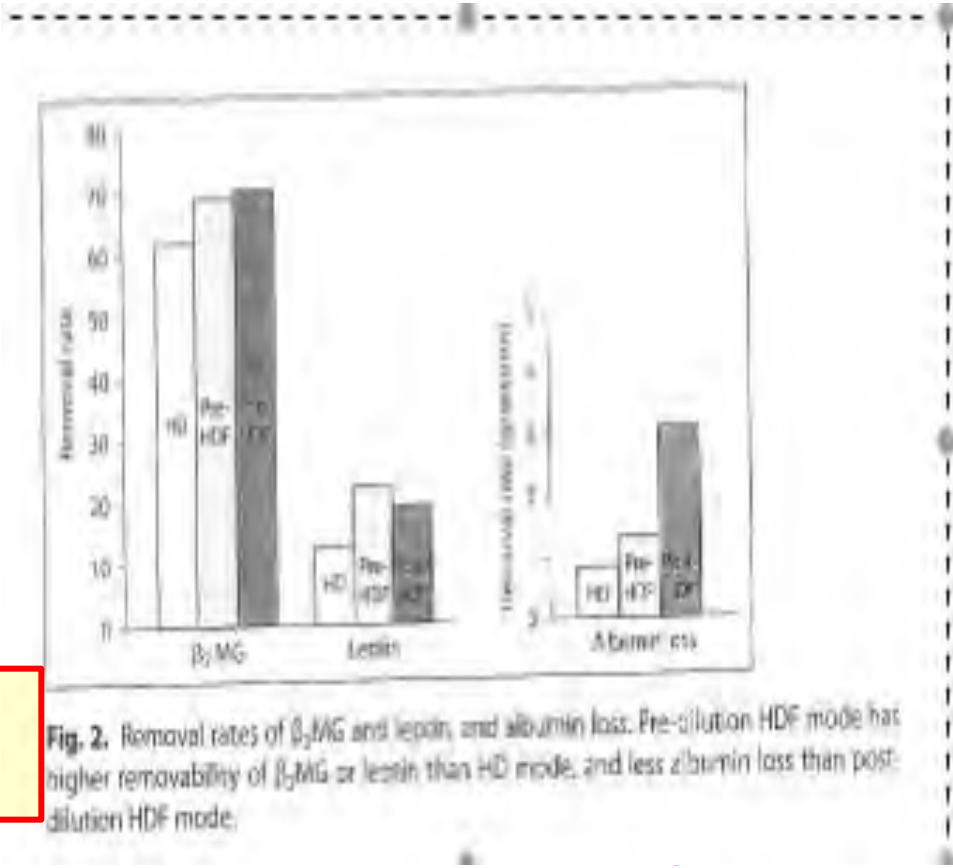


Fig. 2. Removal rates of β2MG and leptin, and albumin loss. Pre-dilution HDF mode has higher removability of β2MG or leptin than HD mode, and less albumin loss than post-dilution HDF mode.

Recommandations for a « standard » dialysate

	Endotoxines
FRANCE	< 0,25 UI / ml
ISO 23500	< 0,5 UI / ml
JAPON	< 0,05 UI / ml

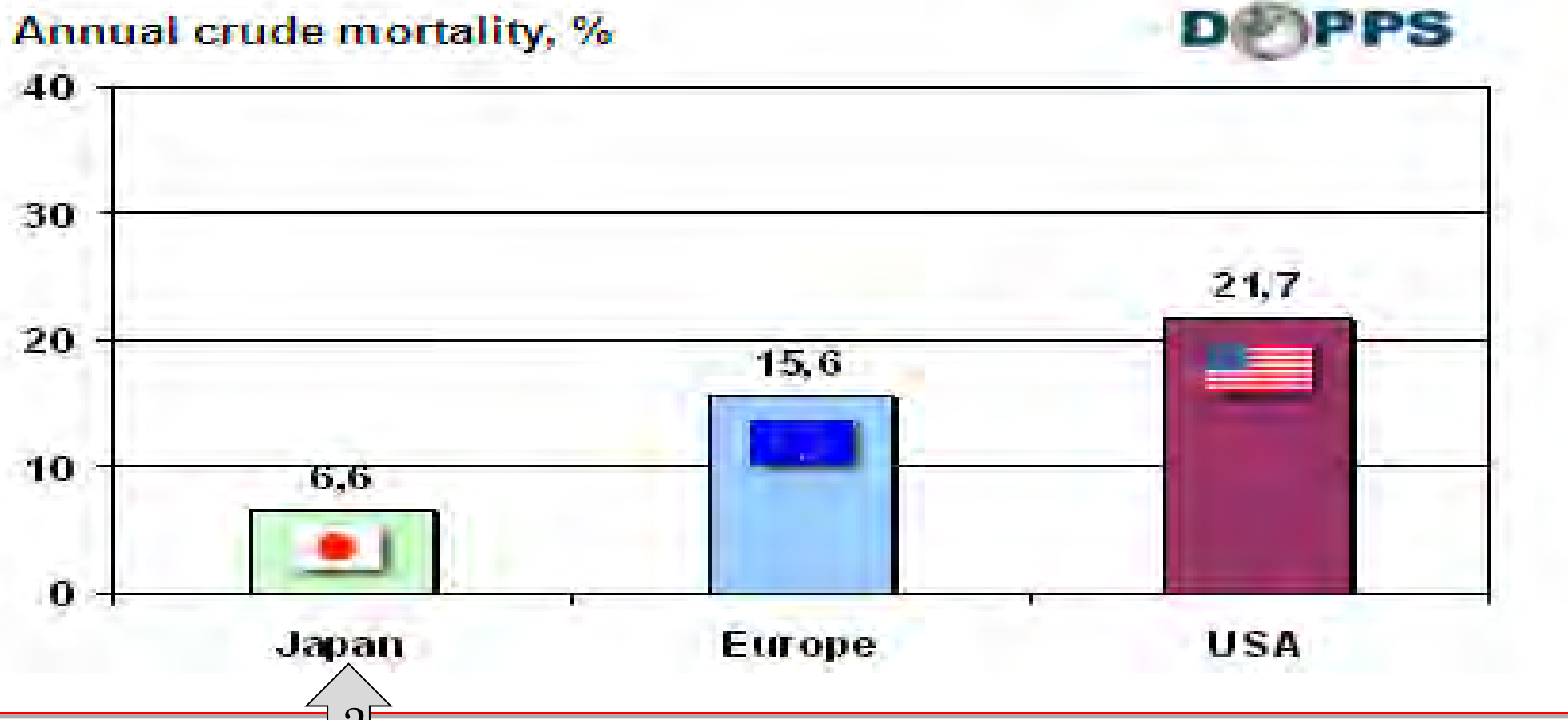
Recommandations for an « ultrapur » dialysate

	Endotoxines
FRANCE	< 0,25 UI / ml
ISO 23500	< 0,03 UI / ml
JAPON	< 0,001 UI / ml

Recommandations for the substitution fluid (convective volume)

	Endotoxines
FRANCE	< 0,05 UI / ml
ISO 23500	< 0,03 UI / ml
JAPON	< 0,001 UI / ml

A.Ragon, P.Brunet, D.Jaubert, G.Lebrun, A.Duval-Sabatier
Pôle Urologie – NéphrologieAssistance Publique – Hôpitaux de Marseille. Décembre 2012



mortality risk:

dialysis fluids purity ?

HDF predilution ?

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HDF : substitution fluid optimization (convective volume)

- Pressure control (Gambro) : maximal efficient PTM assessed to obtain a gain of convective volume (PTM « pulses »)
- Filtration fraction (Fresenius) : inititally based on on line hematocrite (and historically on total proteins given by the medical prescription…), improved by viscosity (« doppler ») on line assessment : autosub +
- Conclusion : importance of the total amount of water, not only related to the proteins (filtration fraction <50%) but also to the blood cells (hematocrite « outlet » <50%); interest of « viscosity » assessment (Fesenius/autosub+)

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HDF optimization of convective volume

Overall, with new dialysis machines, *the convective flow is automatically optimized* either as a pressure or a volume control tool (Gambro) or as a viscosity control tool (Fresenius Medical Care; Autosub+) and thereby is directly *dependent on the achieved blood flow*.

In case (“oftently” in children) of low blood flow or of a risk of clotting (high haematocrit or high protein levels in the blood) *pre-dilution is more effective than post-dilution* as it preserves an effective convective flow throughout the dialysis session.

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On line HDF is not a self-fulfilly prophecy: it must be used ***wisely***

Kuhlmann MK. J Am Soc Nephro 2012; 23: 974-5

(CONTRAST « commentaries »)

- Advantages of OL-HDF both « purity and purification »:
  - higher removal of creatinine, phosphate, β2 m and some protein bound uremic compounds
  - lower incidence of intradialytic hypotension, nutritional status, prevention of inflammation and better preservation of residual renal function
- However, it remains a matter of debate whether these latter effects may have been related primarily *to the treatment made itself or secondary to improved dialysis purity*.
- Significantly improved outcome observed (Contrast/Turkish HDF study) in the subgroup of patients treated with the highest convection volumes: OL-HDF is easy to apply, ***high efficiency HDF i.e. large convective volumes need more practical implication (fistulla quality, session time, membrane, dialysate)***

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Dialysis membranes: practical parameters

- Capillary membrane, biocompatible (EO free), high flux (polysulfone, PAN); area= BSA in m^2
- Priming blood volume, ie area related, quality of restitution+++
- Molecular permeability : urea clearance=blood flow other uremic toxins, ie phosphate and beta-2-microglobulin (>60%, better 80%) ; osmotic risk (limited by iso-osmotic substitution fluid)
- Hydraulic permeability/UF coefficient: use for HF or HDF procedure (20-40 mL/h/mm Hg/m^2); back filtration risk if applyed for HD
- « Loss » of substances in the dialysate (albumin; vit C)
- Cost, cost effectiveness: more effective in HDF than in HD (cardiovascular preservation/reduced protein wasting)

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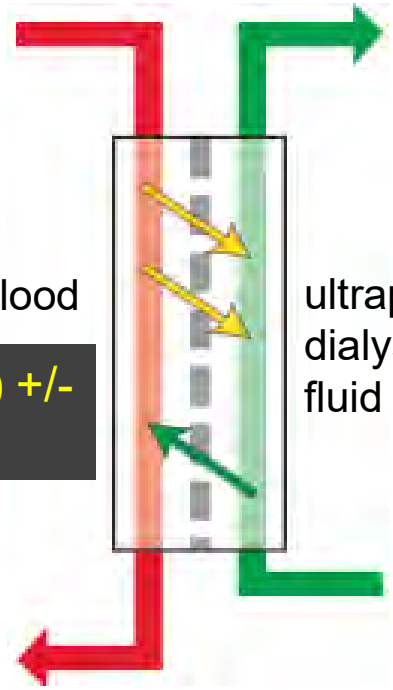
High-flux dialysis: limitations ?

1) not determined and low-dose mode of convective flow
2) purity of the dialysate ?

Not determined and internal convective flow, compenstate by **backfiltration**

High-flux HD

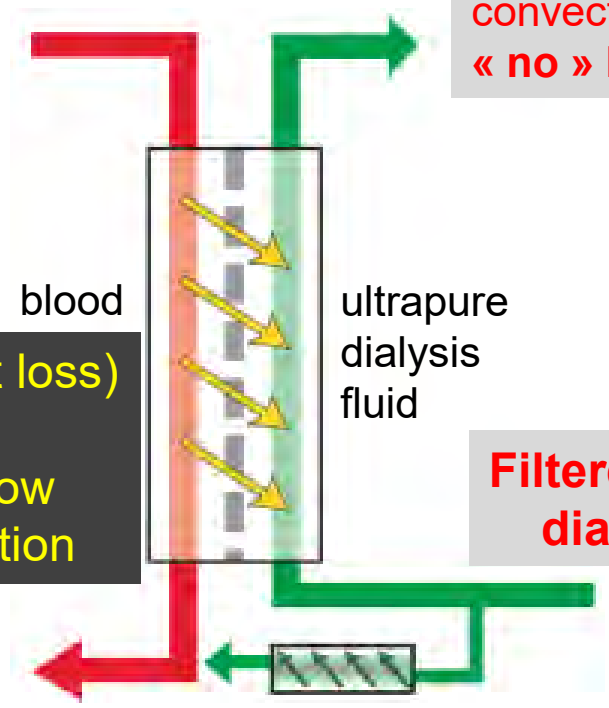


UF = (weight loss) +/- backfiltration

uncontrolled and unknown convective removal

On-line HDF

Determined and high convective flow = **« no » backfiltration**



UF = (weight loss) + convective flow No backfiltration

Filtered / pure dialysate

controllable and measurable convective removal

Lebedo I, Blankestijn PJ (2010) Haemodiafiltration – optimal efficiency and safety. Nephrol Dial Transplant Plus 3:8-16

Adequate HDF prescription: « quality » of a high convective volume *importance of the membrane*

- Hydraulic permeability : high convective volume

  (> 15-25 L for adults or 12- 15L/m²/session in postdilution)

- Molecular permeability : extraction coefficient

  (phosphate and β_2 m 80 %)

- Loss of albumine (< 5 gr in adults)
- Purity of the dialysis fluids

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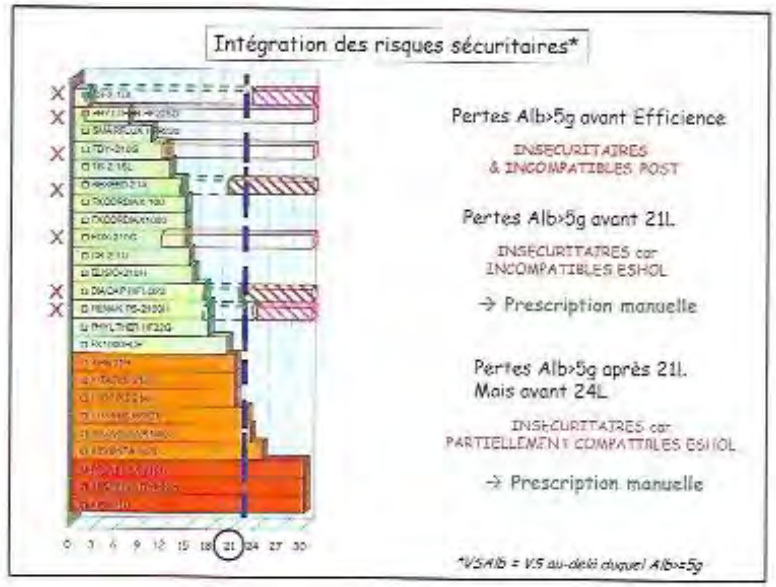

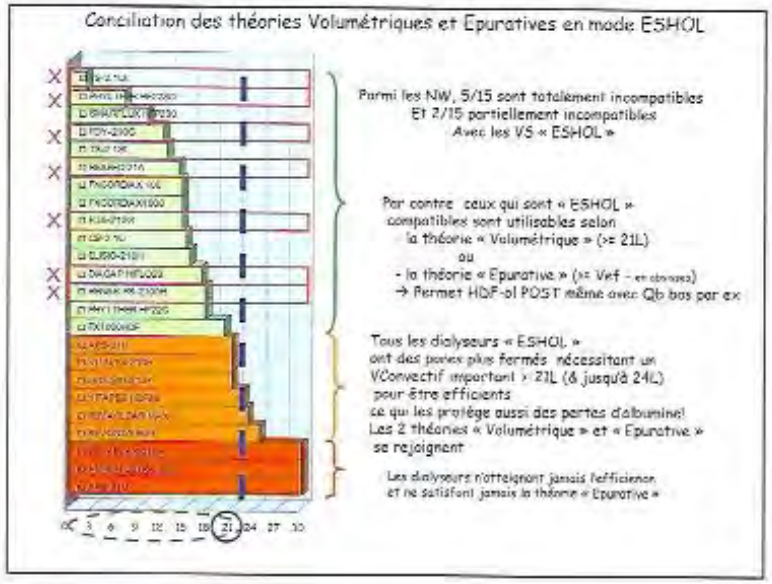

J Potier
Journées Experts HDF
FMC- Paris Novembre 2014

The “new wave” dialysis membranes have different capacities:

1) Ability to obtain a “ESHOL” (Maduell 2014) convective volume, > 21L

2) Molecular permeability, extraction coefficient of beta-2-microglobulin >80 % (alpha-1-microglobulin > 65%)

3) Loss of substrate in the dialysate, a function of the convective volume (albumin < 5 gr)

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- Optimal anticoagulation is necessary so as to prevent filter clotting, particularly in post-dilution HDF. A single dose of low molecular weight heparin is effective for a 4 hour session. Alternatively, a continuous heparin infusion can be used.
- The dialysate composition is similar to that used in HD, but careful attention to dialysate sodium concentration is important, particularly when high convective volumes are infused, as with pre-dilution HDF. To avoid the risk of a positive sodium balance the dialysate sodium concentration required is lower than in conventional HD.

High-efficiency postdilution OI-HDF reduces all-cause mortality in hemodialysis patients

Maduell F et al. J. Am Soc Nephrol 2013; 24:487-497

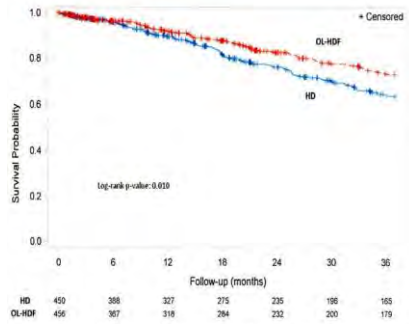

Figure 2. Kaplan–Meier curves for 36-month survival in the intention-to-treat population ($P=0.01$ by the log-rank test). HD, hemodialysis.

They found that high-efficiency OL-HDF (>24L) in patients with ESRD on hemodialysis was associated with **a 30 % reduction in all-cause mortality** compared with conventional high-flux hemodialysis

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Hypertension in Pediatric Long-term Hemodialysis Patients in the United States.

Chavers BM et al. Clin J Am Soc Nephrol 2009; 4:1363-9

- Cross sectionnel study of all US pediatric long-term HD patients (n=624; mean age 13.8±3.8 y)
- *Hypertension was present in 79 % of patients* (85 % predialysis and 75 % post dialysis): only 8 % would be recategorized from hypertensive predialysis to normotensive post dialysis
- 62 % used anti hypertensive medication(s)
- *hypertension was uncontrolled in 74 % of treated patients*
- **These data suggest that great potential exists for improving BP control in pediatric long-term HD patients**

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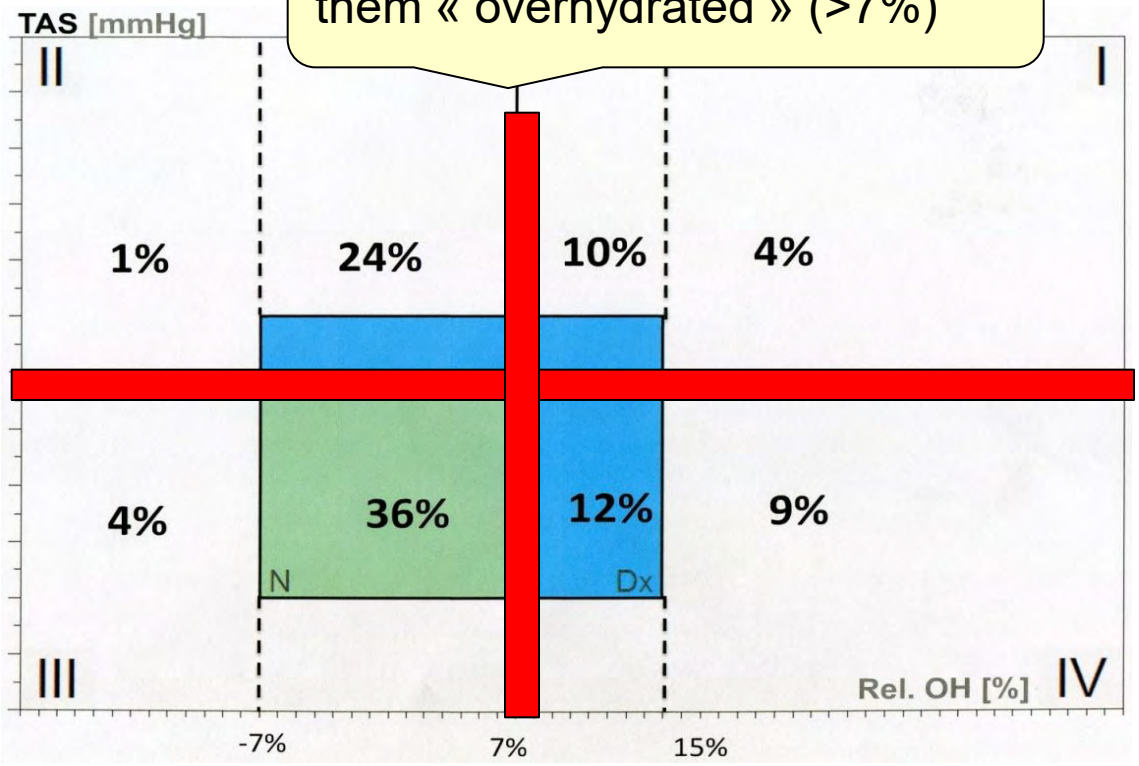
Hydration measurement by bioimpedance spectroscopy and blood pressure management in children on hemodialysis.

Zaloszyc A…Fischbach M (2013). Pediatr Nephrol; 28:2169-2177

39% high BP, but only 36% of them « overhydrated » (>7%)

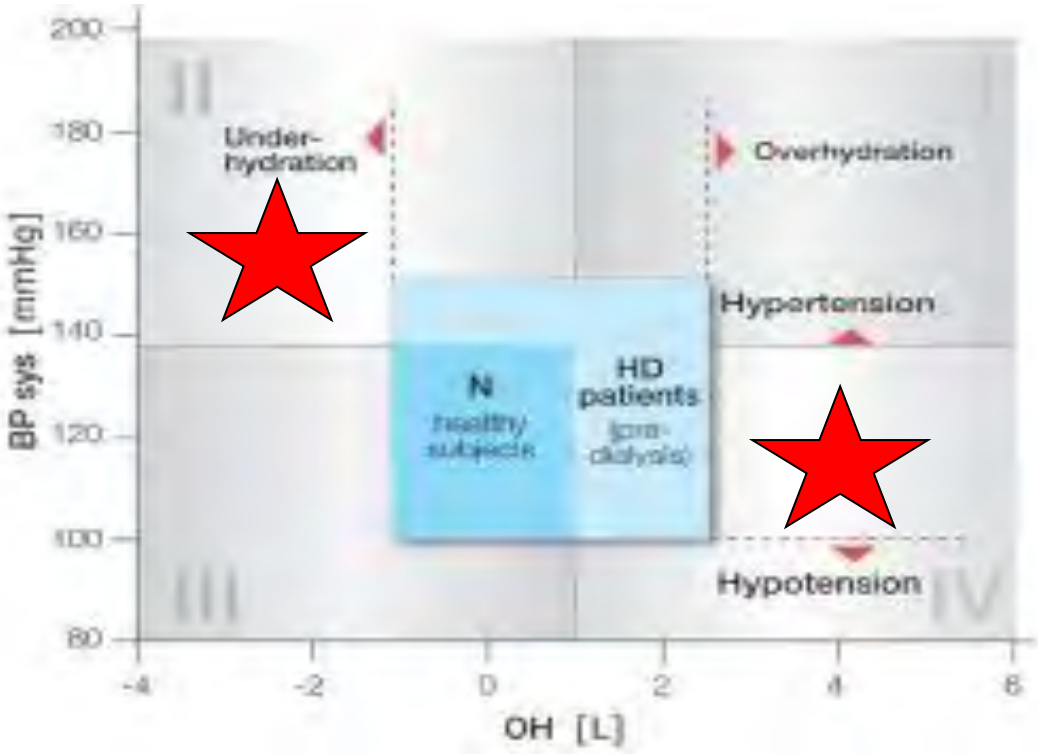


36 % : normo OH

35% overhydrated (>7%), but only 40% of them with high BP

The relation BP versus hydration in children on chronic hemodialysis : « far from clear »: *to probing dry weight we need to add sodium balance*

Blood Pressure versus hydration in patients on dialysis : « box plot », importance of the BCM evaluation



Volume dependent high BP (natural relation) needs an UF prescription in mL (water and/or water and sodium)

Volume non dependent BP vascular reactivity ?, complex situation: needs more than a «weight loss/water» prescription, importance of sodium balance, nutrition, non osmotic sodium (Tietze)…

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BP management in dialysed children : *the vicious cercle*

- Elevated BP is mostly correlated by the doctors as “overweight”. Therefore, the usual prescription adaptation is more UF: *“a water prescription”*.
- Being hypertensive, children on dialysis received antihypertensive drugs. Therefore, *the achievement a the fixed dry weight is at hypotensive risk*, balanced by increased sodium dialysate, and/or stopped UF.
- *“High” sodium dialysate concentration (NaD>Napl)* (post dialytic thirst) and/or stopped UF are factors of too elevated interdialytic weight gain, inducing a high BP

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High efficiency HDF : reconsider the dialysis fluids composition, at least Na_D

- Need for adapted Na_D in case of high convective volume
- Ca balance ? Bicarbonate concentration ?
- Thermic control (cooling)

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HDF and Na_D (sodium in dialysate)

- The substitution fluids (convective volume/dose) have the same sodium concentration as the dialysate (Na_D): « on-line »
- Napl : the diffusible sodium
- Na_D versus Napl, BCM®, BVM® , on line « Na diffusable »
- In predilution Na_D 134 – 138 mmol/L
- In postdilution Na_D 138 – 142 mmol/L

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UF rate< 1.25%/h BW (floating dry weight) IDWG<4% ? Euvolemia ? Cooling T_D=36°

M Fischbach et al Pediatr Nephrol 2015

How to achieve BP control:

Euvolemia, **no overhydration *but also* no underhydration**: importance of body composition assessment (BCM, *bioimpedance*)

Only probing a lowered dry weight could be risky, and in nearly 40% of the hypertensive patients is ineffective : importance of the sodium balance (sodium diet control; dialysis sodium removal: UF and ***NaD*** to Napl gradient)

Retrict the UF demand to 1.25% BW loss per hour, apply “cooling” technollogy (T_D=36°) to preserve from cardiac and cerebral ischemia (Chris W. McIntyre)

Limit the IDWG<4%: ***more sessions***

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UF rate< 1.25%/h BW (floating dry weight) IDWG<4% ? Euvolemia ? Cooling T_D=36°

M Fischbach et al Pediatr Nephrol 2015

- Huang SH, Filler G, Lindsay R, McIntyre CW (2014) Euvolemia in hemodialysis patients: a potentially dangerous goal? Semin Dial doi: 10.1111/sdi 12317
- Flyth JF, Brunelli SM (2011) The risk of high ultrafiltration rate in chronic hemodialysis : implications for patient care. Semin Dial; 24:259-265
- Paglialonga F, Consola S, Galli, MA, Testa S, Edefonti A (2015). Interdialytic weight gain in oligo anuric children and adolescents on chronic haemodialysis. Pediatr Nephrol 2015
- Movilli E, Gaggia P. Zubani R, Camerini C, Vizzardi V, Parrinello G, Savoldi S, Fischer MS, Londrino F, Cancarini G (2007) Association between high ultrafiltration rates and mortality in uraemic patients on regular haemodialysis. A 5-year prospective observational multicentre study. Nephrol Dial Transplant; 22:3547-3552

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Association between high ultrafiltration rates and mortality in uraemic patients on regular haemodialysis. A 5-year prospective observational multicentre study

E. Movilli et al. NDT 2007; 22:3547-3552

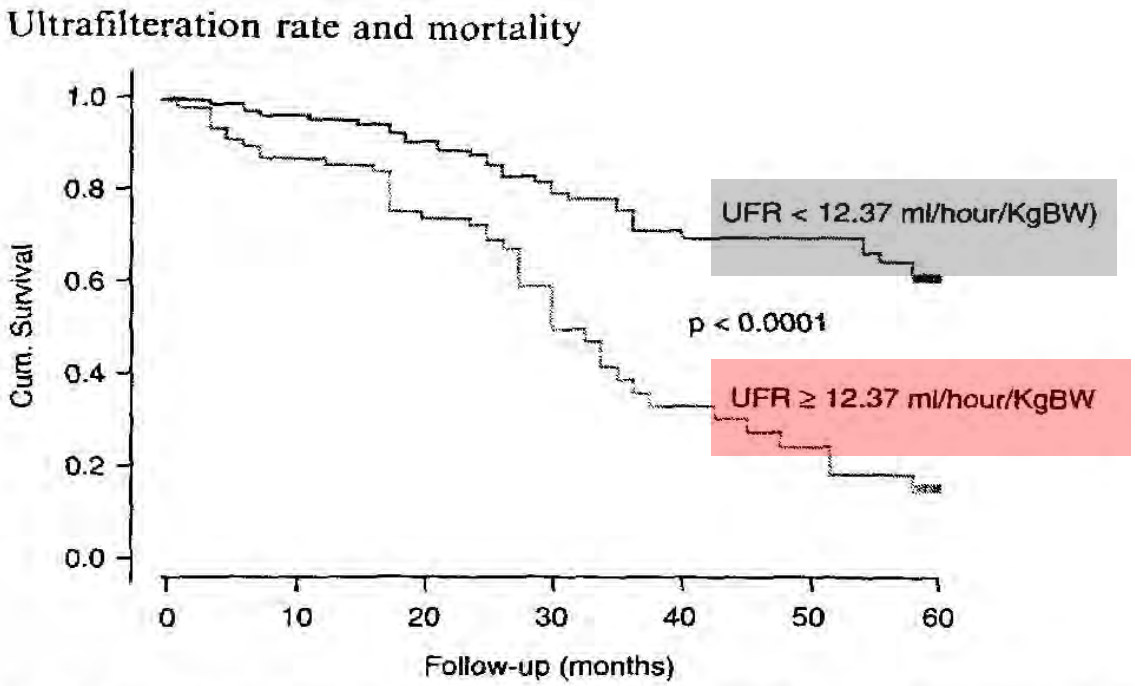
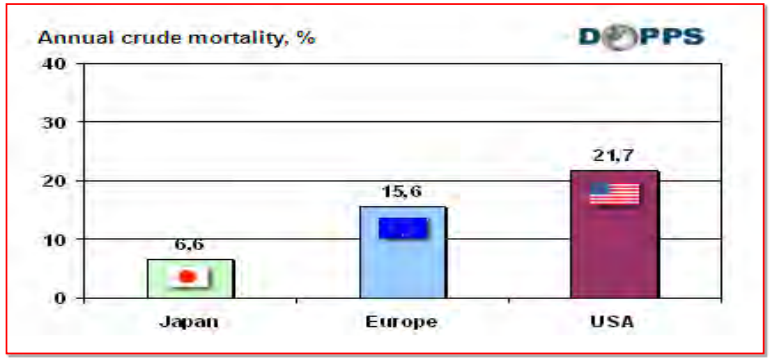


Fig. 3. Survival curves adjusted for significant predictors at Cox regression analysis by using UFR as categorical variable defined according to the receiver operating characteristic (ROC) derived UFR threshold of 12.37 ml/h/kg BW.

Mortality increased

- From 65% to less than 20% survival at 5 years
  if BW loss per hour
  (UF rate) was over
  12mL/H/kgBW
- Importance of dialysis time
- Reduction in UF demands per session

- Replacement fluid that is generated on-line from the dialysate must be ‘ultra-pure’ as discussed above. The microbiological purity (bacterial count and endotoxin level) should be determined regularly at 1-3 monthly intervals.



Masakane Ikuto ASN 2008:
mortality risk and dialysis fluids purity

1) taux d’endotoxines dans le dialysat standard < 0,05 UI/ml dans 93,6 % des centres de dialyse japonais

2) risque de mortalité corrélé au taux d’endotoxines dans le dialysat : RR 1 si < 0.001 ET/ml versus RR 1.48 si 0.1 à 0.25 ET/ml

Endotoxin level: not detectable
CHU Strasbourg 2014

Dialysat :	N° analyse	Résultats	Niveau d’alerte*	Niveau d’action*
Flore aérobie revivifiable à 22°C	E 6813	< 1 UFC/100ml	< 5 UFC/100ml	< 10 UFC/100ml
Endotoxines bactériennes	E 6815	< 0,005 UI/ml	< 0.015 UI/ml	< 0.03 UI/ml

Solution de Substitution :	N°analyse	Résultats	Niveau d’alerte*	Niveau d’action*
Flore aérobie revivifiable à 22°C	E 6814	< 1 UFC/500ml	< 1 UFC/500ml	< 1 UFC/500ml
Endotoxines bactériennes	E 6816	< 0,005 UI/ml	< 0.015 UI/ml	< 0.03 UI/ml

* d’après la norme internationale ISO 23500:2011

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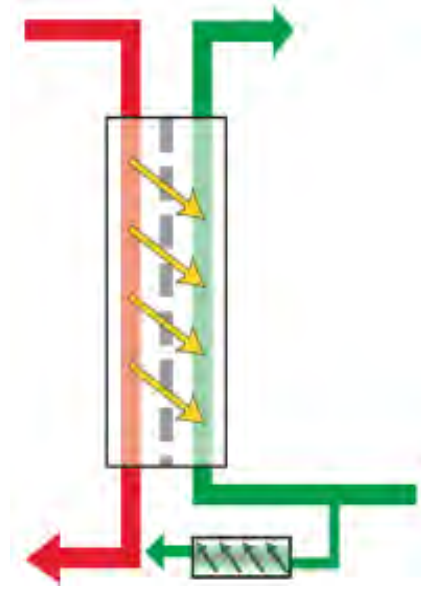
Hemodiafiltration on line : purity

- Substitution fluid for HDF has traditionally been produced by autoclaving bags containing a solution made from sterile water and salts : cost of these bags is a limiting factor for conventional HDF prescription , especially in a predilution modallity
- On line substitution fluid could be obtained *by cold sterilization that is ultrafiltrated ultrapure dialysate*



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The effect of on-line hemodiafiltration on improving the cardiovascular function parameters in children on regular dialysis

FI Fadel et al., Saudi J Kidney Dis Transplant 2015; 26(1):39-46

Converting from HD to OL-HDF predilution, there was:

✓***a significant decrease in hs-CRP (from 7.9±8.9 to 3.4±3 µg/mL) (P=0.01)***

✓a significant decrease in frequency of diastolic dysfunction (*P*=0.04), while ***systolic function (FS and EF) improved significantly (P=0.007 and 0.05, respectively),***

✓but LVMI and MBPI pre or post dialysis did not change

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HDF: a complete dialysis dose

- On-line Urea Kt/V > 1.4 (V « Morgenstern or BCM)
- High convective volume (autosub+) but also of « quality » (impact of the membrane) :
  - beta-2-microglobulin extraction coefficient >80%
  - myoglobin>65%
- « loss » in the dialysate and convective volume (check for albumin, Vit C)
- Dialysis fluids : temperature control (« cooling »; BTM), NaD (on-line diffusive sodium), Ca++, HCO_3^-
- Volume control (BCM), BP, IDWG…

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Impact of high convective volume high efficiency hemodiafiltration

Study name	Threshold volume for suvival benefit (observational studies)
DOPPS (Canaud) 2006	> 15 L
Riscarid (Panichi) 2008	> 23 L
Contrast (Grooteman) 2012	> 21.95 L
Purkush (Ok) 2012	> 17.4 L
ESHOL (Madrid) 2013	> 23.1 L
Children: convective volume, post dilution	? 3 L/m²/h or 12- 15L/m²/session
or predilution (easier to achieve?)	? 18-27 L/m²/session

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http://www.kidney-international.org clinical investigation
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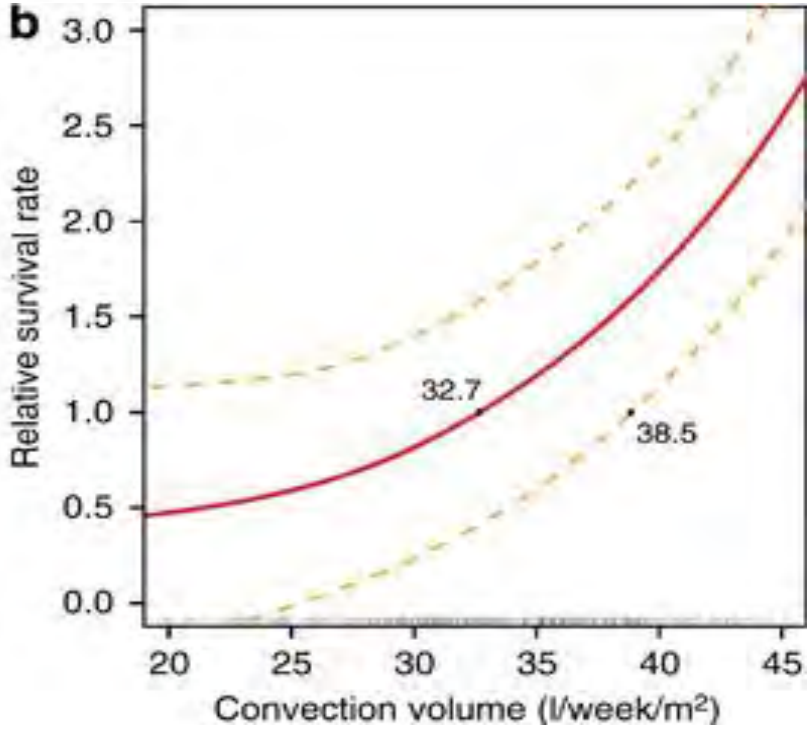
OPEN

Optimal convection volume for improving patient outcomes in an international incident dialysis cohort treated with online hemodiafiltration

Bernard Canaud[1,2], Carlo Barbieri[2], Daniele Marcelli[2,3], Francesco Bellocchio[2], Sudhir Bowry[2], Flavio Mari[2], Claudia Amato[2] and Emanuele Gatti[2,3]

[1]Montpellier University I, UFR Medicine, Montpellier, France; [2]Fresenius Medical Care, Bad Homburg, Germany and [3]Danube University, Krems, Austria



Improvement becames significant: over 32.7 L/week/m2 BSA (56.8 L/week), and shows a linear increase until 45 L/week/m2 BSA (75 L/week = 25 L/session/3times per week)

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As a result, there is a growing interest in the delivery of more intensive hemodialysis, that is:

- ✓ OL-HDF (purity of the dialysis fluids),
- ✓ high efficient convective volume (hydraulic permeability; autosub+: viscosity control)
- ✓ titrating treatment length (4.5 hours ?; reduction in UF demands per dialysis session; UF rate< 1.25%/h BW; IDWG<4%; Cooling T_D=36° ; Euvolemia ?)
- ✓ daily “optimyzed” dialysis (floating dry weight; BCM®; diffusible Napl on-line; Kt/V on-line; BVM®; BTM®)

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Cardiovascular benefits of daily haemodialysis : peeling the onion

Chris W. McIntyre. Nephrol Dial Transplant 2014; 29:1-4

Extended dialysis (longer, more frequent) must be delivered (« adequately ») with a realistic reduction in circulatory stress that is : *a good quality dialysis*

- reduced exposure to endotoxins (*ultrapure dialysis fluids*)
- optimized volume control (not « simply a « weight loss », but also *a more efficient depuration of sodium*)
- reduction in UF demands per dialysis session (volume, rate), (interest of the concept of *« floating » dry weight*)
- « *cooling/thermic control* », cardiovascular preservation

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Daily on line hemodiafiltration : the perfect « stimulus package » to induce growth

F. Schaefer. Editorial comments. Nephrol Dial Transplant 2010; 25:658-660

- 35 % to 50 % of children with ESRD still grow up to became small adults with a final height below the third percentile of the general population
- Growth failure is a common end point of a variety of abnormalities associated with CKD :
  - Protein energy malnutrition due to anorexia and chronic inflammation (cachexia)
  - Metabolic acidosis via the UPS and direct suppression of endogenous GH secretion
  - Partial resistance to GH, multifactorial (somatomedin inhibitors ; accumulation of IGFBP ; decreased IFG1 response to GH and deficit of IGF1 action ; activation of the post GH receptor intracellular signalling : JAK2-STAT5; activation and upregulation of the S0CS family (inflammation+++)

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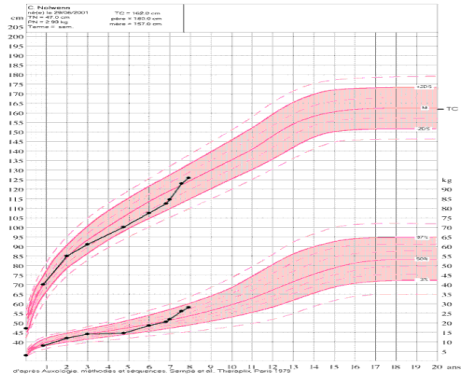
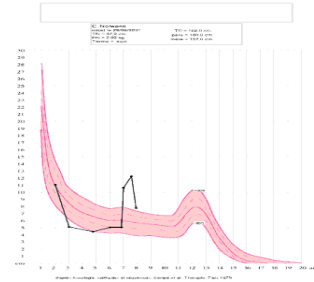
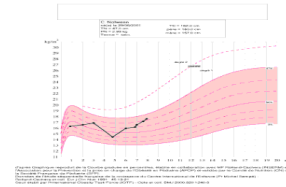
Daily on line HDF (high efficiency HDF) promotes catchup growth in children on chronic dialysis

FISCHBACH M, TERZIC J, MENOUER S, DHEU C, SEUGE L, ZALOSCZIC A.

Nephrol Dial Transplant 2010; 25: 867-73







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Patients

- **15 children in the « growth »study : sept 2004 to sept 2007**
- **mean age : 7 years 4 months (2 y 10 m to 16 y 8 m)**
- 7/17 converted from at home chronic peritoneal dialysis to in center daily on-line hemodiafiltration ; 5/12 from hemodiafiltration (3 times weekly; 3 x 4/5hours)
- GFR was less than 3 mL/min/1.73 m² at study entry
- Vascular access was a fistula (n=13) or a catheter (n=4)
- End point of DIH was kidney transplantation

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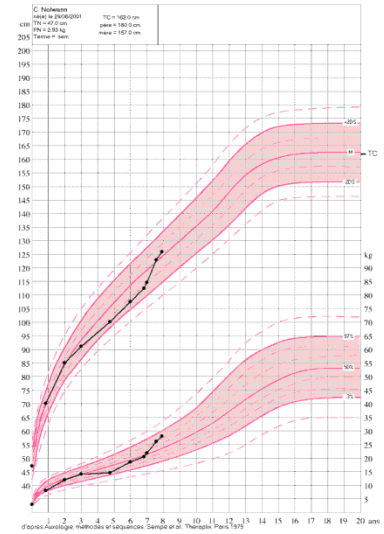
Results

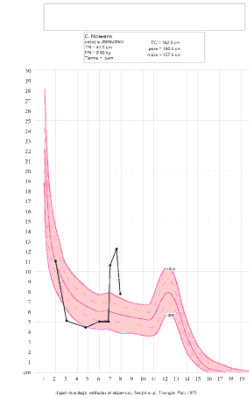
- Mean time on daily OL-HDF (untill KTP): 20.5+/-8 months
- **Growth velocity:**

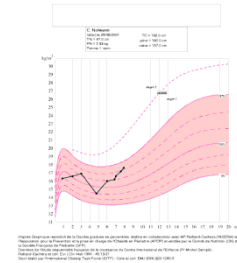
  the year before daily: 3.8+/-1.1 cm/y

  first year of daily: 14.3+/-3.8 cm/y

  mean over daily: 8.9+/-2.2 cm/y







- Height (SDS)

  start: -1.5+/-0.3

  end: +0.2+/1.1

  target parental height: -0.3

  end- target: +0.5

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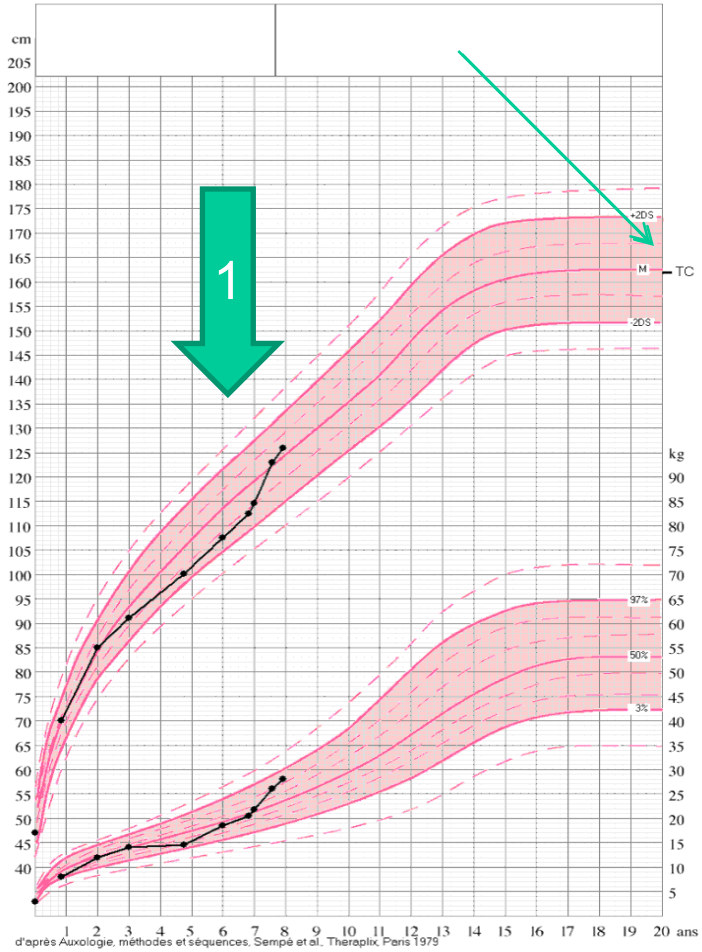
Patient 1 on daily OL-HDF

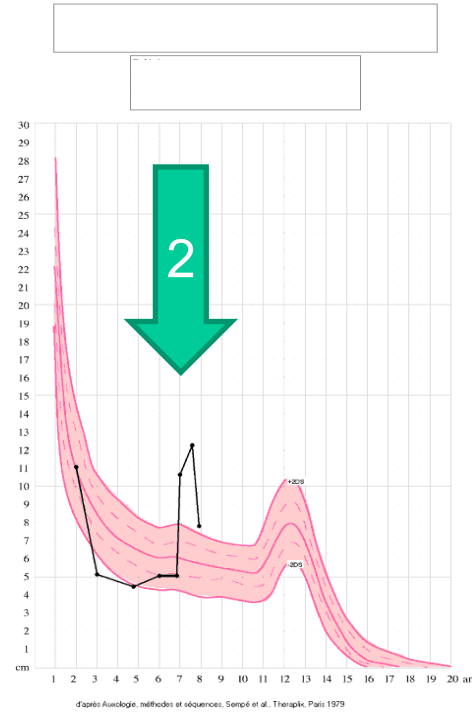
PDI (g/kg/d) : 2.7 ± 0.2

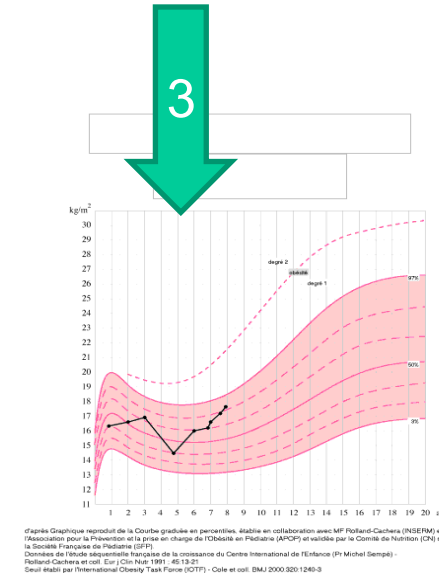
nPNA (g/kg/d) : 1.44 ± 0.15

Mean growth velocity (cm/year) : 10.4

Achieved height versus familial expected height (SDS) : +0.2







1 growth in SD 2 growth velocity 3 BMI

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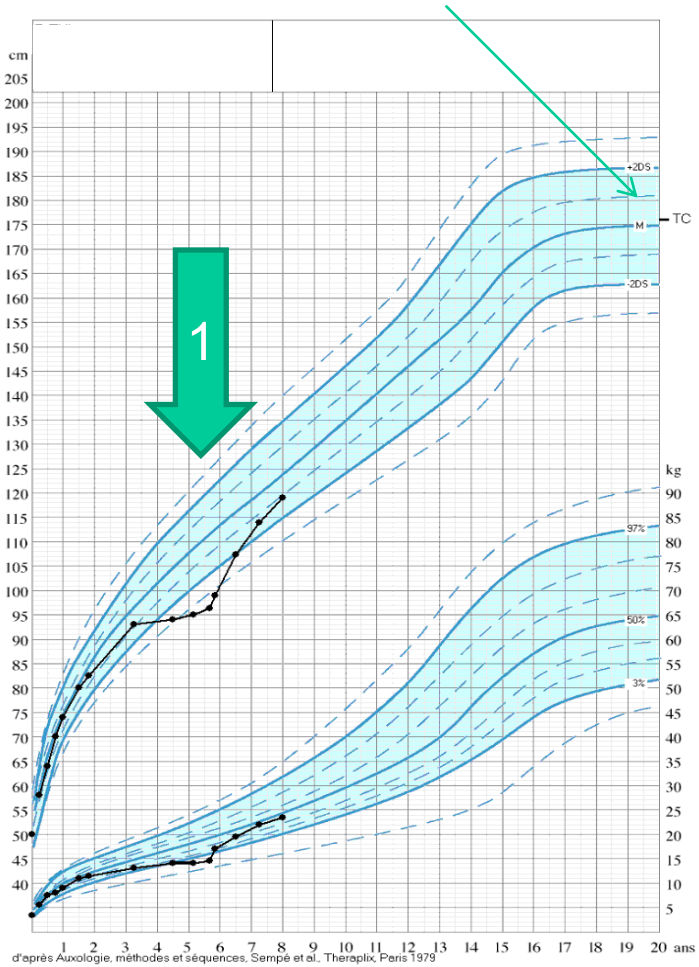
Patient 2 on daily OL-HDF

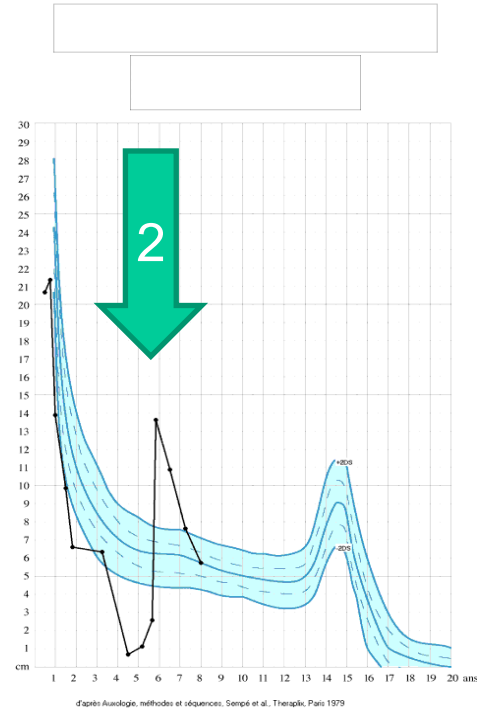
PDI (g/kg/d) : 2.9 ± 0.3

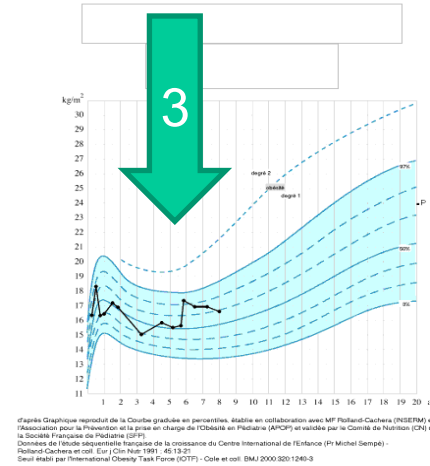
nPNA (g/kg/d) : 1.31 ± 0.11

Mean growth velocity (cm/year) : 8.1

Achieved height versus familial expected height (SDS) : -1.3

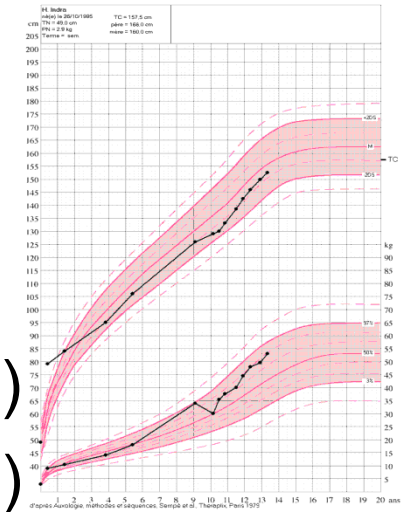


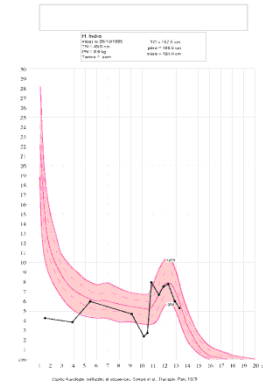


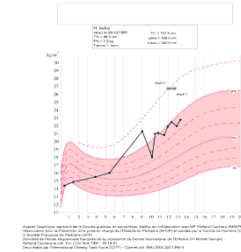


1 growth in SD 2 growth velocity 3 BMI

Results







- BMI kg/m^2 (%)

  start of daily 16.5±2.0 (48±24)

  end of daily 18.0±2.4 (65±26)

- Diet protein intake, mean 2.5+/-0.2 (g/kg/d)
- nPNA, mean 1.35+/-0.12 (g/kg/d)
- CRP in 13/15, <4mg/L but in two cases (chronic bronchitis, ciliopathy) 47 and 32mg/L
- β_2 microglobuline (predialysis) 15.3±3.3 mg/L
- TAD urea 2.4+/- 0.5; TAD bicar 0.65+/-0.13

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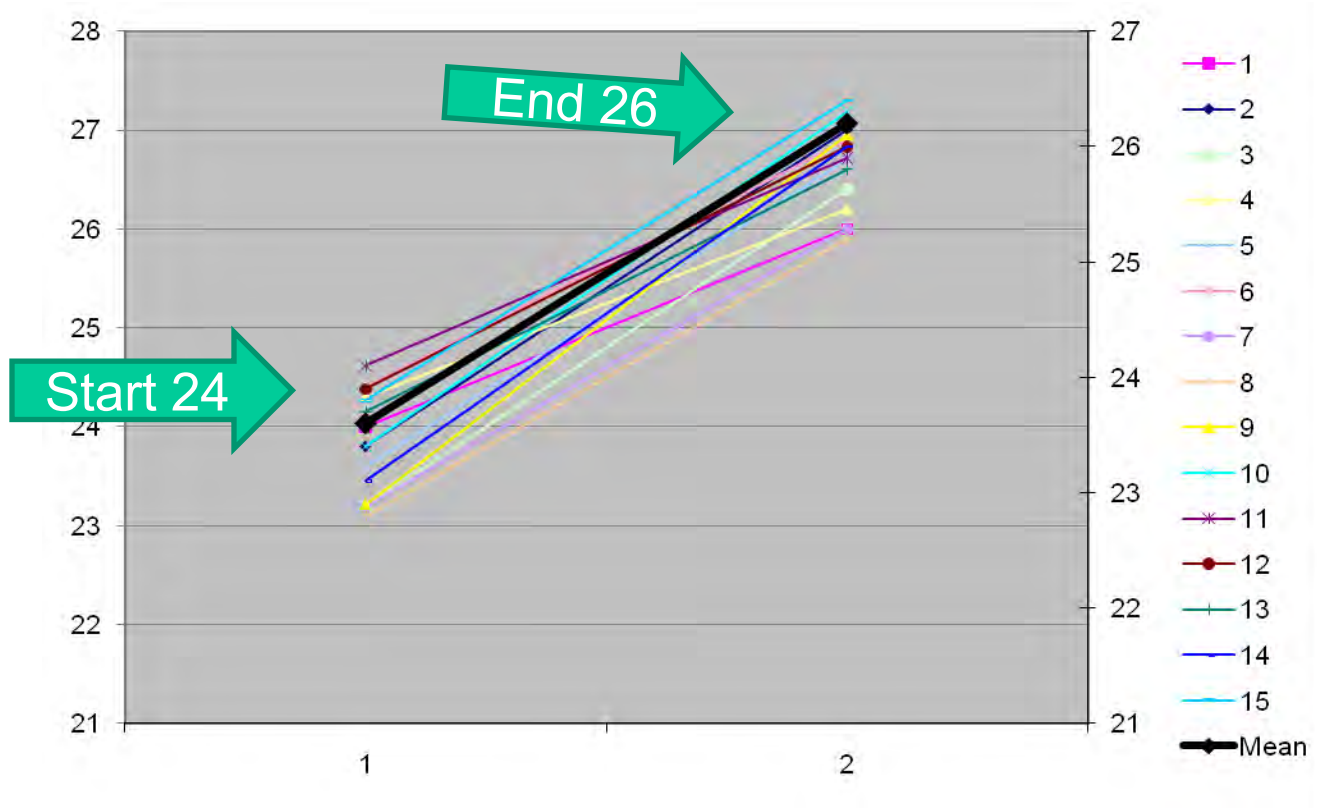
Bicarbonatemia, measured pre post dialysis , mean of monthly determinations over the patient follow up on D-OL-HDF

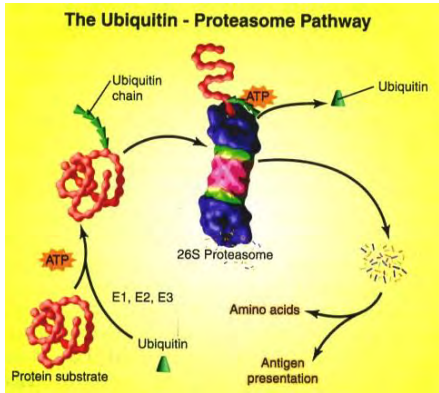
TAD bicar 0.65+/-0.13

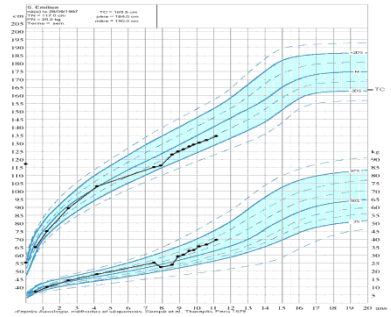


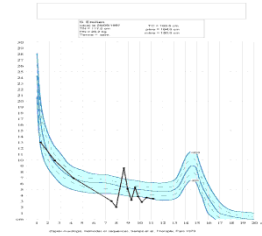
Reduced « acidosis / alcalosis dialytic » waves

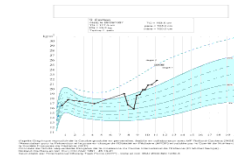
This anabolic impact of daily HDF, intensified dialysis, (*large convective volume, high efficiency HDF*) is presumed to be secondary to a « stimulus package » :

- *better cardiovascular control (BP, LVH)*
- *less acidosis, less inflammation*
- *improved nutririon : less malnutrition, less cachexia*
- *improved uremic toxins detoxification ($\beta_2$microglobuline)*
- *improved physical activity, less sleep disturbances*









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As a result, there is a growing interest in the delivery of more intensive hemodialysis, that is:

- ✓ OL-HDF (purity of the dialysis fluids),
- ✓ high efficient convective volume (hydraulic permeability; autosub+: viscosity control)
- ✓ titrating treatment length (4.5 hours ?; reduction in UF demands per dialysis session; UF rate< 1.25%/h BW; IDWG<4%; Cooling T_D=36° ; Euvolemia ?)
- ✓ daily “optimyzed” dialysis (floating dry weight; BCM®; diffusible Napl on-line; Kt/V on-line; BVM®; BTM®)

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Daily on line hemodiafiltration: the optimal dialysis package

- Daily dialysis : dialysis time, from CKD5 to CKD3
- On line hemodiafiltration :
  - Highly permeable membrane (molecular permeability, water permeability)
    - » Convective flow
    - » Ultrapure dialysate
  - From « cachexia » to catch up growth : less inflammation, no acidosis, optimal purification, appetite/nutrition, less sleep disturbances, more physical activity, less rhGH resistance

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Until the 1980's, HD was only prescribed as twice weekly dialysis sessions lasting 4 to 6 hours at one time: often poorly tolerated, only offering "survival", without quality of life

This led to changes in the dialysis regime over the 1990's: twice weekly sessions were replaced by procedures performed three times a week.

Nevertheless, despite decades of experience and technical improvements in performing three times a week in-center HD (3x4.5 hours), patients/children treated by this conventional dialysis regime still have:

- ✓an increased risk of cardiovascular morbidity/mortality (Ph; inflamation/CrP),
- ✓bad volume control (overhydration; high BP; LVH) and
- ✓malnutrition due to protein wasting, impaired growth

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How much « GFR » is delivered by conventional dialysis ?

- HD, three times a week, highly permeable membranes, session of 4,5 hours: 12 to 15 mL/min GFR equivalency
- PD, APD, day dwell and day exchange: 8 to 10 mL/min GFR equivalency
- « normal kidneys » GFR> 90mL/min

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Daily on line hemodiafiltration : the perfect « stimulus package » to induce growth.

F. Schaefer. Nephrol Dial Transplant 2010; 25:658-660

- 35 % to 50 % of children with ESRD still grow up to became small adults with a final height below the third percentile of the general population
- Growth failure is a common end point of a variety of abnormalities associated with CKD :
  - Protein energy malnutrition due to anorexia and chronic inflammation (cachexia)
  - Metabolic acidosis via the UPS and direct suppression of endogenous GH secretion
  - Partial resistance to GH, multifactorial (somatomedin inhibitors ; accumulation of IGFBP ; decreased IFG1 response to GH and deficit of IGF1 action ; activation of the post GH receptor intracellular signalling : JAK2-STAT5; activation and upregulation of the S0CS family (inflammation+++)

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HDF: extracorporeal blood circulation, vascular access,lines, filter

- Vascular access: fistula (double/single puncture), central line
- Blood flow: 150mL/min/m^2 ; dialysate flow $Q_D \geq 1$ to1.5 Q_B
- Kurea (osmotic syndrom risk/initially): 3-5 mL/min/kg BW
- Anticoagulation: low molecular weight heparin
- Lines and filter volume: 10-15 mL/kg BW
- Filter (molecular and water permeabilities): square meter theory, urea clearance>blood flow,beta-2- microglobulin extraction (>80%),water permeability (Cuf;PTM), dialysate loss (albumine)

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HDF practical prescription, why and how to do

- dialysis fluids, purity, composition (Na_D; T_D)
- extracorporeal blood circulation, vascular access, lines, filter (hydraulic and molecular permeabilities)
- a complete dialysis dose (ureaKt/V and a determined convective volume)
- volume control, dry weight (BCM®; on-line plasma diffusive sodium)

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HDF : dialysis fluids, purity, composition

- Water, dialysate (ultrapure HD), substitution fluid (convective flow/volume; HF)
- Purity, germ free, endotoxin free (bacteria/fungus) ?
- Daily sterilization (heating process), choarcal filtration (0.2 µ), double reverse osmosis
- Control of quality (cost)
- Dialysis fluids (dialysate and substitution fluid) composition, impact of the total convective volume per session (NaD, Ca++,HCO3-) and temperature

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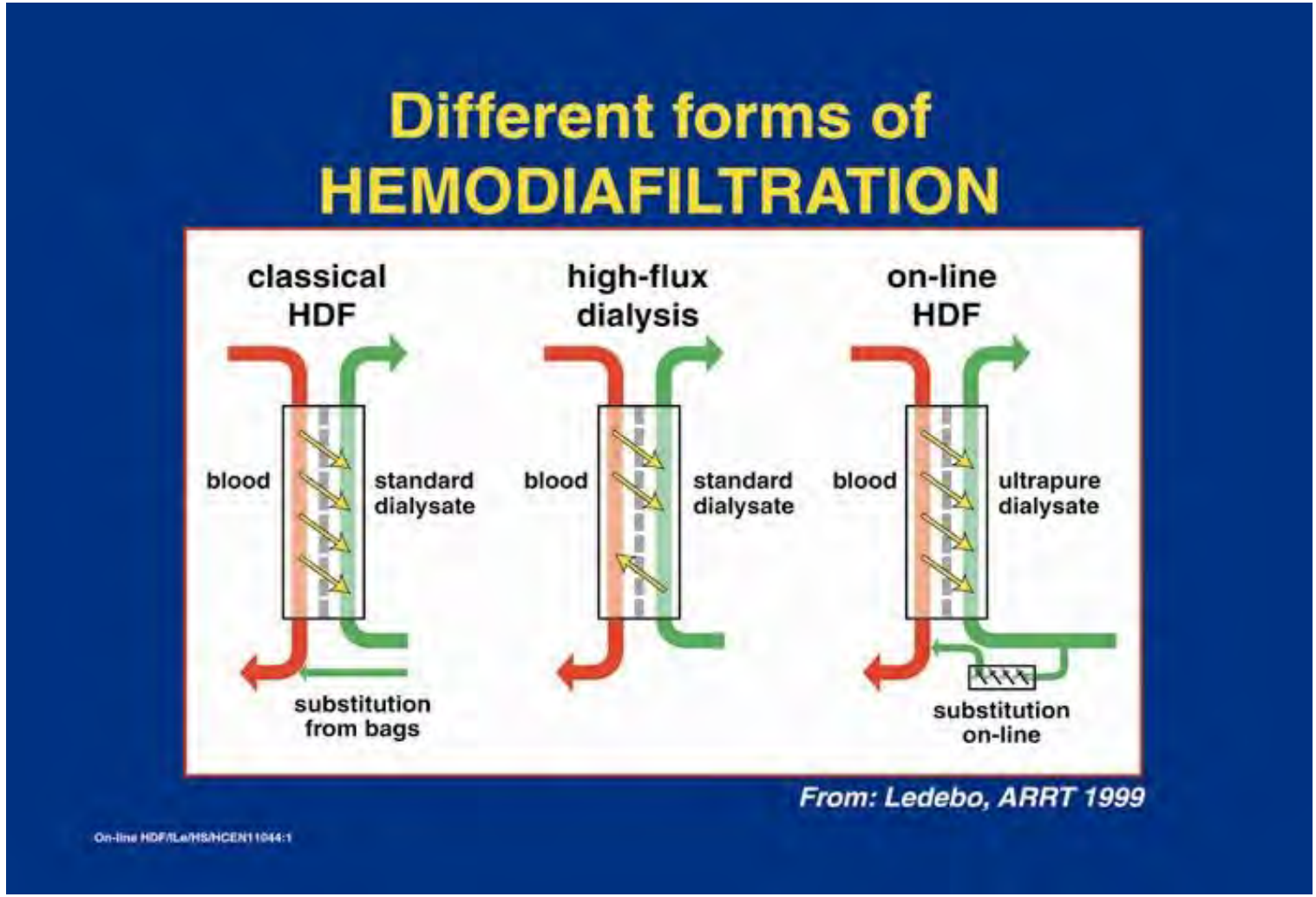
Different forms of HDF: internal HDF, classical HDF (with bags), on-line HDF



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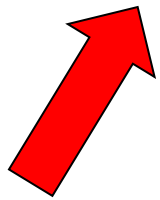
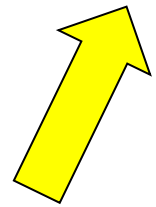
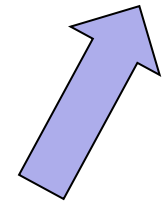
*On line HDF, a determined dose of convective flow
*Highflux HD = internal, ” uncontrolled” HDF, i.e.low efficiency HDF, at risks/dialysate quality ?

	on-line HDF	high-flux HD
membrane	high-flux, synthetic	high-flux, synthetic
dialysis fluid quality	ultrapure	ultrapure
Diffusive process	determined by QB, QD, K0A	determined by QB, QD, K0A
Convective flow	measurable, determined by operator	not possible to measure or to control; internal filtration determined by KUF, delta P
Dialysis fluid quality (substitution fluid)	sterile, non-pyrogenic	dialysate backfiltered through dialyzer membrane







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Effect of ultrapure dialysate on markers of inflammation, oxidative stress, nutrition and anemia parameters: a meta-analysis

Susantitaphong P, Riella C, Jaber BL. NDT 2013; 28:438-446

Conclusions:

Use of ultrapure dialysate in HD patients results in a decrease in markers of inflammation (CRP -3,2mg/L), an increase in serum albumine (+0.11 g/dL) and hemoglobin (+0.40 g/dL) and a decrease in the weekly erythropoietin dose (-273 units/week)

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The effect of on-line hemodiafiltration on improving the cardiovascular function parameters in children on regular dialysis

FI Fadel et al., Saudi J Kidney Dis Transplant 2015; 26(1):39-46

Converting from HD to OL-HDF predilution, there was:

✓*a significant decrease in hs-CRP (from 7.9±8.9 to 3.4±3 µg/mL) (P=0.01)*

✓a significant decrease in frequency of diastolic dysfunction (*P*=0.04), while systolic function (FS and EF) improved significantly (*P*=0.007 and 0.05, respectively),

✓but LVMI and MBPI pre or post dialysis did not change

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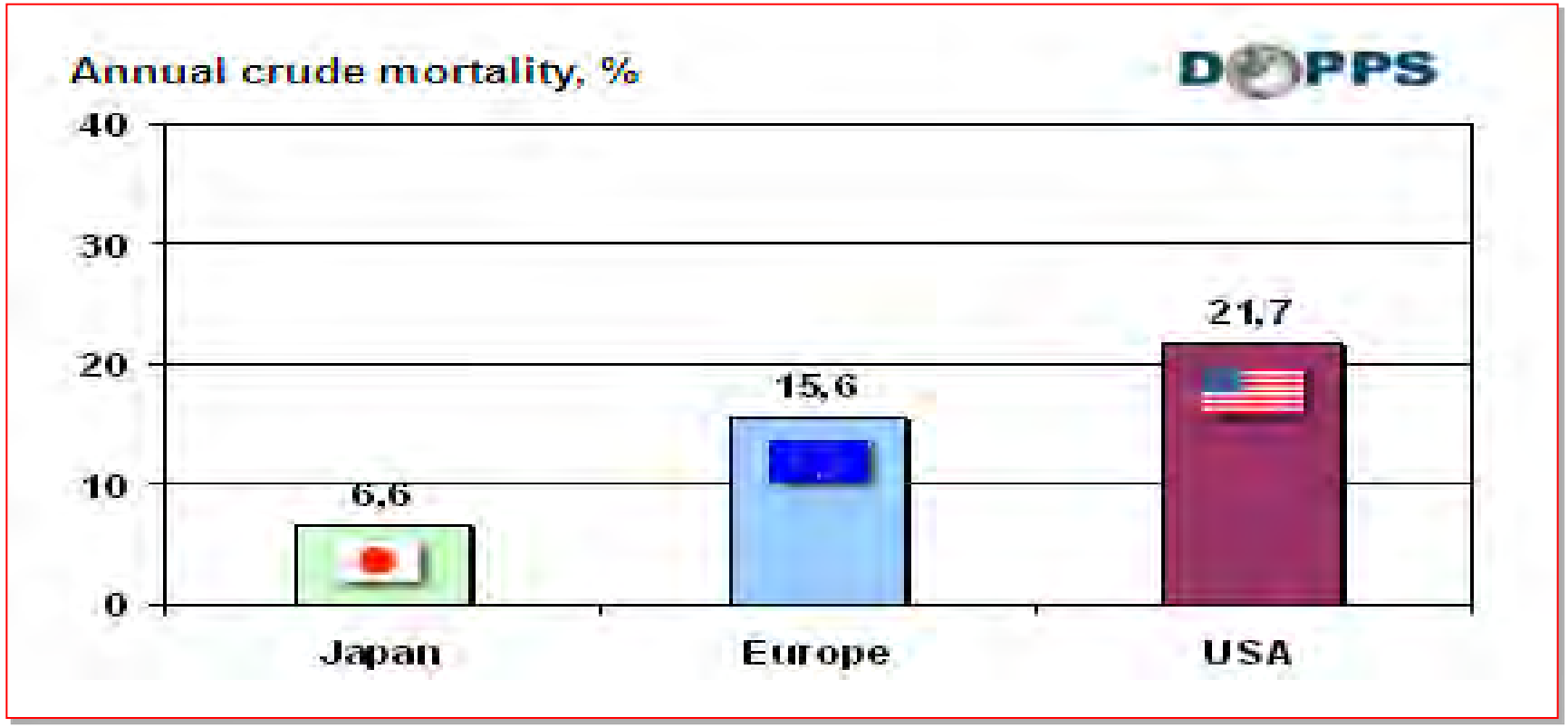

Masakane Ikuto ASN 2008: mortality risk and dialysis fluids purity

1) taux d'endotoxines dans le dialysat standard < 0,05 UI/ml dans 93,6 % des centres de dialyse japonais

2) risque de mortalité corrélé au taux d'endotoxines dans le dialysat : RR 1 si < 0.001 ET/ml versus RR 1.48 si 0.1 à 0.25 ET/ml

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Recommandations pour un dialysat « standard »

	Endotoxines
FRANCE	< 0,25 UI / ml
ISO 23500	< 0,5 UI / ml
JAPON	< 0,05 UI / ml

Recommandations pour un dialysat « ultrapur »

	Endotoxines
FRANCE (2007)	< 0,25 UI / ml
ISO 23500	< 0,03 UI / ml
JAPON	< 0,001 UI / ml

Recommandations pour un liquide de substitution

	Endotoxines
France (2007)	< 0,05 UI / ml
ISO 23500	< 0,03 UI / ml
JAPON	< 0,001 UI / ml

A.Ragon, P.Brunet, D.Jaubert, G.Lebrun, A.Duval-Sabatier
Pôle Urologie – NéphrologieAssistance Publique – Hôpitaux de Marseille. Décembre 2012

Endotoxin level: not detectable
CHU Strasbourg 2014

Dialysat :	N° analyse	Résultats	Niveau d'alerte*	Niveau d'action*
Flore aérobie revivifiable à 22°C	E 6813	< 1 UFC/100ml	< 5 UFC/100ml	< 10 UFC/100ml
Endotoxines bactériennes	E 6815	< 0,005 UI/ml	< 0.015 UI/ml	< 0.03 UI/ml

Solution de Substitution :	N°analyse	Résultats	Niveau d'alerte*	Niveau d'action*
Flore aérobie revivifiable à 22°C	E 6814	< 1 UFC/500ml	< 1 UFC/500ml	< 1 UFC/500ml
Endotoxines bactériennes	E 6816	< 0,005 UI/ml	< 0.015 UI/ml	< 0.03 UI/ml

* d'après la norme internationale ISO 23500:2011

Dialysis water and fluid purity : more than endotoxin

Glorieux G et Al. Nephrol Dial Transplant 2012; 27 (11) 4010-21

- Necessity for ultrapure dialysis fluid (back filtration and back diffusion processess) and for sterile non pyrogenic substitution fluid
- Chronic exposure of HD patients to low level of cytokine-inducing microbial components can significantly contribute to the microinflammatory status of these patients

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β2 microglobulin removal with HDF (what is purity of the dialysate ?)

*M.Fischbach Nephron **1989**; 53:110-4*

- HDF > HF > HD in terms of β2 microglobulin dialytic removal
- Highly permeable membrane optimal use: HDF (limited retrofiltration)
- Despite enhanced removal of β2 microglobulin during conventional HDF, no decrease over time of the β2 microglobulin serum level in children: retrofiltration of conventional dialysate (endotoxins / inflammation / β2microglobulin enhanced production) ? : need for dialysis fluids purity, not only germs but also endotoxins (from conventional HDF, bags and « normal » dialysate to OL-HDF)

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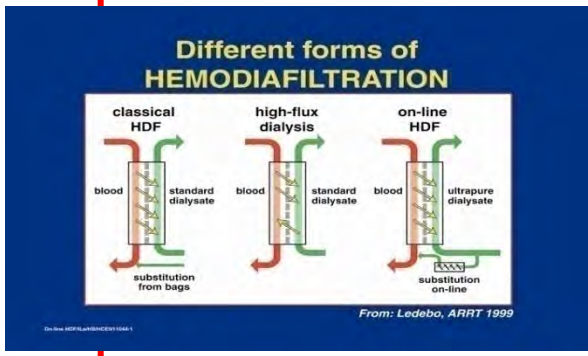
Nephron 1989;53:110–114

Beta-2-Microglobulin in Hemodiafiltered Children: Long-Term Efficiency Follow-Up

M. Fischbach[a], *G. Hamel*[b], *C. Koehl*[c], *J. Geisert*[a]

[a] Service de Pédiatrie 3 – Néphrologie – Dialyse – Transplantation, Hôpital de Hautepierre,
[b] Laboratoire de Biochimie (Pr. J. Mark), Hôpital de Hautepierre et
[c] Laboratoire d'Analyses, Institut de Chimie biologique (Pr. J. Vincendon), Strasbourg, France



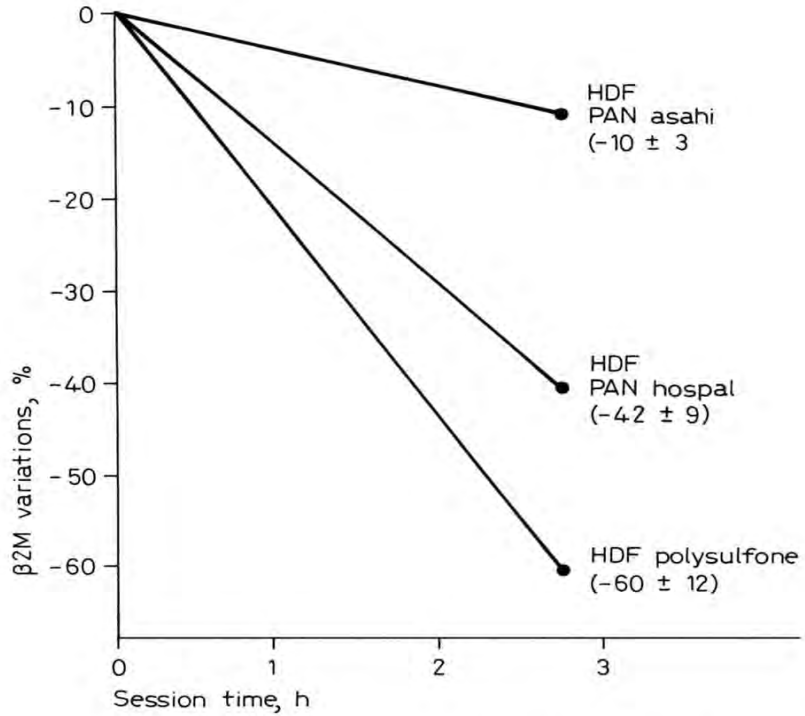


Fig. 1. β_2M serum level variations in HDF with different membranes (mean = SEM, n = 30 sessions).

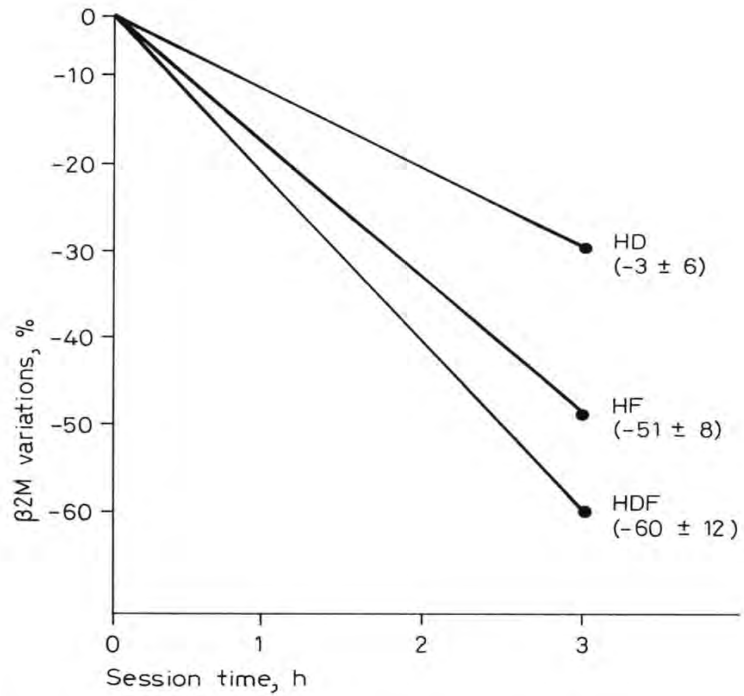


Fig. 2. β_2M Serum level variations with a polysulfone membrane versus condition of dialysis managment: HF, HD or HDF (mean ± SEM; n = 30 sessions).

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Nephron 1989;53:110–114

Beta-2-Microglobulin in Hemodiafiltered Children: Long-Term Efficiency Follow-Up

M. Fischbach[a], *G. Hamel*[b], *C. Koehl*[c], *J. Geisert*[a]

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[c] Laboratoire d'Analyses, Institut de Chimie biologique (Pr. J. Vincendon), Strasbourg, France

Table 2. β_2M serum levels with the same polysulfone membrane in HD, HF or HDF (n = 30 sessions), versus pooled dialysate and/or filtrate extraction (mean ± SE)

	Pooled dialysate and/or filtrate			Serum, mg/l	
	volume l	β_2M		pre	post
		mg/l	mg		
HF	9 ± 0.6	3.4 ± 0.5	30.6 ± 6	39 ± 4	27 ± 6
HD	91.5 ± 0.6	0.5 ± 0.15	45 ± 3	39 ± 6	21 ± 4
HDF	98.7 ± 1.3	0.8 ± 0.2	75 ± 4	38 ± 7	15 ± 4

Table 4. HDF treatment in the 5 children described in table 3

	HDF PAN 150	HDF polysulfone
Treatment	3 × 3 h/week 1.5 years	3 × 3 h/week 3.5 years
β_2M sieving coefficient	0.015 ± 0.001	0.504 ± 0.029
β_2M removal per HDF session, mg	3 ± 0.5	75 ± 4

β_2M sieving coefficient from ref. 8.

Table 3. Evolution of β_2M serum levels in 5 anuric children under HDF treatment

	Jan 83	Jan 84	Jan 85	Jan 86	Jan 87	Jan 88
Mean weight, kg	22 ± 1	23 ± 1.3	24 ± 0.8	25 ± 1.4	26.5 ± 1.5	27.4 ± 1.2
β_2M serum mg/l	35 ± 7.5	42 ± 8	39 ± 4.8	42 ± 6.3	39.6 ± 4.5	41.3 ± 8.2

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« Practical » conditions for On-Line fluid preparation

Condition	Practical solution
Ultrapure water	Ultrafiltration of water for dialysis (Eur Ph/AAMI)
High quality concentrate	On-line prepared bicarbonate from powder cartridge
Hygienic flow path	Specially designed on-line machine, eg, no dead ends
Effective disinfection	Prophylactic disinfection to prevent formation of biofilm during tandstill
Effective ultrafiltration	Validated ultafilters with defined lifetime single use in most critical position
Microbiological awareness	Education

no machine movements

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High convective volume : need for a change of the dialysate composition (Na_D) ?

- Since 1981,we perform HDF in children, mainly pre dilution (EPO ; blood flow 80-200 ml/min)
- For many years, our standard Na_D was between 140 and 144 mmol/L, even with daily HDF (since 2002)
- In the last years (2012), we changed our amount of substitution flow rate due to the new softwares (Autosub and Autosub +)

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High convective volume : need for a change of the dialysate composition (Na_D) ?

At bedside, we learned the need to decrease the Na_D of the substitution fluid applying Autosub+.

We believe on the need to redefine dialysate/substitution fluid composition in case of high convective volume prescription.

Almost all children on high convective volume need of lowered Na_D, between 134 and 138 mmol/L.

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High efficiency OL-HDF : (re)consider the Na_D

Ali, 3 years old, congenital nephrotic syndrom, anuric, 14 kg BW, 0.75 m² BSA, central catheter :

On pre dilution HDF, 4008

- Blood flow 80 ml/min,
- Substitution flow 80 ml/min
- Na_D 140 mmol/L
- BP 95/47 mmHg
- CorDiax 60 (large surface area of the membrane, to achieve pre dilution flow and hope for enhanced phophate removal

Converted on HDF 5008 Autosub +

- Blood flow 80 ml/min,
- Pre dilution flow 280-300 mL/min
- Na_D 140 mmol/L
- CorDiax 60
- After 4 weeks, volume overloaded with high blood pressure 145/95 mmHg, after decreasing Na_D to 134 mmol/L : normalization of BP (95/45)

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High efficiency HDF : reconsider the dialysis fluids composition, at least Na_D

- Need for adapted Na_D in case of high convective volume
- Ca balance ? Bicarbonate concentration ?
- Thermic control (cooling)

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HDF and Na_D (sodium in dialysate)

- The substitution fluids (convective volume/dose) have the same sodium concentration as the dialysate (Na_D): « on-line »
- Napl : the diffusible sodium
- Na_D versus Napl, BCM®, BVM® , on line « Na diffusable »
- In predilution Na_D 134 – 138 mmol/L
- In postdilution Na_D 138 – 142 mmol/L

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HDF: extracorporeal blood circulation, vascular access,lines, filter

- Vascular access: fistula (double/single puncture), central line
- Blood flow: 150mL/min/m^2 ; dialysate flow $Q_D \geq 1$ to1.5 Q_B
- Kurea (osmotic syndrom risk/initially): 3-5 mL/min/kg BW
- Anticoagulation: low molecular weight heparin
- Lines and filter volume: 10-15 mL/kg BW
- Filter (molecular and water permeabilities): square meter theory, urea clearance>blood flow,beta-2- microglobulin extraction (>80%),water permeability (Cuf;PTM), dialysate loss (albumine)

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The International Journal Of Pediatric Nephrology / Vol. 5 no. 3, 1984 / p.p. 151-154

Hemodiafiltration versus hemodialysis in children

M. Fischbach, Y. Attal, J. Geisert

Service de Nephrologie et d'Hemodialyse
Service de Pediatrie 3
Hopital de Hautepierre
Strasbourg, France

HDF with bags « lactate »

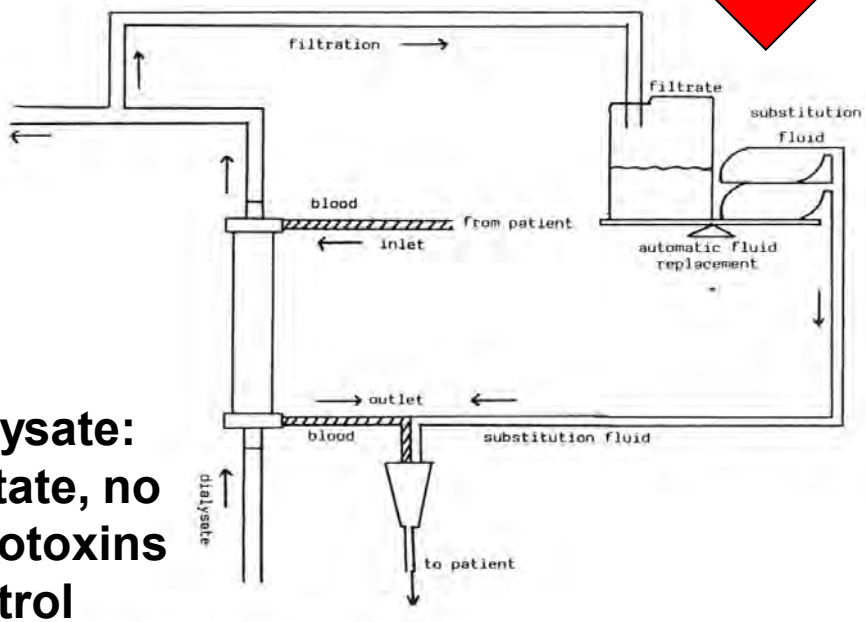

Fig. 1 Hemodiafiltration schema.

Dialysate: acetate, no endotoxins control

TABLE I - PARAMETERS USED FOR THE STUDY

HD (12 months)	HDF (12 months)
plate (0.92 m2) cuprophane Q_B 120-160 ml/min Q_D 500 ml/min 3 X 5 h/week	capillary (1 m2) PAN Q_B 120-160 ml/min Q_D 500 ml/min 3 X 3 h/week substitution fluid 7-9 (lactate) TMP less than 300 mmHg

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Strasbourg, France

Increased « osmotic » tolerance

TABLE I - PARAMETERS USED FOR THE STUDY

HD (12 months)	HDF (12 months)
plate (0.92 m2) cuprophane	capillary (1 m2) PAN
Q_B 120-160 ml/min	Q_B 120-160 ml/min
Q_D 500 ml/min	Q_D 500 ml/min
3 X 5 h/week	3 X 3 h/week
	substitution fluid 7-9 (lactate)
	TMP less than 300 mmHg

TABLE IV - RELATIONSHIP BETWEEN UREA, CREATININE CLEARANCE IN HD (K_{HD}) AND IN HDF (K_{HDF})

	Urea		Creatinine
	ml/min	ml/min/kg body weight	ml/min
K_{HD}	90 ± 2	4.3	93 ± 10
K_{HDF}	131 ± 9	6.3	115 ± 17

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HDF versus HD : advantages

- **Optimal blood purification capacities, both for urea and « middle molecular weight compounds » (Ph)** : high level dialysis dose easely achieved .
- A high dialysis dose usually induce a good nutrition status, especially with an increased caloric intake (apetite)
- Hemodynamic stability over the session : increased tolerance to weight loss and blood pression control improvement (hemofiltration effect) : osmotic stability, compartiment preservation, peripheral vascular resistances, myocardial contractility

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Hemodiafiltration with high permeable membranes in children

M Fischbach, G Hamel, E Tarral, J Geisert. Blood purification 1984; 2:203-206

	HD 15 h/week cuprophane 12 months	HDF 9 h/week PAN 12 months	HDF 9 h/week polysulfone 12 months
TAc urea mmoL/L	28±4	18±3	20±2
PCRn g/kg/j	0.7±0.2	1±0.1	1.8±0.3
Phosphate mmL/L	1.65±0.28	1.34±0.15	1.15±0.18
Aluminium prescription g/day	3	1.5	0.5
Hemoglobin g/dl	7.4	8.3	8.9
Need of transfusion per year	5	2	1
Date	1981	1982	1983

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Hemodiafiltration with high permeable membranes in children

M Fischbach, G Hamel, E Tarral, J Geisert. Blood purification 1984; 2:203-206

	HD 15 h/week cuprophane 12 months	HDF 9 h/week PAN 12 months	HDF 9 h/week polysulfone 12 months
TAc urea mmoL/L	28±4	18±3	20±2
PCRn g/kg/j	0.7±0.2	1±0.1	1.8±0.3
Phosphate mmL/L	1.65±0.28	1.34±0.15	1.15±0.18
Aluminium prescription g/day	3	1.5	0.5
Hemoglobin g/dl	7.4	8.3	8.9
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- A high dialysis dose usually induce a good nutrition status, especially with an increased caloric intake (apetite)

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HF and HDF predilution, reduce intradialytic hypotension in ESRD

F. Locatelli et al. J Am Soc Nephrol 2010; 21:1798-1807

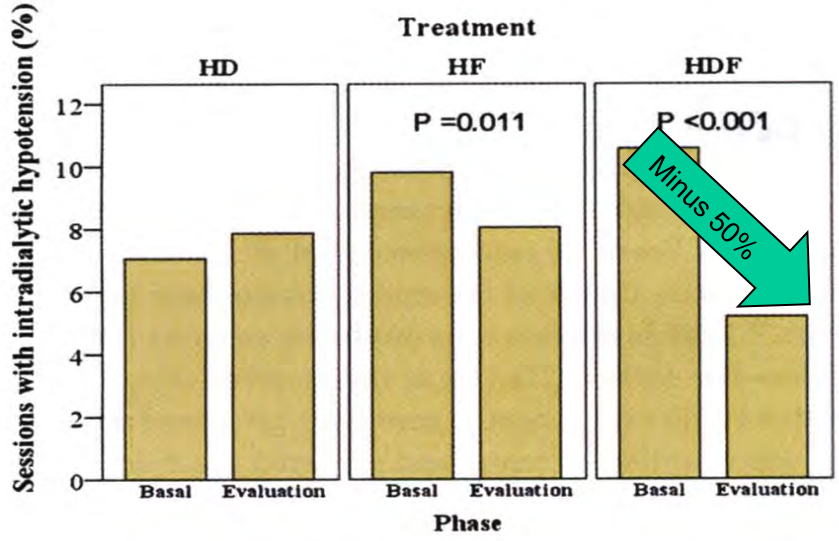

Figure 2. 7.5% of all of the 28,950 sessions were complicated by ISH. In the evaluation period compared with the basal run-in, there was a statistically significant decrease of sessions with ISH in HF (9.8 to 8.0%, decrease of 18.4%; $P = 0.011$) and in HDF (10.6 to 5.2%, decrease of 50.9%; $P < 0.001$) compared with low-flux HD group (7.1 to 7.9%, increase of 9.9%).

Intradialytic symptomatic hypotension occurrence was reduced in on line predilution HF and HDF

This lower frequency of ISH was associated in HDF, with a significant increase in predialysis SBP values (from 137.3 to 141.3 mmHg)

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HDF in children : optimized dialysis tolerance (UF and Kt/V per hour)

- Osmotic tolerance : less intradialytic symptoms, despite short sessions and increased urea clearance (Ku: mL/min/kg BW)
- Weight loss/UF per hour : tolerance increased, due to hemofiltration effect (cooling ? or more)
- BVM profile : often a « plateau » after a rapid decrease (extracorporeal filling); plateau significance: osmotic stability, UF rate = refilling rate

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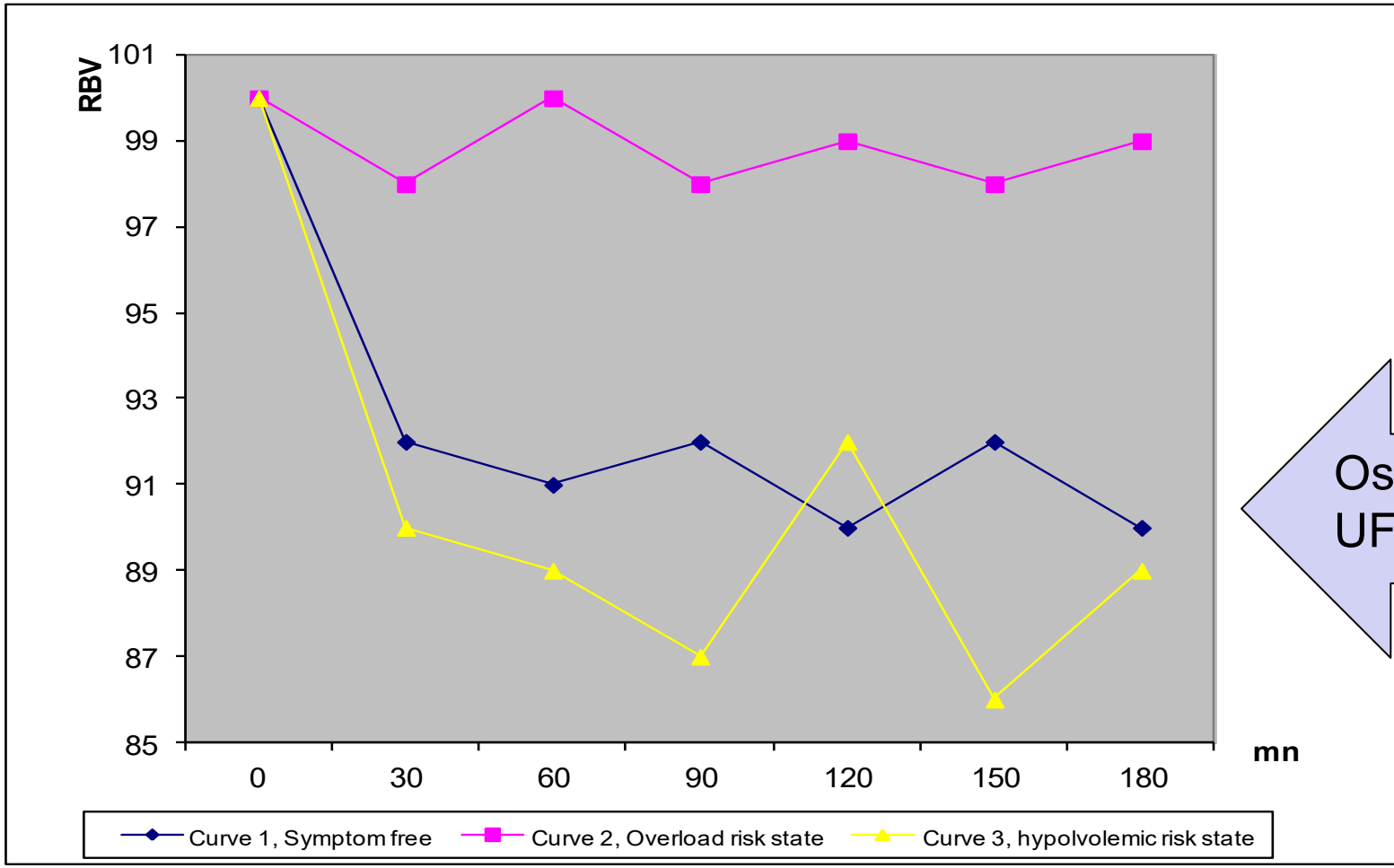
Schematic reconstructed curve shape from the original on screen recorded curves. Three major blood volume profiles could be described, i.e. curve shapes (C Dheu et al. Pediatr Nephrol 2009):



Osmotic stability,
UF= refilling rate

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Dialysis membranes: practical parameters

- Type of membrane : biocompatibility, hihg flux
- Initial blood volume need, ie area related, quality of restitution
- Molecular permeability : maximal clearance for urea and the other uremic toxins, ie phosphate and beta-2-microglobulin ; osmotic risk
- Hydraulic permeability : possibility of use for HF or HDF procedure ; back filtration risk
- « Loss » of substances in the dialysate (albumin)
- Cost

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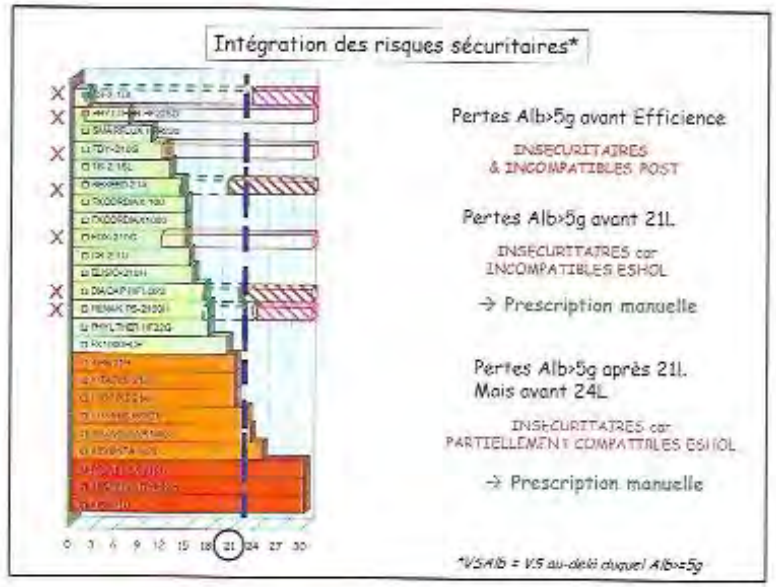

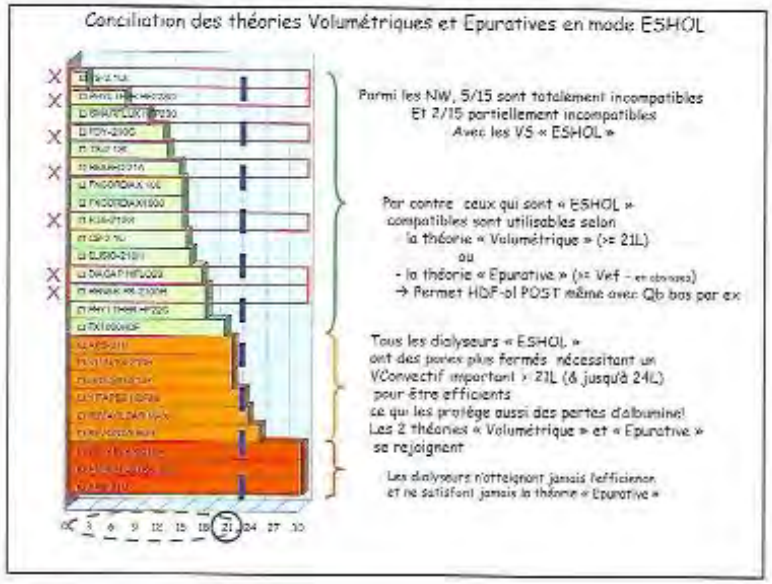

J Potier
Journées Experts HDF
FMC- Paris Novembre 2014

The “new wave” dialysis membranes have different capacities:

1) Ability to obtain a “ESHOL” (Maduell 2014) convective volume, > 21L

2) Molecular permeability, extraction coefficient of beta-2-microglobulin >80 % (alpha-1-microglobulin > 65%)

3) Loss of substrate in the dialysate, a function of the convective volume (albumin < 5 gr)

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Adequate HDF prescription: *importance of the membrane*

- Hydraulic permeability : high convective volume

  (> 25 L in postdilution; > 60L in predilution)

- Molecular permeability : extraction coefficient

  (phosphate and β_2 m 80 %)

- Loss of albumine (< 5 gr)

- Purity of the dialysis fluids (backfiltration/convective flow)

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Blood purification dialysis modalities : diffusion versus convection

Diffusive Process (hemodialysis)

Membrane area

Mass transport coefficient

Concentration gradient

Blood flow x extraction coefficient

$$K_{HD} = Q_B \times \frac{c_i - c_o}{c_i}$$

i, o : in outlet solute concentrations

Convective mass transport (hemofiltration)

Ultrafiltrate flow (Q_{UF})

Hydraulic permeability

Transmembrane pressure (TMP ; mmHg)

Sieving coefficient (S)* Molecular permeability

$$*S = \frac{2\,C_{UF}}{c_i + c_o}$$

C_{UF} : ultrafiltrate solute concentration

$K_{HF} = Q_{UF} \times S$ (postdilution)

$Q_{UF} < 1/3\ Q_B$ (in practice)

Simultaneous purification: diffusion process and convection mass transport i.e. hemodiafiltration

one minute of dialysis « is equal» to two minutes of purification, one of HD and another one of HF

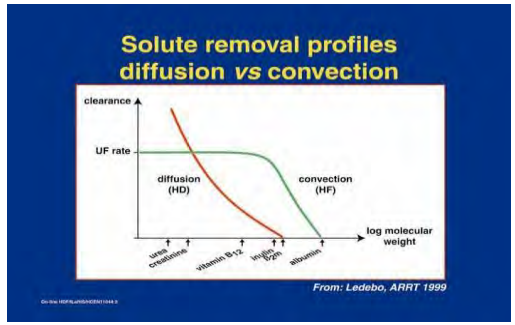
$$K_{HDF} = K_{HD} + x\ Q_{UF} \times 0.46$$

$$K_{HDF} = K_{HD}\ (1 - Q_{UF} \times S/Q_B) + K_{HF}\ \text{(Granger)}$$

with $Q_{UF} \times S = K_{HF}$ and $Q_B = K_{max}$

$$K_{HDF} = K_{HD} + K_{HF} - \frac{K_{HD} \times K_{HF}}{K_{max}}$$

If K_{HD} is equal to K_{max} then $Q_{HDF} = K_{HD}$



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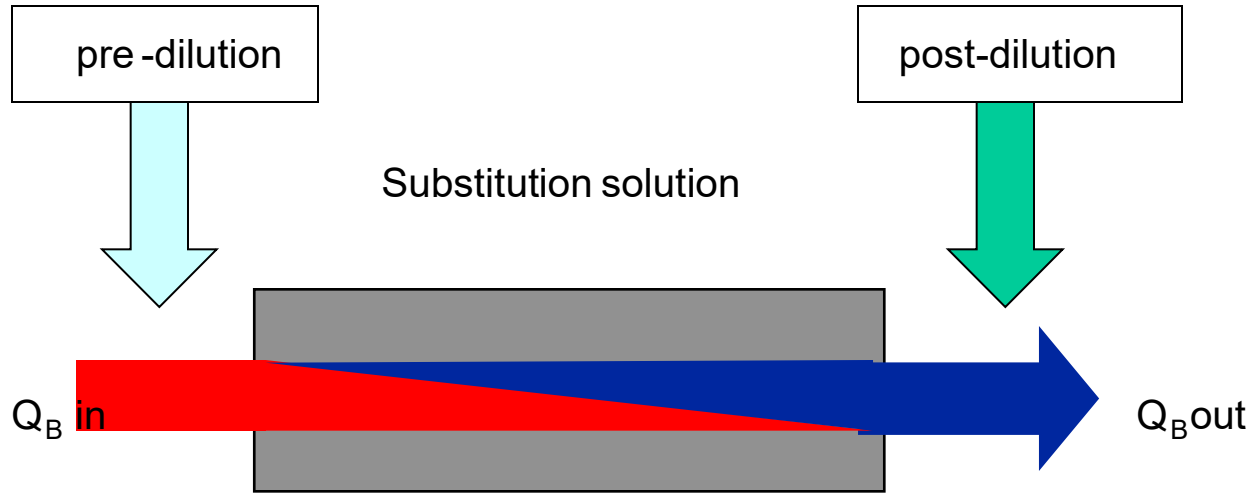
Hemodiafiltration : pre/post dilution

The convective transport requires ultrafiltration (UF) of fluid, i.e. the convective flow. If the convective flow exceeds the desired weight loss, the fluid balance is maintained by an infusion of replacement fluid, as applied in HF.



In HDF addition of substitution solution can be made before the filter called *predilution* mode, after the filter, *postdilution* mode, or mixed

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HDF: a complete dialysis dose

- On-line Urea Kt/V > 1.3 (V « Morgenstern or BCM)
- Beta-2-microglobulin extraction coefficient >80%; high convective volume (autosub+)
- « loss » in the dialysate and convective volume (check for albumin)
- Dialysis fluids : temperature control (« cooling »; BTM), NaD (on-line diffusive sodium), Ca++, HCO_3^-
- Volume control (BCM), BP, IDWG…

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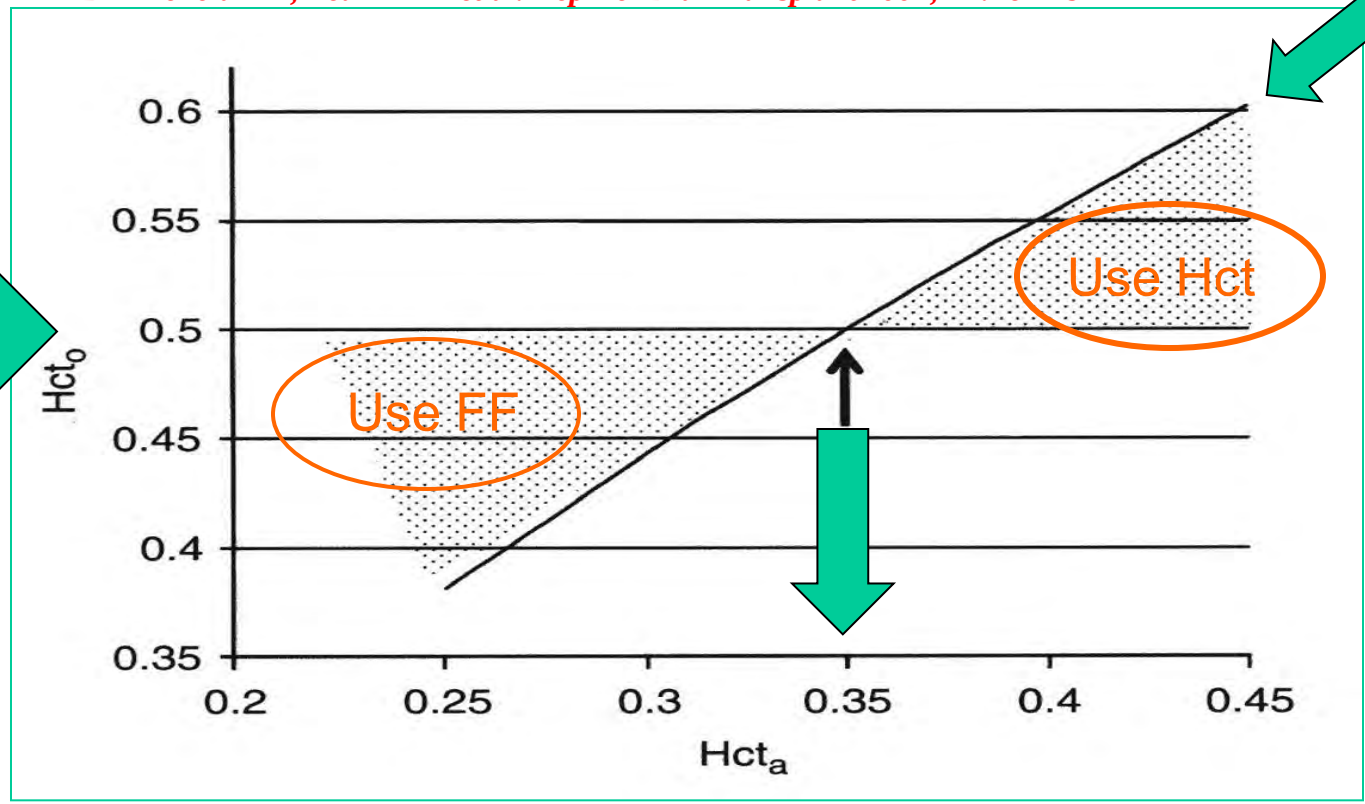
New strategies in HDF *Feliciani A, Pedrini AL et al. Nephrol Dial Transplant 2007; 22:1672-9*



Hct_{outlet} at which fractional filtration of plasma water is 0.50 for any level of Hct_a. This relationship is independent of Qb_a

For an Hct_a less than 0.35, Hct_0 « could allow » a higher FF (untill 0.50) resulting in membrane fouling (high protein concentration)

For an Hct_a a higher than 0.35, a FF of 0.5 results in an Hct_0 over 0.5 ; not safe, use Hct_{outlet}

Conclusions : the safest use for Q_{UF} should be based on :

- $Hct_{0outlet} \leq 0.5$ if $Hct_a > 0.35$
- FF < 0.5 if $Hct_a < 0.35$

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Choice of modality with the use of High-Performance Membrane and evaluation for clinical effects

Ikuo Masakane. Saito A, Kawanishita H, Yamashita AC, Mineshima M (eds):High-Performance Membrane Dialyzers. In Contrib Nephrol. Basel, Karger; 2011, vol 173, pp 84-94.

- The golden target for dialysis therapy should be to guarantee longer survival and to give a higher quality of life without dialysis-related complications.
- Generally, we choose a dialysis modality for better solute removal and better biocompatibility. In this issue we would like to propose that the patients preference for dialysis therapy is a useful parameter in prescribing the dialysis modality.
- *In our recent experience chronic dialysis patients have had preferences on a dialysis modality and membrane, and* ***pre dilution online HDF.***

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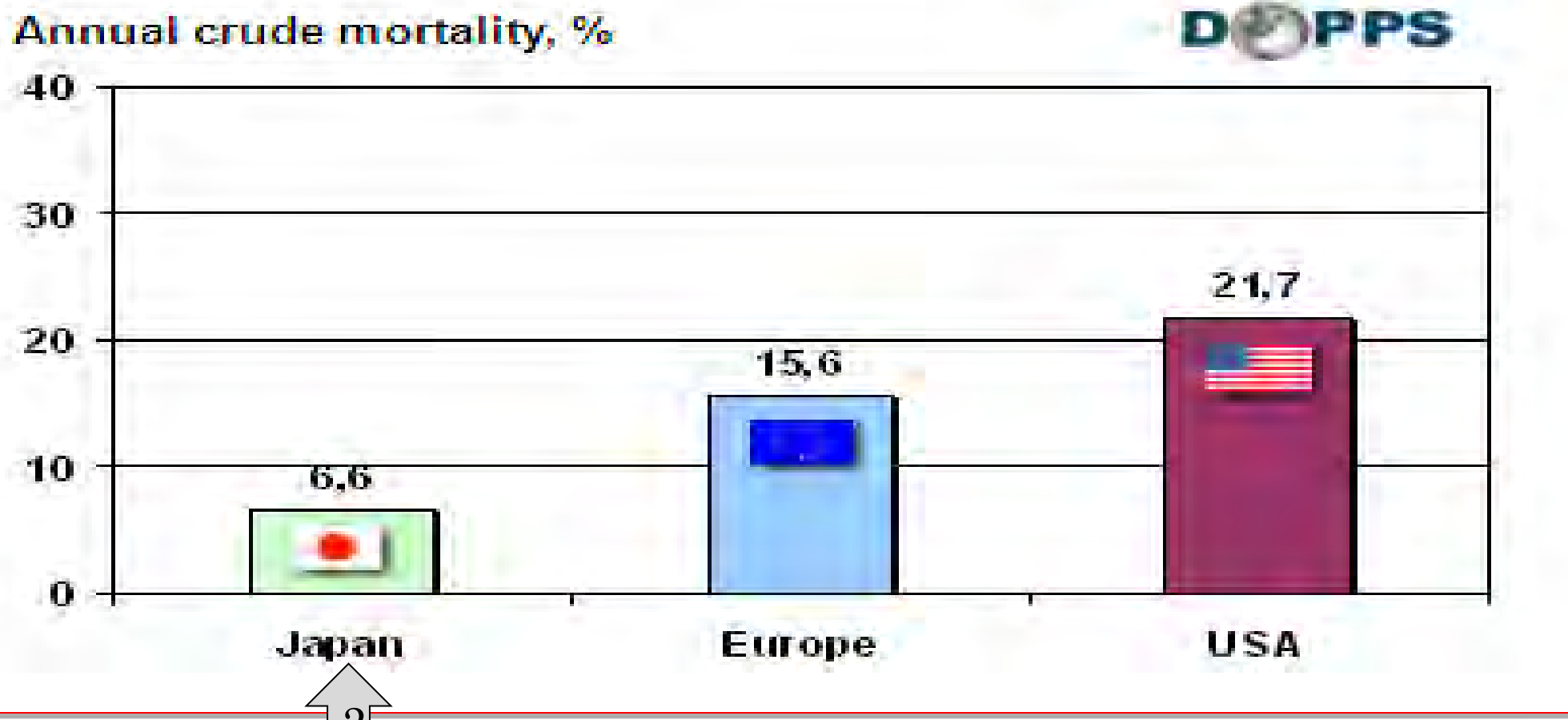

mortality risk:

dialysis fluids purity ?

HDF predilution ?

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Adequate HDF prescription: *importance of the membrane*

- Hydraulic permeability : high convective volume

  (> 25 L in postdilution; > 60L in predilution)

- Molecular permeability : extraction coefficient

  (phosphate and β_2 m 80 %)

- Loss of albumine (< 5 gr)

- Purity of the dialysis fluids (backfiltration/convective flow)

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On-line HDF: *a combination of solute removal, « purification » and dialysis fluids purity*

Maduell F. Hemodialysis International 2005 ; 9:47-55

HDF and blood purification impacts

- Nutrition, uremic toxins and anorexia (leptin)
- Anemia, improved erythropoietin response
- Cardiovascular disease, AGE removal
- Infectious complications, complement factor D removal
- Joint pain, dialysis related amyloidosis

HDF and ultrapure dialysis fluid impacts

- Amyloidosis
- Anemia
- Nutrition
- Joint pain, dialysis related amyloidosis

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Hemodiafiltration in children 1981-2002

- Reduced intradialytic symptoms (tolerance to weight loss, hemodynamic stability, rapid osmotic clearance tolerance)
- Lowered TAC_{urea} (Ku ml/min/kg increased)
- Phosphate managment improved, less phosphate chelators
- Transfusions rate decreased, anemia control

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HDF : volume control, dry weight

- Clinically and cinical team experience
- Blood pressure assessment (accuracy) and hydration evaluation (BCM)
- On-lin relative plasma volume change (hematocrite on-line): plasma refilling rate versus ultrafiltration rate (sodium blood to dialysate diffusive gradient; Na_D, T_D, Kurea)
- Interdialytic weight gain
- UF rate per hour

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Dialysis adequacy today, a European perspective : morbidity,mortalty,cardiovascular outcome, nutrition,

Locatelli F, Canaud B. Nephrol Dial Transplant 2012; 27:3043-8

1) One should consider, as a new standard in HD, that the minimal treatment time of 270 min (4.5 h, depending on the patient's weight or V) be delivered and an UF rate of no >10 ml/h/kg applied for patients treated as a thrice weekly schedule (Movelli E et al. NDT 2007)
2) Highly permeable membranes for « all »
3) Assessing and correcting underlying chronic inflammation: purity of the dialysis fluids, the Japanese experience (Endotoxin <0.001 U/ml)
4) The volume of substitution, a surrogate of the convective dialysis dose, should be considered as a critical factor for patient survival.
5) Technological improvement will never replace neither the expertise of caregivers or individualized care.

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Association between high ultrafiltration rates and mortality in uraemic patients on regular haemodialysis. A 5-year prospective observational multicentre study

E. Movilli et al. NDT 2007; 22:3547-3552

Ultrafilteration rate and mortality

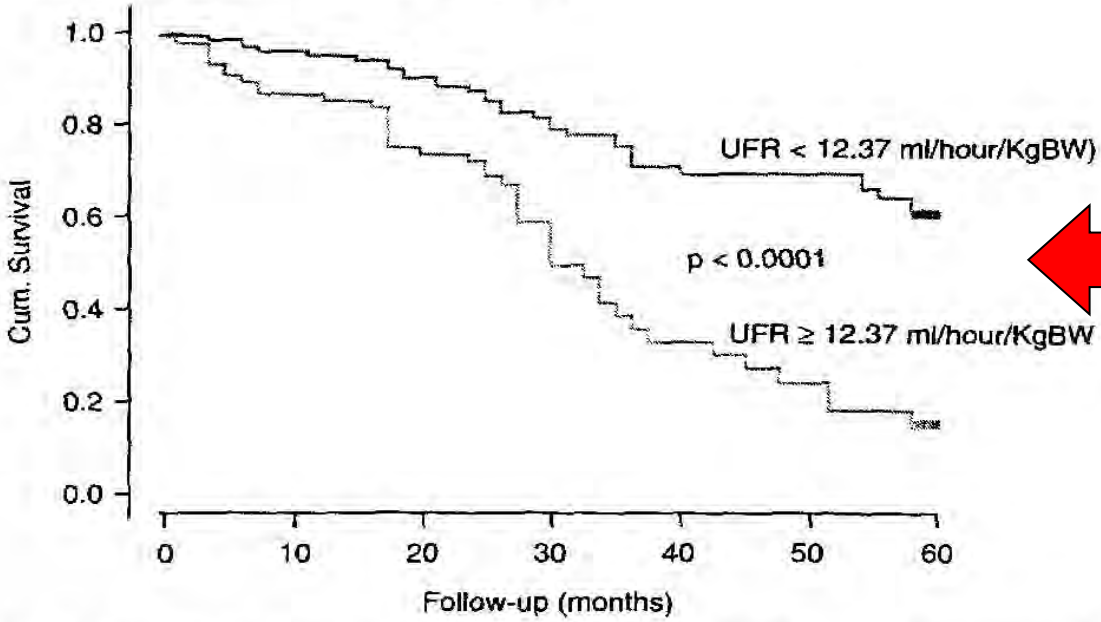

Fig. 3. Survival curves adjusted for significant predictors at Cox regression analysis by using UFR as categorical variable defined according to the receiver operating characteristic (ROC) derived UFR threshold of 12.37 ml/h/kg BW.

From 65% to less than 20% survival at 5 years

if BW loss per hour (UF rate) was over 1.25%

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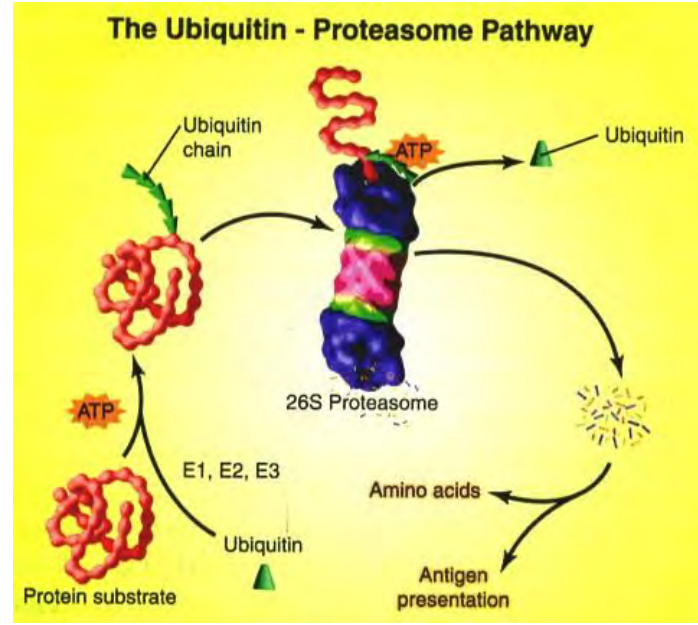
Cachexia in uremic patients : loss of protein stores, muscle wasting, growth impairment :

ATP-dependent, ubiquitin-proteasome system

- Volume overload (+/-high BP)
- Malnutrition
- Metabolic acidosis
- Inflammation
- Insuline resistance (PTH)
- GH-IGF1 axis anomalies



Muscle wasting in chronic kidney disease : the role of the ubiquitine proteasome system and its clinical impact
VR Royan, WE Mitch. Pediatr Nephrol 2008; 23:527-35

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Fluid management in dialysis (a proposal for a « volume first » approach)

- Interdialytic weight gain (IDWG)
- Ultrafiltration rates (% body weight loss per hour)
- Target weight (dry weight) (BCM®: UF needs to be a water prescription and a NaD prescription)

represent reasonable metrics for fluid management but their independent causative associations with outcomes are not defined (relative influence is unknown)

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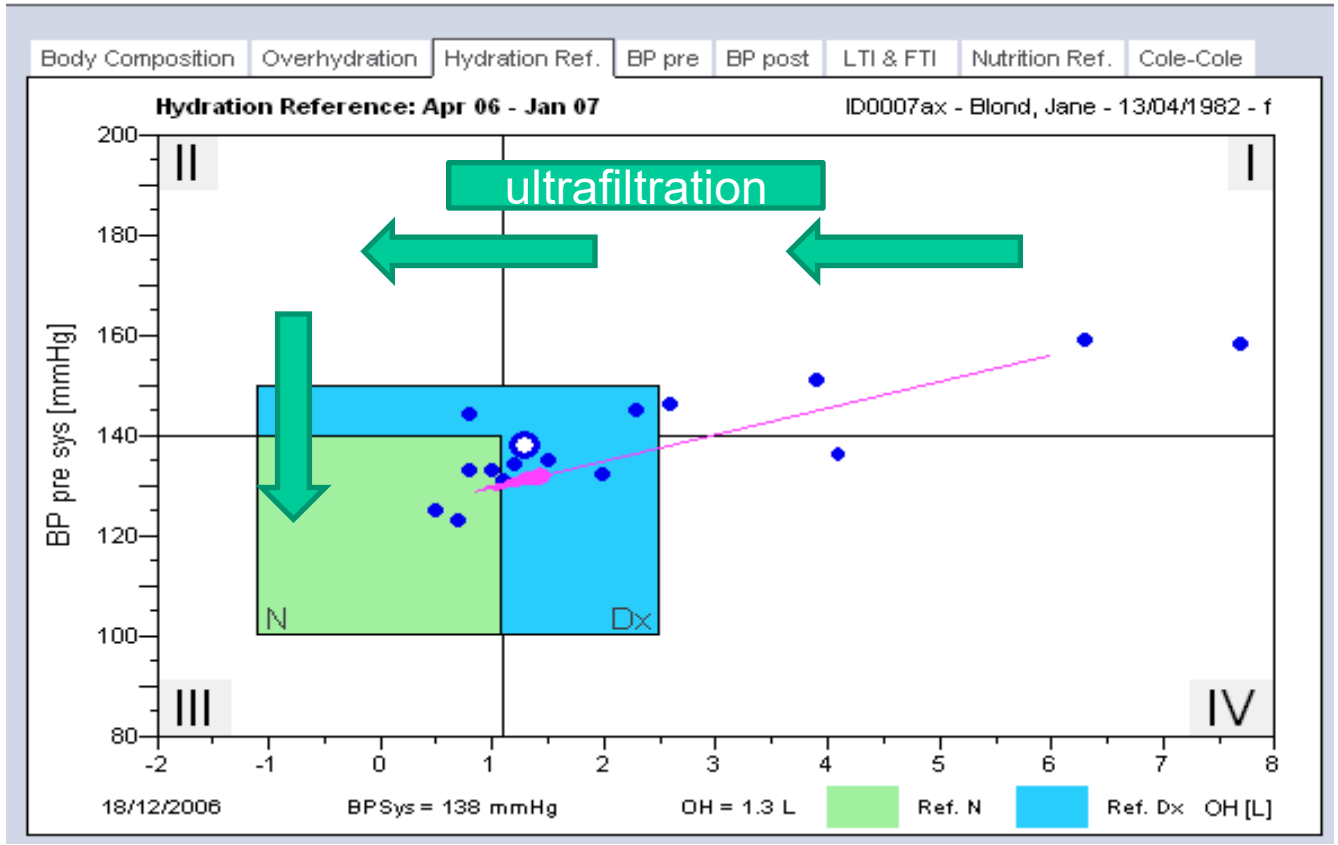
Blood Pressure versus hydration: weight loss and NaD

NaD



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BP management in dialysed children : *the vicious cercle*

- Elevated BP is mostly correlated by the doctors as “overweight”. Therefore, the usual prescription adaptation is more UF: *“a water prescription”*.
- Being hypertensive, children on dialysis received antihypertensive drugs. Therefore, *the achievement a the fixed dry weight is at hypotensive risk*, balanced by increased sodium dialysate, and/or stopped UF.
- *“High” sodium dialysate concentration (NaD>Napl)* (post dialytic thirst) and/or stopped UF are factors of too elevated interdialytic weight gain, inducing a high BP

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UF rate< 1.25%/h BW (floating dry weight) IDWG<4% ? Euvolemia ? Cooling T_D=36°

- Huang SH, Filler G, Lindsay R, McIntyre CW (2014) Euvolemia in hemodialysis patients: a potentially dangerous goal? Semin Dial doi: 10.1111/sdi 12317
- Flyth JF, Brunelli SM (2011) The risk of high ultrafiltration rate in chronic hemodialysis : implications for patient care. Semin Dial; 24:259-265
- Paglialonga F, Consola S, Galli, MA, Testa S, Edefonti A (2015). Interdialytic weight gain in oligo anuric children and adolescents on chronic haemodialysis. Pediatr Nephrol
- Movilli E, Gaggia P. Zubani R, Camerini C, Vizzardi V, Parrinello G, Savoldi S, Fischer MS, Londrino F, Cancarini G (2007) Association between high ultrafiltration rates and mortality in uraemic patients on regular haemodialysis. A 5-year prospective observational multicentre study. Nephrol Dial Transplant; 22:3547-3552

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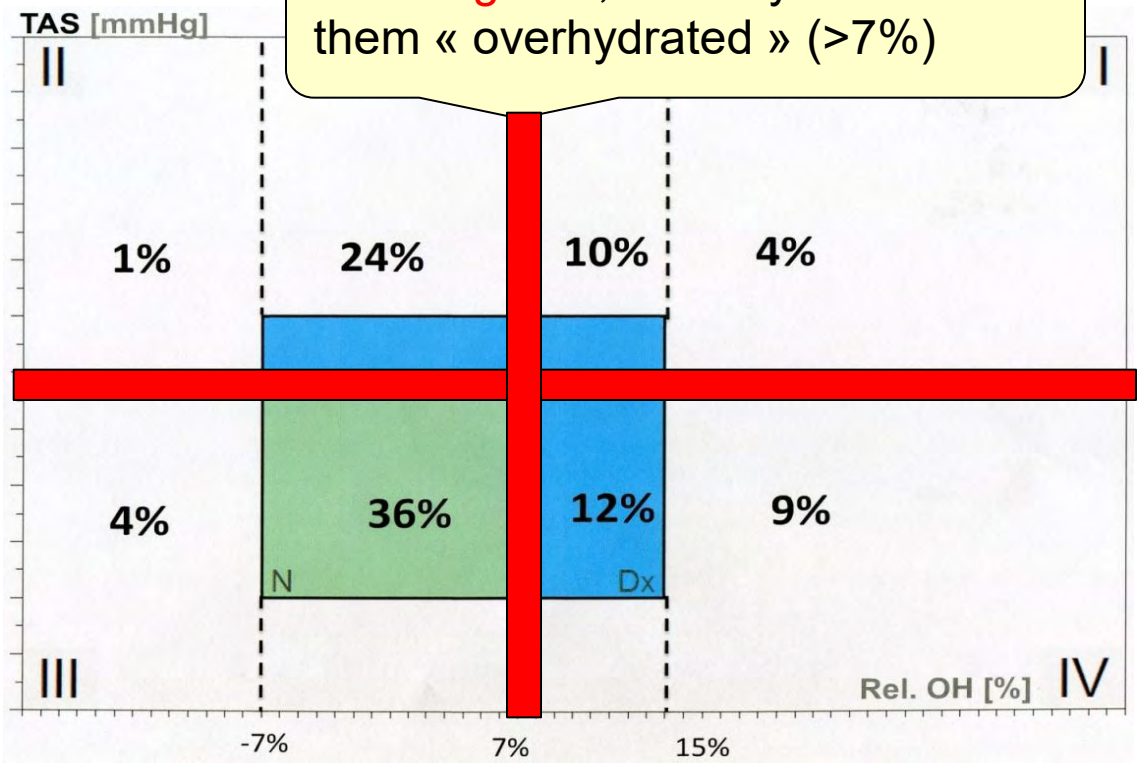
Hydration measurement by bioimpedance spectroscopy and blood pressure management in children on hemodialysis.

Zaloszyc A…Fischbach M (2013). Pediatr Nephrol; 28:2169-2177

39% high BP, but only 36% of them « overhydrated » (>7%)



36 % : normo OH

35% overhydrated (>7%), but only 40% of them with high BP

The relation BP versus hydration in children on chronic hemodialysis : « far from clear »

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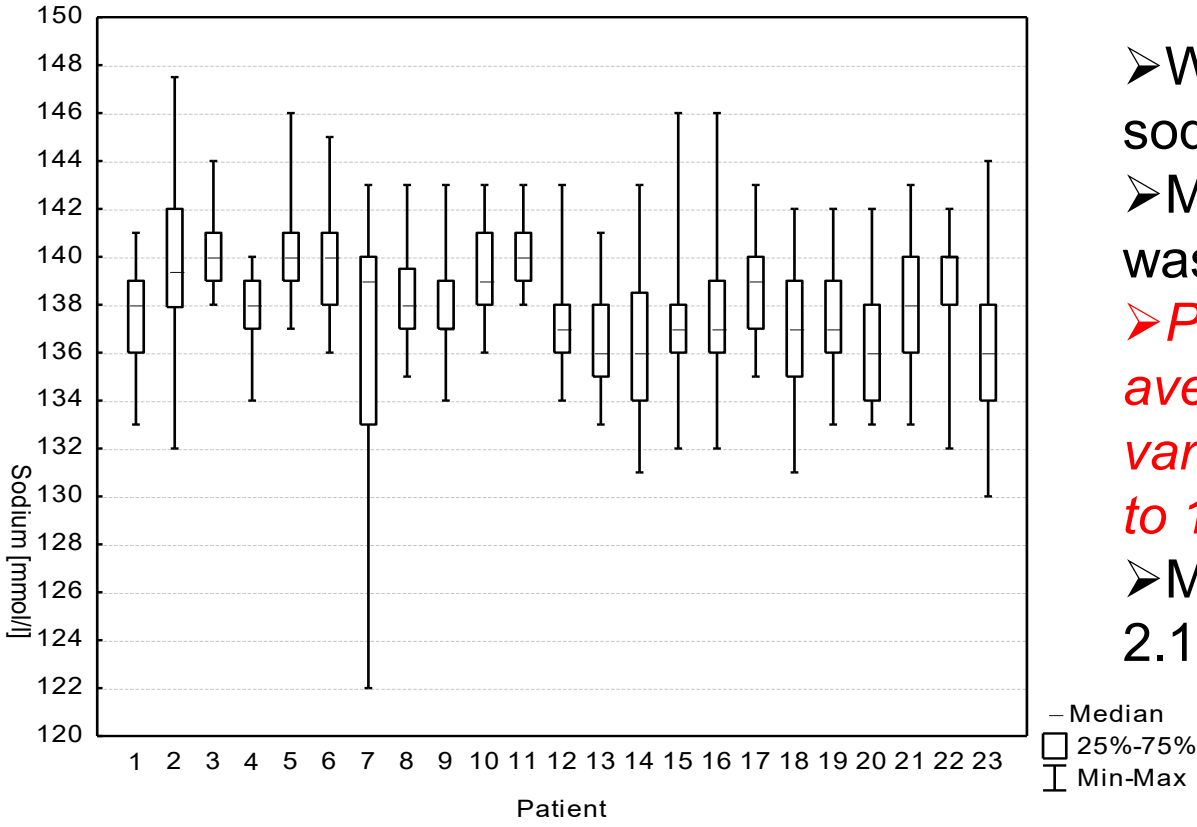
Plasma sodium variability in children: a fixed set point ?



- We collected 905 pre-dialytic sodium values.
- Mean pre-dialytic sodium value was 138 ± 1.4 mmol/l.
- *Pre-dialytic sodium values averaged over the study period, varied from 135.6 ± 3.12 mmol/l to 140.2 ± 1.6 mmol/l.*
- Mean NaD value was 140.2 ± 2.1 mmol/l.

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Dry-weight: A concept revisited in an effort to avoid medication-directed approaches for blood pressure control in hemodialysis patients

R. Agarwal, MR. Weir. Clin J Am Soc Nephrol 2010; 5:1255-1260

- *Restricting dialysate sodium* is a simpler but underexplored strategy that can reduce thirst, limit interdialytic weight gain, and assist the achievement of dry-weight.

- *It is likely that too much medication may actually limit the opportunity to probe dry-weight and lead to BP resistance through expanded volume.*

- *Avoiding medication-directed control of BP may enhance the opportunity to probe dry-weight, facilitate removal of volume (water and sodium): to achieve the dry weight*

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On line HDF is not a self-fulfilly prophecy: it must be used ***wisely***

Kuhlmann MK. J Am Soc Nephro 2012; 23: 974-5

(CONTRAST « commentaries »)

- Advantages of OL-HDF both « purity and purification »:
  - higher removal of creatinine, phosphate, β2 m and some protein bound uremic compounds
  - lower incidence of intradialytic hypotension, nutritional status, prevention of inflammation and better preservation of residual renal function
- However, it remains a matter of debate whether these latter effects may have been related primarily *to the treatment made itself or secondary to improved dialysis purity*.
- Significantly improved outcome observed (Contrast/Turkish HDF study) in the subgroup of patients treated with the highest convection volumes: OL-HDF is easy to apply, ***high efficiency HDF i.e. large convective volumes need more practical implication (fistulla quality, session time, membrane,dialysate)***

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Cardiovascular benefits of daily haemodialysis : peeling the onion

Chris W. McIntyre. Nephrol Dial Transplant 2014; 29:1-4

Extended dialysis (longer, more frequent) must be delivered (« adequately ») with a realistic reduction in circulatory stress that is : *a good quality dialysis*

- reduced exposure to endotoxins (*ultrapure dialysis fluids*)
- optimized volume control (not « simply a « weight loss », but also *a more efficient depuration of sodium*)
- reduction in UF demands per dialysis session (volume, rate), (interest of the concept of *« floating » dry weight*)
- « *cooling/thermic control* », cardiovascular preservation

Daily on line hemodiafiltration : the perfect « stimulus package » to induce growth.

F. Schaefer. Nephrol Dial Transplant 2010; 25:658-660

- 35 % to 50 % of children with ESRD still grow up to became small adults with a final height below the third percentile of the general population
- Growth failure is a common end point of a variety of abnormalities associated with CKD :
  - Protein energy malnutrition due to anorexia and chronic inflammation (cachexia)
  - Metabolic acidosis via the UPS and direct suppression of endogenous GH secretion
  - Partial resistance to GH, multifactorial (somatomedin inhibitors ; accumulation of IGFBP ; decreased IFG1 response to GH and deficit of IGF1 action ; activation of the post GH receptor intracellular signalling : JAK2-STAT5; activation and upregulation of the S0CS family (inflammation+++)

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Phosphate and Klotho

M. Kuroo-o. Kidney Int 2011; 79(suppl 121):520-523

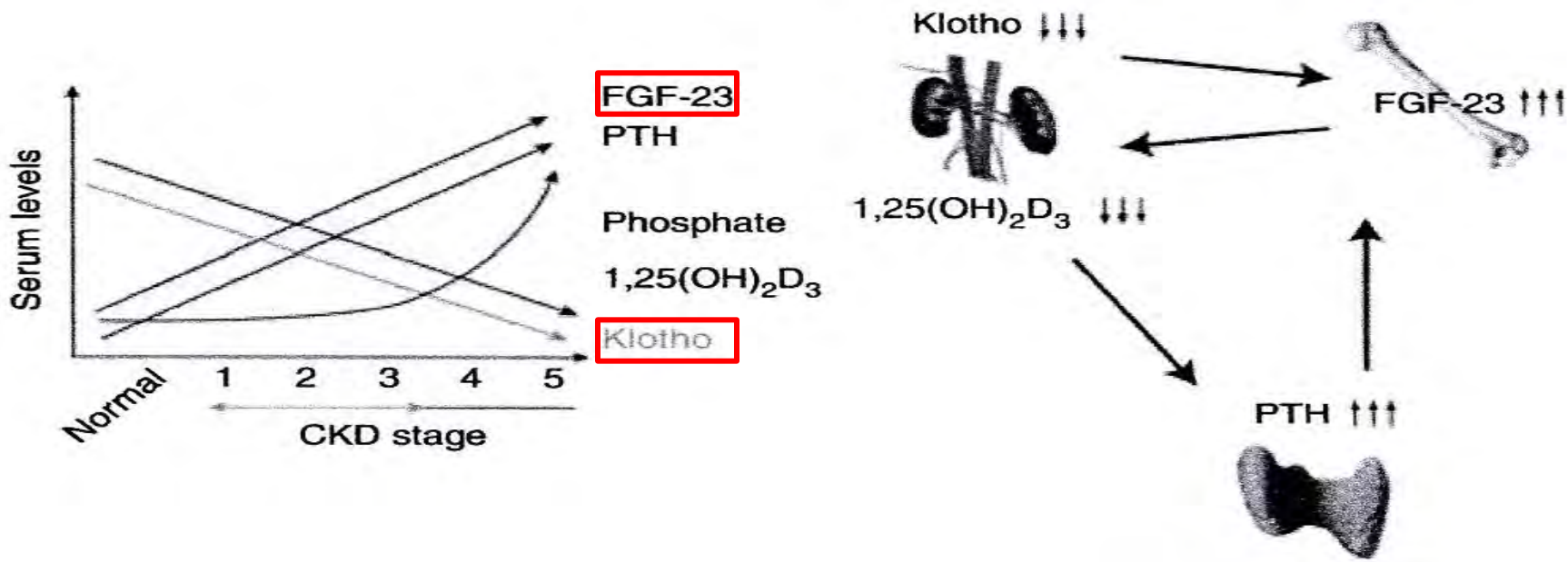

Figure 2 | Changes in Klotho protein, FGF-23, PTH, $1,25(OH)_2D_3$, and phosphate as CKD progresses. When Klotho expression first decreases, FGF-23 increases, lowering circulating $1,25(OH)_2D_3$, which depresses Klotho expression further and increases PTH expression. Increased PTH induces further FGF-23 increases, causing large decreases in $1,25(OH)_2D_3$ and large increases in PTH. This cycle results in hyperphosphatemia in late stages of CKD. CKD, chronic kidney disease; FGF-23, fibroblast growth factor-23; PTH, parathyroid hormone.

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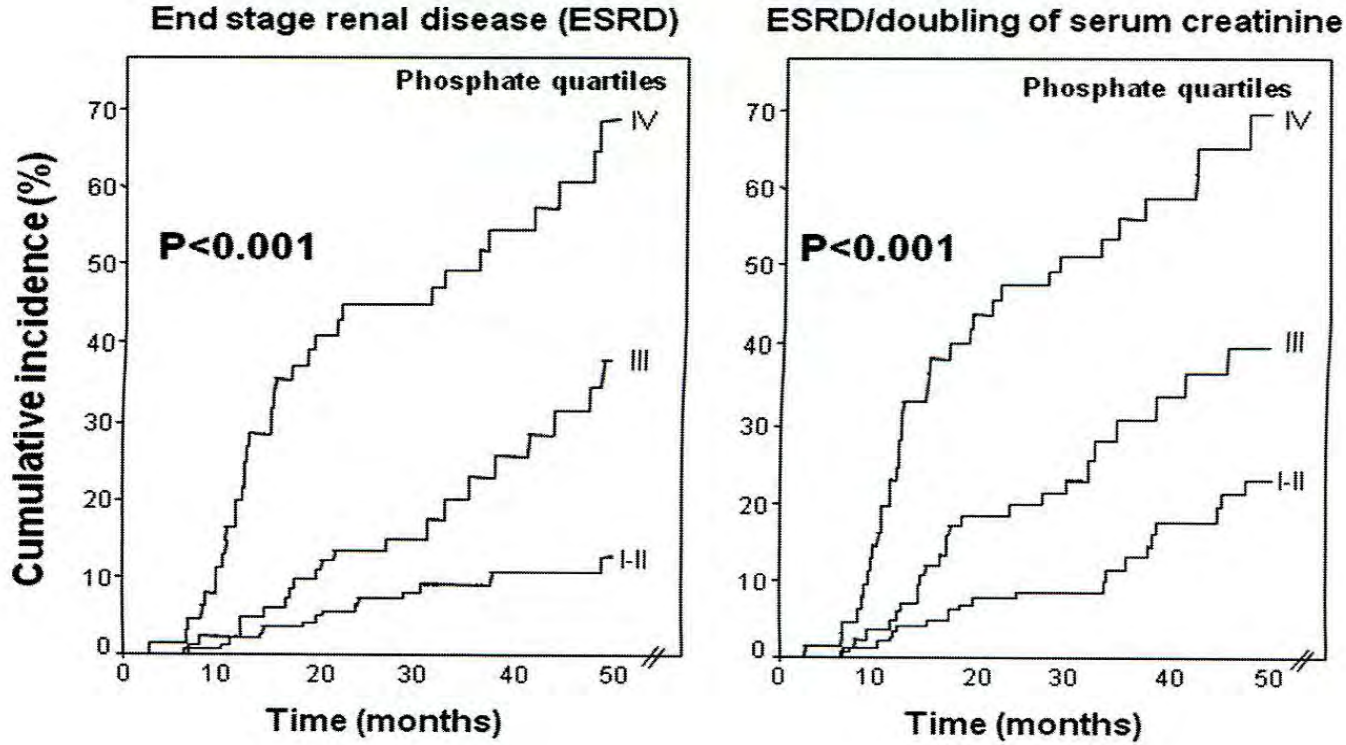
The phosphate renal aging process : an independent pathogenic role

C. Zoccali et al. J Am Soc Nephrol 2011; 22:1923-1930



- The higher phosphate levels progressively attenuated the renoprotective effect of ramipril.
- Whether this is due to higher serum phosphate per se, elevated FGF23 levels or reduced klotho expression is a question to explore

Serum iPTH, calcium and phosphate, and the risk of mortality in a European haemodialysis population

Floege J, Kim J, Ireland E et al. and on behalf of the ARO investigators. Nephrol Dial Transplant. Advance access published April 25, 2010

Both, hypophosphatemia, denutrition/cachexia and hyperphosphatemia are a factor of increased mortality risk

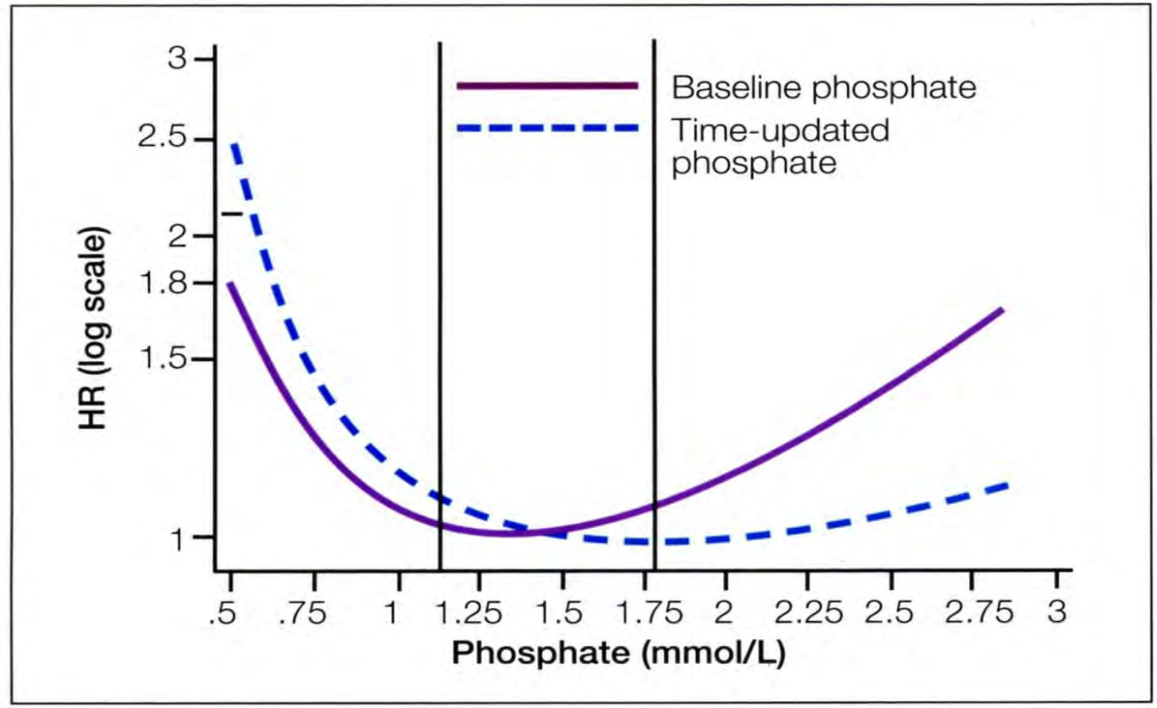
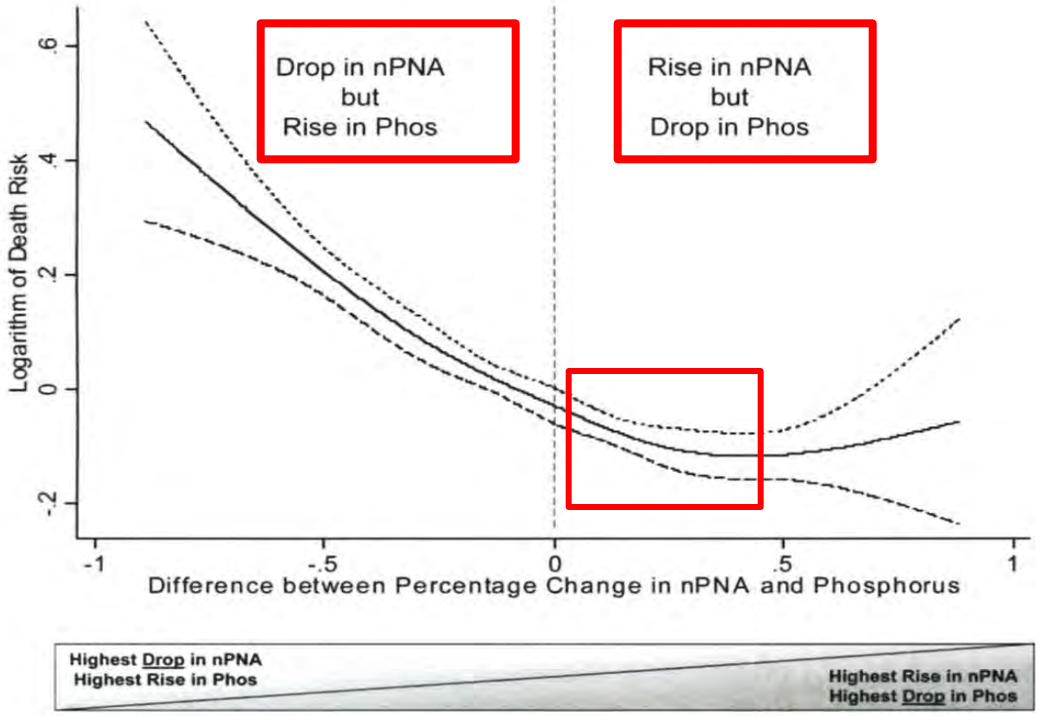


Fig. 2: *Relative risk of all-cause mortality for serum phosphate comparing baseline versus timedependent Cox regression.*

Understanding sources of dietary phosphorus in the treatment of patients with chronic kidney disease

K. Kalantar-Zadeh et al. Clin J of Am Soc Nephrol 2010; 5:519-530



- Patients whose protein intake raises while their serum P declined over time showed the greatest survival(optimal nutrition/anabolism)
- Otherwise, the decline in Phoshate only due to decline in protein intake is associated with an increase in the risk of death (cachexia,protein wasting,denutrition) *(Shinaberger CS et al. Am J Clin Nutr 2008; 88:1511-8)*

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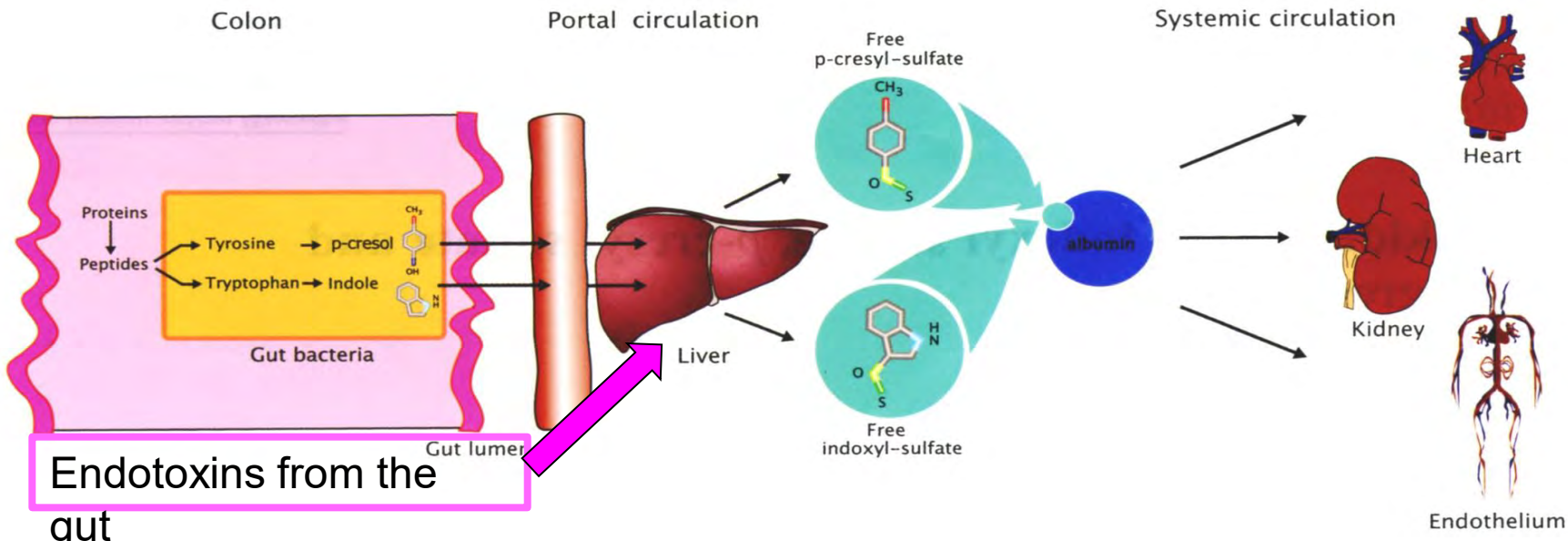
The gut-kidney axis:
indoxyl sulfate, *p-cresyl* sulfate, endotoxins and CKD progression

Björn KI Meijers and Pieter Evenepoel.
Nephrol Dial Transplant 2011; 26:759-761



CKD : a systemic disease with cross talk between the gut and the "body" (CKD-MBD-CardioVascular)

- ✓ Uremic toxins production
- ✓ "leaky" gut (endotoxins)

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P-cresyl sulfate and indoxyl sulfate in hemodialysis patients

Muijers BK et al. Clin J Am Soc Nephrol 2009; 1932-8

- These « uremic toxins » originate from bacterial protein fermentation in the large intestine
- *Indoxyl sulfate : toxin impacting on progression of CKD (factor of loss of residual function)*
- *P-cresol : pro inflammatory toxin , endothelial dysfunction, cardiovascular disease, mortality*
- They are competitive binding inhibitors for the same albumin binding site ; their serum concentrations are not related ; they are interchangeable risk markers

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Intradialytic hypotension and risk of cardiovascular disease

BV Stefansson et al. JASN 2014; 9:2124-32

- Intradialytic hypotension occurred in 31.1 % patients.
- IDH was associated with cardiovascular morbidity and mortality.
- IDWG reduction should be considered to reduce IDH, possibly by titrating treatment length.

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Cardiovascular benefits of daily haemodialysis : peeling the onion

Chris W. McIntyre. Nephrol Dial Transplant 2014; 29:1-4

Extended dialysis (longer, more frequent) must be delivered (« adequately ») with a realistic reduction in circulatory stress that is : *a good quality dialysis*

- reduced exposure to endotoxins (*ultrapure dialysis fluids*)
- optimized volume control (not « simply a « weight loss », but also *a more efficient depuration of sodium*)
- reduction in UF demands per dialysis session (volume, rate), (interest of the concept of *« floating » dry weight*)
- « *cooling/thermic control* », cardiovascular preservation

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Hemodialysis treatment time : a fresh perspective

E. Lacson Jr.and S.M. Brunelli. Clin J Am Soc Nephrol 2011; 6:2522-2530

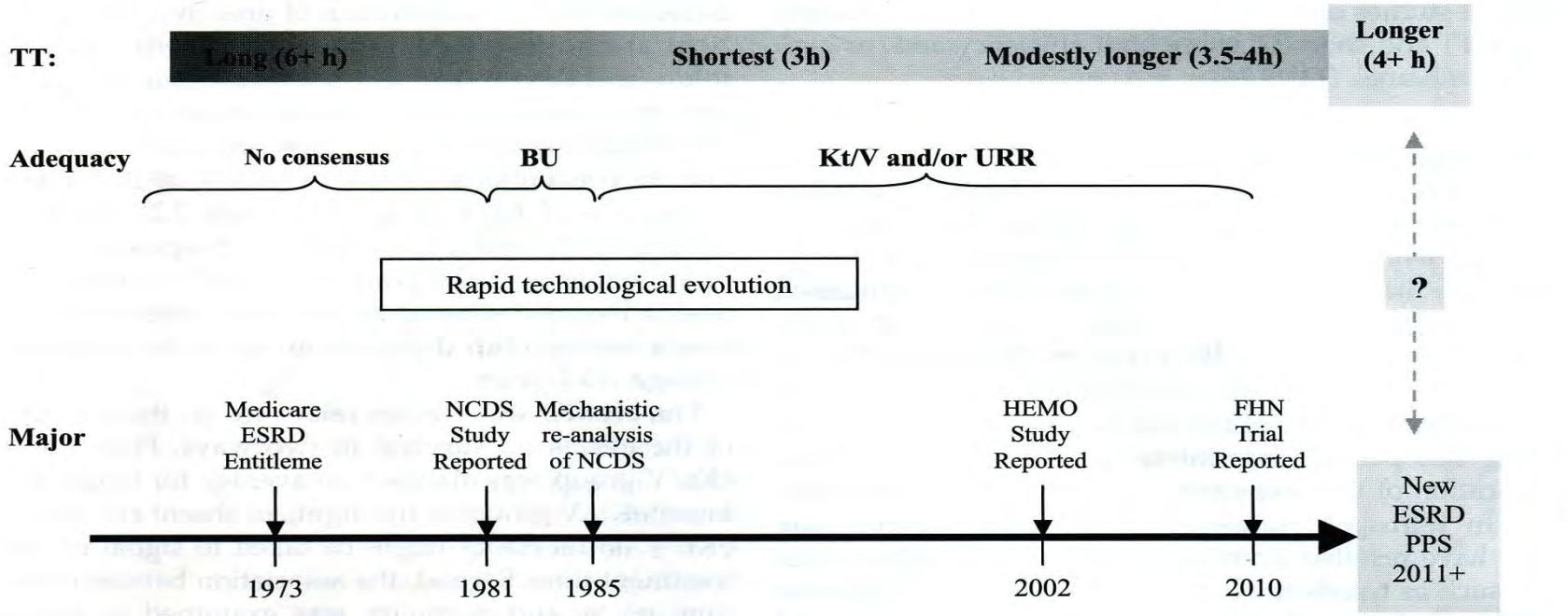

Figure 1. | Timeline of the evolution of dialytic treatment time and associated events. TT, treatment time; BU, blood urea; URR, urea reduction ratio; NCDS, National Cooperative Dialysis Study; FHN, Frequent Hemodialysis Network; PPS, prospective payment system; HEMO Study, Hemodialysis Study.

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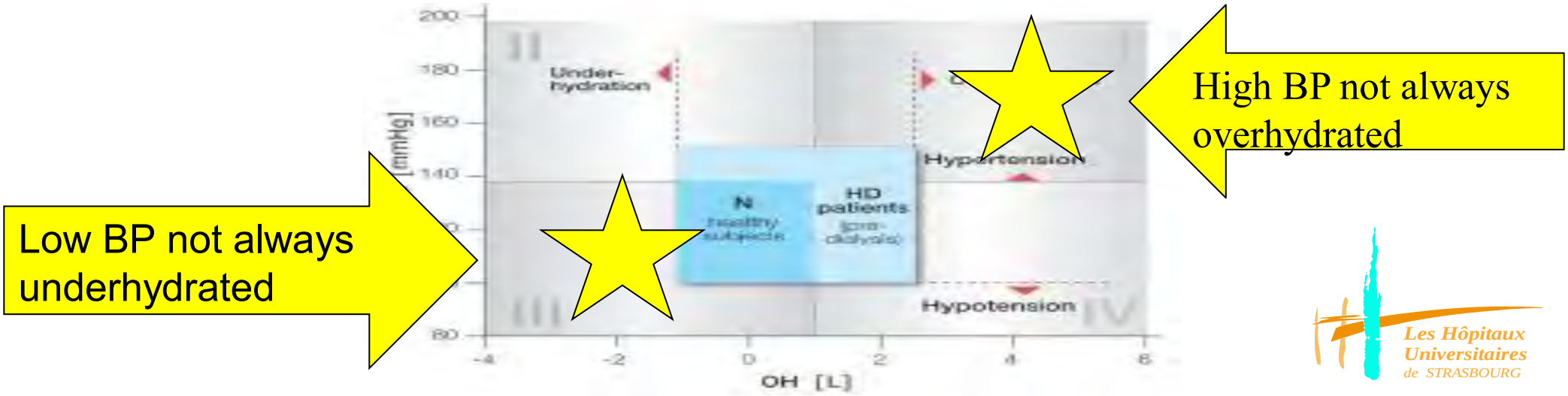
Blood Pressure versus hydration in dialysed patients : « box plot »

- BP and hydration (dry weight) : BCM evaluation
  - High BP despite normohydration, the « other » causes of high BP (renal disease, endocrinopaty, vasculopaty)
  - Use of antihypertensive drugs can mask overhydration (normal BP despite overhydration)
  - Low BP regardless of fluid status, even overhydration



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Dry-weight: A concept revisited in an effort to avoid medication-directed approaches for blood pressure control in hemodialysis patients

R. Agarwal, MR. Weir. Clin J Am Soc Nephrol 2010; 5:1255-1260

- *Restricting dialysate sodium* is a simpler but underexplored strategy that can reduce thirst, limit interdialytic weight gain, and assist the achievement of dry-weight. *It is likely that too much medication may actually limit the opportunity to probe dry-weight and lead to BP resistance through expanded volume.*
- Conclusions : Avoiding medication-directed control of BP may enhance the opportunity to probe dry-weight, facilitate removal of volume (water and sodium), and limit the risk for pressure-volume overload, which may be a significant concern leading to myocardial remodeling in the hemodialysis patient. Probing dry-weight among patients with ESRD has the potential to improve dismal, miserable and depressing cardiovascular outcomes.

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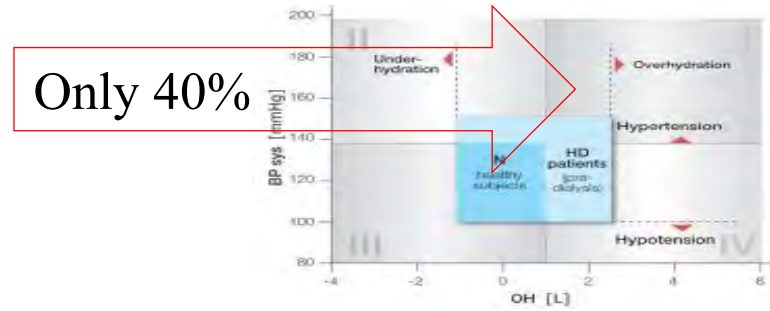
Dialysis prescription : adequate, before optimal

- *Dialysis modality* should permit the achievement of the blood pressure control (without antihypertensive medications for the majority of children), normal myocardial morphology and function
- The « at bedside » concept that *an elevated blood pressure should benefit from enhanced ultrafiltration* (increased weight loss/UF per session) could be inaccurate in some cases, **even at risk**



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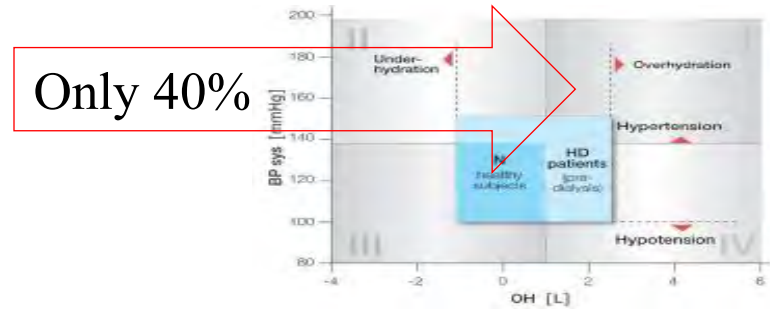

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Inflammation and cachexia in chronic kidney disease

Cheung WW, Paik KH, Mak RH. Pediatr Nephrol 2010; 25:711-724

- **The nutritional importance of « volume control »: BP, dry weight, LVH**

- Brink M. Price SR, Chrast J. Bailey JL, Anwar A, Mitch WE, Delafontaine P (2001) *Angiotensin II induces skeletal muscle wasting* through enhanced protein degradation and down-regulates autocrine insulin-like growth factor I. Endocrinology 142:1489-1496

- Zhang L, Du J, Hu Z, Han G, Delafontaine P, Garcia G, Mitch WE (2009) IL-6 and serum amyloid A synergy mediates *angiotensin II induced muscle wasting*. J Am Soc Nephrol 20:604-612

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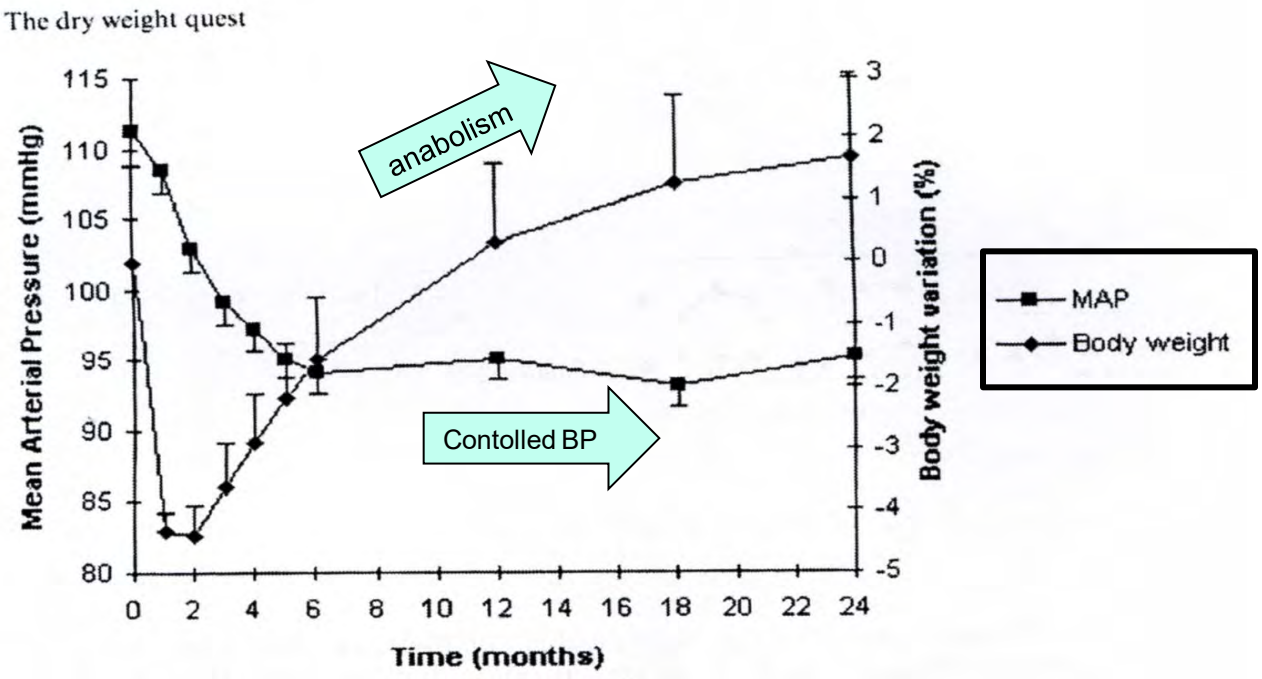
The Janus-faced aspect of « dry weight »

C. Chazot, B. Charra, C. Vo Van et al. Nephrol Dial Transplant 1999; 14:121-124



The anabolic effect of the optimal control of fluid overload
(Tassin,Lyon,France)

After the second month of dialysis treatment, the simultaneous increase of post-dialysis body-weight and decrease of pre-dialysis MAP are related to the effects of two processes, i.e. increased weight as the result of anabolism induced by the HD treatment on the one hand and normalization of blood pressure by fluid removal on the other

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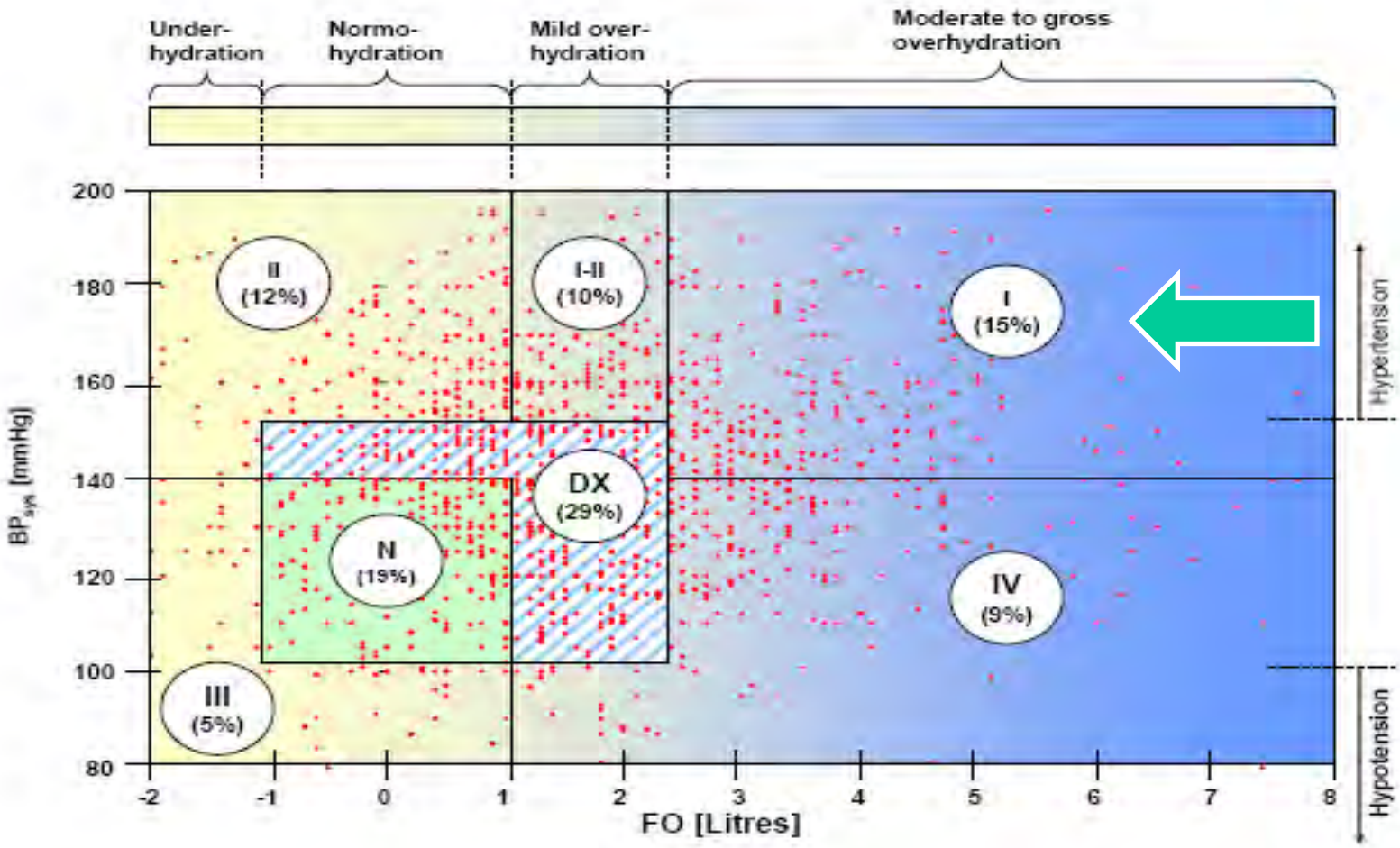
Towards improved cardiovascular management : the necessity of combining blood pressure and fluid overload.

Wabel P, Moissl U, Chamney P, Jirka T, Machek P, Ponce P, Taborsky P, Tetta C, Velasco N, Vlasak J, Zaluska W, Wizemann V. *Nephrol Dial Transplant. 2008, S23(9):2965-71*



37% patients hypertensive

« only » 40% of them on overhydration

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dialysis dose and outcome:
more intensive, more frequent, a « complete » dialysis dose
Kt/Vurea reassessment, addition of a convective volume

- Recognition of the salutary effects of enhanced dialysis dosis on growth (*A. Tom, J Pediatr 1999; 134:464-71 ; Katz A, Pediatr Nephrol 2000;14:700-2)* warrants reassessment of pediatric HD guidelines

- Reassessing hemodialysis adequacy in children « the case for more » (Sharme A. Pediatr Nephrol 2001 ; 16:383-90)

- Daily and intensive OL-HDF : might improve statural growth, allow optimal phosphate dialytic purification (CaxP) despite « free » diet and thereby participate to cardiovascular preservation
(Fischbach M : Neprol Dial Transpl 2004; Pediatr Nephrol 2006; Clinical Nephrology 2008)

high KT/V : weekly KT/V of ~ 10 ?
Complete dialysis dose: diffusive dose and convective dose
Longer or more frequent sessions

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Hemodialysis prescription : passed, present and near future

- *In 1965*, one session per week : only short survival
- *In 1975*, two sessions per week : survival
  GFR equivalency : less than 10%
- *In 1980/85*, three sessions per week: a degree of rehabilitation
  GFR equivalency : 10 to 20 %
- *Today*, daily and intensive hemodialysis;
  GFR equivalency :30 to 40%

it is time to change a 25 years old dialysis strategy and not to only use « « daily » as a rescue modality

Intensified hemodialysis regimens : neglected treatment options for children and adolescents *Muller D.et al. Pediatr Nephrol 2008; 23:1729-36*

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Intensified and more frequent hemodialysis regimens: some advantages and limits

Michel Fischbach , Céline Dheu, Laure Seuge, Soraya Menouer, Joëlle Terzic

Clinical Nephrology 2008, 69,4: 279-84

	In center		At home
	Day	Over night	Over night
Distance from center	Contra	Contra	Pro
Charge at work	+ Nurses	++	Family (or nurse)
School attendance	Reduced (?)	Normal	Normal
Personal school support	+	—	—
Coaching (second family)	+	+	Free (alone)
Puncture of the vascular access	Nurse	Nurse	Family (or nurse)
Dialysis procedure	OL-HDF	HD or HDF	HD
Social life			
•Night	At home	In hospital	At home
•Dialysis center	3 h	8 h	8 h
•"Night life"	Possible	Restricted	Restricted

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How to improve conventional hemodialysis

- Tools for hemodialysis: on line monitoring during the session, Kt/Vurea, BVM, dialysate modelling (sodium, dialysate temperature), UF modelling
- BCM (multiimpedancemetry) (Vurea, nutrition, high BP management)
- *Prescribe high flux membrane for all at risk patients*, children : backfiltration = non determined convective flow but need for ultrapure dialysate
- Consider not only a urea dialysis dose (diffusive process) but also a convective dialysis dose (middle molecular weight compounds) :

  HDF is superior to HD, HDF adds convective flow to HD
- Dialysis time *: from intermittent (and some « rescue sessions ») to daily dialysis (dialysis without stress)*

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HDF : mise en place

- Traitement de l'eau : pureté, désinfection (stérilisation thermique, thermochimique)
- Membrane d'HDF : « autocontrol » pre, post, mixed
- Membrane d'HDF :
  - Volume convectif (perméabilité hydraulique)
  - Coefficient d'extraction (perméabilité moléculaire, β_2 m 80 %)
  - Pertes d'albumine (pré/post ; volume convectif)
- Dialysat, liquide de substitution (HDF-OL) :
  - Acide acétique ? (balance calcique)
  - Na_D et balance sodée
  - Température

Prescription adéquate de l'HDF

- Volume convectif (> 25 L)
- Coefficient d'extraction moléculaire (β_2 m 80 %)
- Perte d'albumine (< 5 gr)

Optimal Hemodialysis Prescription: Do children need more than a urea dialysis dose? the importance of the convective volume

M Fischbach et al. Inter J Nephrol 2011

1) Dialysis: diffusion (HD), convection (HF) and combination therapy (HDF) : uremic toxins removal
2) Kt/V urea: diffusive dialysis dose (HD)
3) Convective volume (HF, HDF): **β_2 microglobulin, phosphate**
4) A complete dialysis dose : Kt/V urea (>1.4) and the convective volume (?, >14L postdilution /adult; impact on β_2 microglobulin, phosphate)

Long±term effects of high efficiency on-line hemodiafiltration on uremic toxicity; a multicentre prospective randomized study

Pedrini LA et al. Nephrol Dial Transplant; 2011: 26:2617-24

- High efficiency OL-HDF is superior to high flux HD (Cheung AX: Hemo Study. JASN 2003; Locatelli F: MPO Study. JASN 2009; Canaud B. DOPPS : Kidney Int 2006; Villar E: JASN 2009.
- Synthetic highly biocompatible membranes and ultrapure dialysate/infusate were used in both treatment modalities. [EBPG. NDT 2002; 17(suppl 7):7-109].
- *OL HDF resulted in enhanced in removal and lower basal levels of small, medium sized and protein-bound solutes, which contribute to lower inflammation, hyperparathyroidism, dyslipidemia and mean predialytic BP*

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Hemodiafiltration:
The addition of convective flow to hemodialysis:
"*a complete dialysis dose*".

M. Fischbach, H. Fothergill, A. Zaloszyc, L. Seuge Pediatr Nephrol 2012, 27: 351-6

HDF offers a complete dialysis dose: not only an urea dialysis dose i.e. diffusive dose expressed as Kt/V urea, but also a convective dialysis dose i.e. convective volume per session.

Hemodiafiltration is without doubt superior to HD with low flux membranes, although this is difficult to prove in prospective, randomized studies.

It is hoped that ongoing studies will definitively demonstrate the differences in patient outcome achieved with on-line HDF compared to high flux HD, only a non determined small convective volume with dialysate as substitution fluid.

When given on a daily basis, on-line HDF offers the "perfect stimulus package" for inducing catch up growth in children : no protein wasting.

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Uremic toxins versus volume and water as the major factor that matters with dialysis

A. Covic et al. NDT 2012; 27:58-62

- Lower risk of mortality in HDF patients compared with conventional HD (low flux)
- DOPPS : 35 % significant lower relative risk of mortality. B. Canaud et al. Kidney Int 2006; 69:2087-93
- RISCAVID cohort : 34 % significant lower relative risk of mortality. V. Panichi et al. NDT 2008 ; 23:2337-43

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Mortality risk for patients receiving HDF versus HD: European results from the DOPPS

Canaud B et al. Kidney Int 2006

- The *relative risk of mortality* after adjustments for several variables (age, comorbid conditions, haemoglobin, Kt/V) was *significantly reduced by 35 % for patients receiving* ***high efficiency HDF*** compared to low flux HD or high flux HD

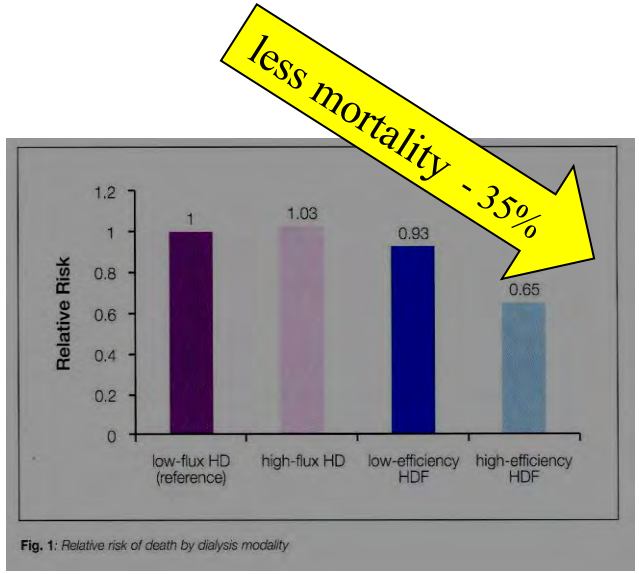

Fig. 1: *Relative risk of death by dialysis modality*

- Several explanations: HDF « package »
  - improved removal of small and larger molecules solutes (Phosphate), « surrogates » of the achieved convective volume
  - enhanced intradialytic hemodynamic stability
  - reduced inflammation due to better biocompatibility (β2 microglobulin
  - regulation of calcification inhibitors, like : fetuin-A, matrixGLA protein, osteoprotegrin

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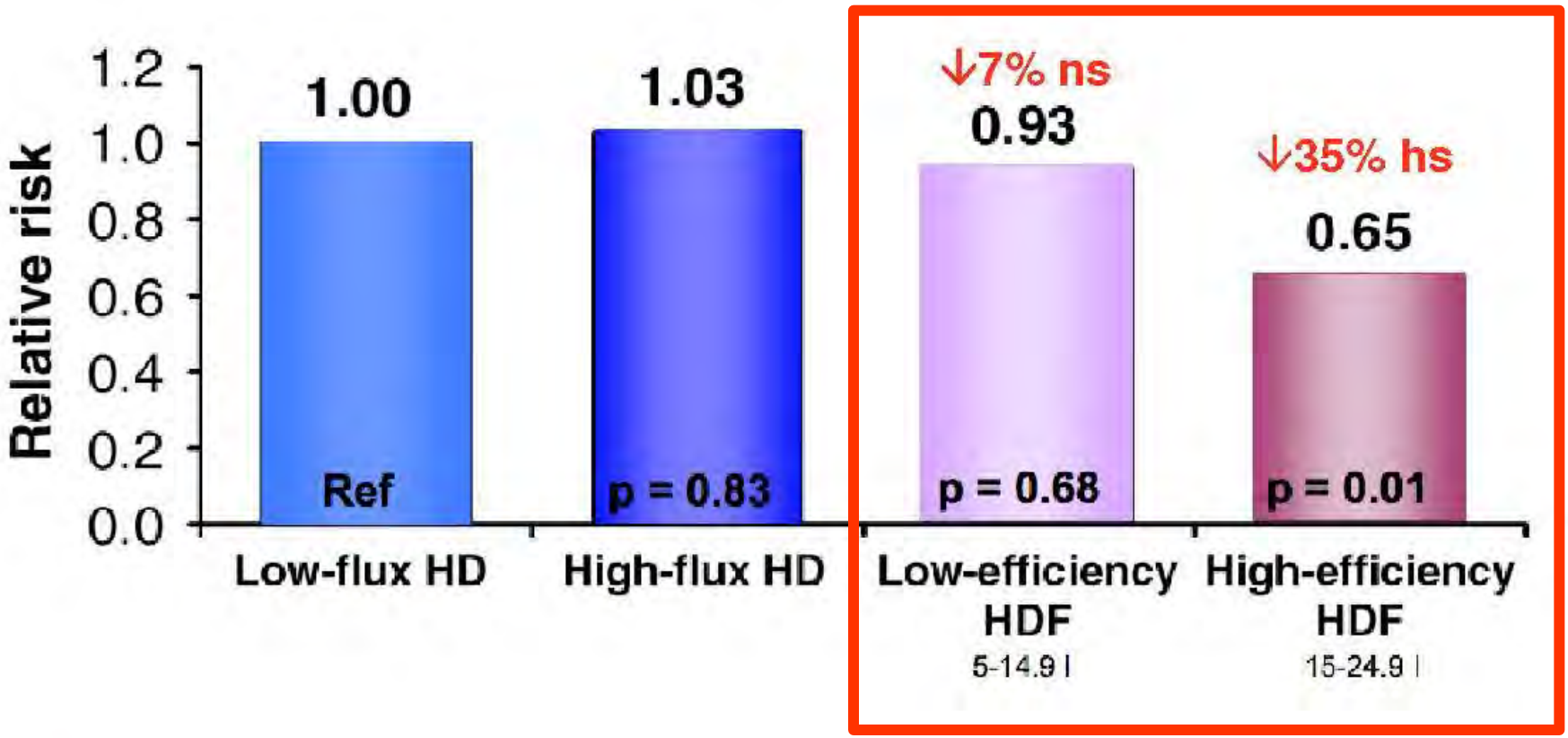
DOPPS study – HDF vs HD:

" clear effect of the amount of the convectif volume"



DOPPS

Canaud B et al, *Kidney Int* 2006; 69:

Uremic toxins versus volume and water as the major factor that matters with dialysis

A. Covic et al. NDT 2012; 27:58-62

- Turkish HDF study (high flux) : high efficiency HDF (>17.42 L per session) improved survival. E. OK et al. ERA-EDTA Congress Praga 2011; LBCT3
- CONTRAST Study (low flux) : only high average convective volumes (>20 L per treatment) was associated with lower relative risk of mortality. M. Grooteman et al. ERA-EDTA Congress-Praga 2011; LBCT3

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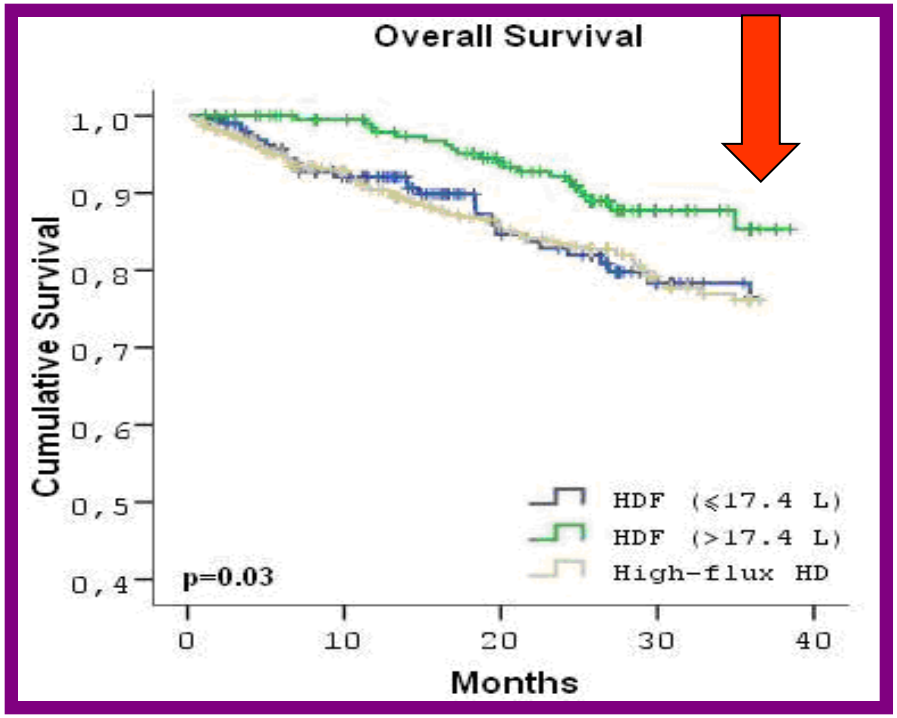
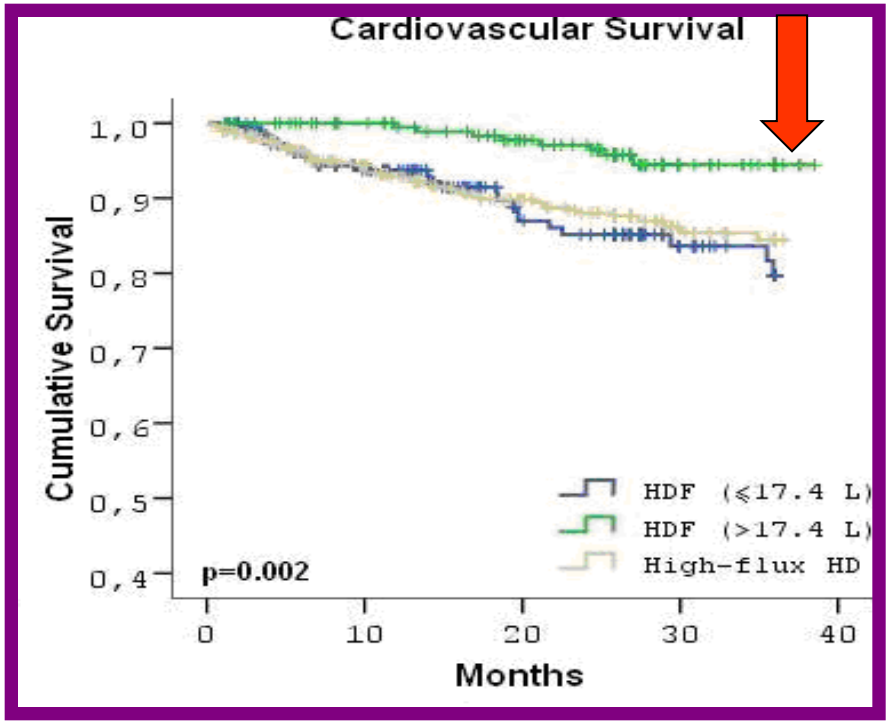
Turkish HDF Study (EDTA 2011): High Efficiency vs Low Efficiency OL-HDF

Overall and cardiovascular survival: impact of the convective volume > 17.4L





Mortality and cardiovascular events in online haemofiltration (OL-HDF) compared with high-flux dialysis: **results from the Turkish OL-HDF Study**

E. Ok, G. Asci, H. Toz et al. NDT 2013; 28:192-202

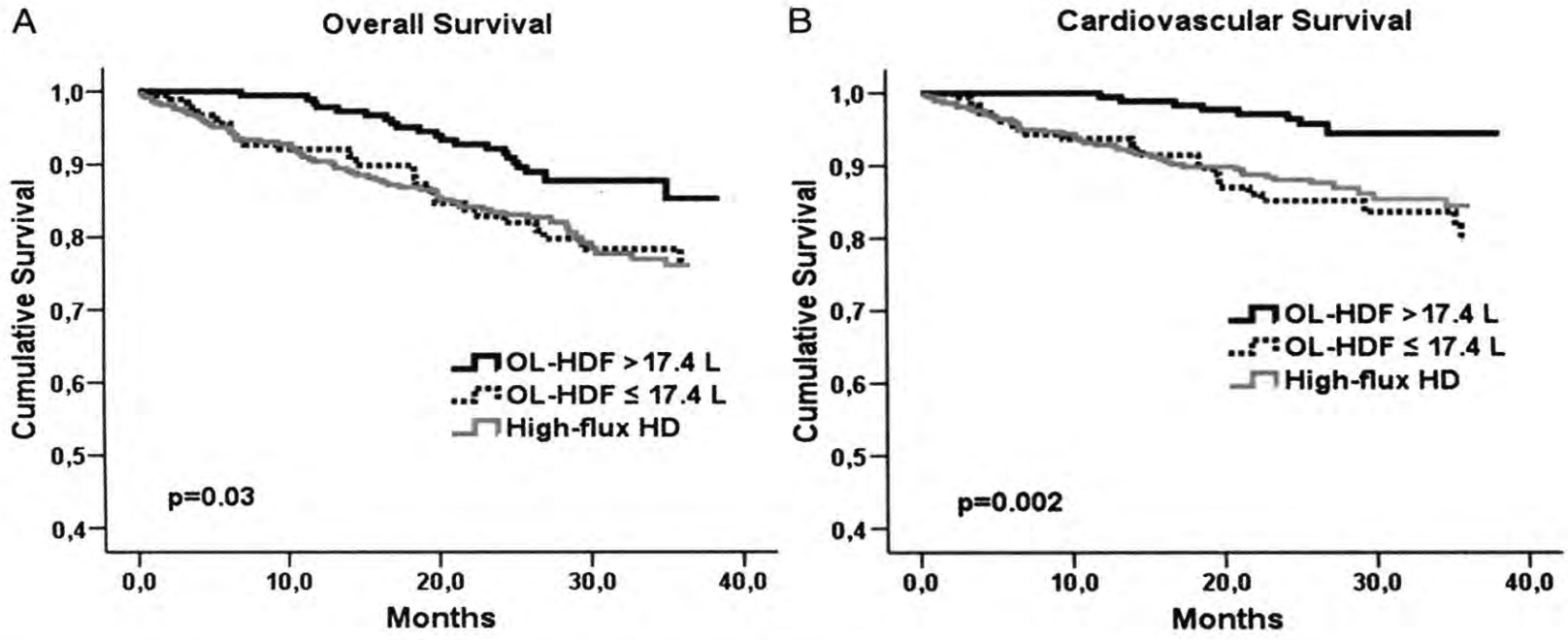


Fig. 3. Overall (**A**) and cardiovascular survival (**B**) among the treatment groups.

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Mortality and cardiovascular events in online haemofiltration (**OL-HDF**) compared with **high-flux dialysis**: **results from the Turkish OL-HDF Study**

E. Ok, G. Asci, H. Toz et al. NDT 2013; 28:192-202

Conclusions:

- The composite of all-cause mortality and nonfatal cardiovascular event rate *was not different* in the OL-HDF and in the high-flux HD groups.
- In a *post hoc* analyis, OL-HDF treatment with substitution *volumes over 17.4L* was associated with *better cardiovascular and overall survival*.
- The results demonstrate that postdilution OL-HDF is a *safe and well-tolerated* treatment in the long term.

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Mortality and cardiovascular events in online haemofiltration (**OL-HDF**) compared with **high-flux dialysis**: **results from the Turkish OL-HDF Study**

E. Ok, G. Asci, H. Toz et al. NDT 2013; 28:192-202

- Comparing the high-efficiency OL-HDF with high flux dialysis and the low efficiency OL-HDF, the risk of reaching *the primary composite endpoint (death and nonfatal cardiovascular events) was 30 % lower for the high-efficiency OL-HDF relative to high-flux HD* (HR=0.70, 95 % CI 0.46-1.08, P=0,26).
- When the patients treated with OL-HDF were grouped as quartiles of their mean replacement volumes (<16.5 L, 16.5-17.4L, 17.4-18.0 L and >18 L), the overall survival rates were, respectively 78.5, 75.5, 82.2 and 90.2 % (log-rank : 8.31, P=0.04) and the cardiovascular survival rates were 81.7, 78.7, 93.6 and 95.4 %, across the quartiles (log-rank:15.03, P=0.002).

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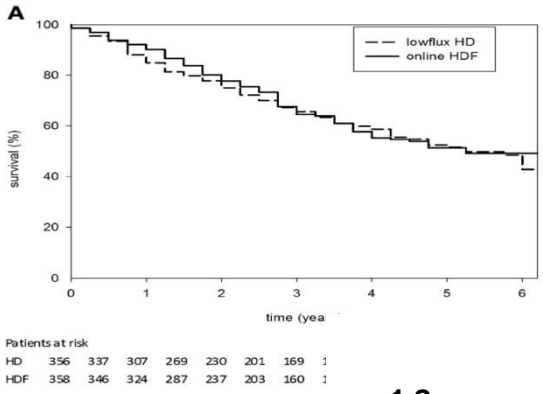
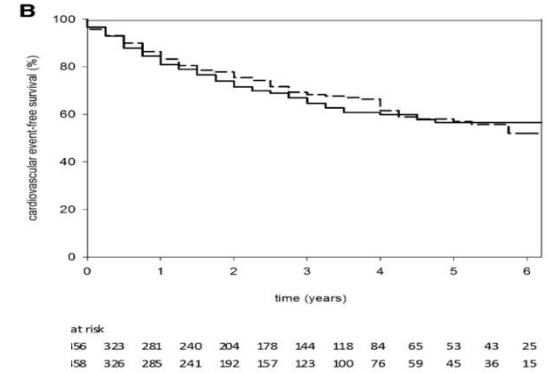
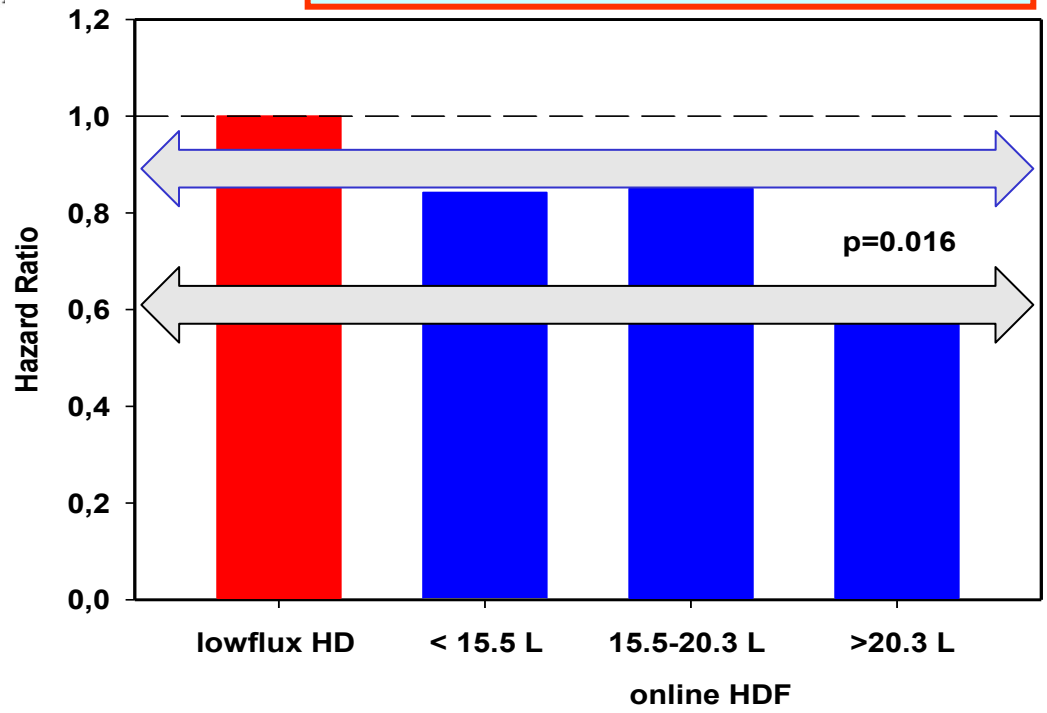
CONTRAST study

Grootemann MPD et al. for the CONTRAST investigators.
J Am Soc Nephrol 2012; 23:1087-1096 JASN 2012



In general, no impact, but 30% did not reach the end point, a « high convective volume »





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Effect of on line HDF on all case mortality and cardiovascular outcome

Grootemann MPD et al. for the CONTRAST investigators.
J Am Soc Nephrol 2012; 23:1087-1096

- **HDF** (n=714) versus **low flux HD** (n=356) follow up of 3.04 years (0.4-6.6 y)

- On treatment analysis suggests the possibility of a survival benefit among patients who receive high volume HDF (>21.95 L) although this subgroup finding requires confirmation.

- Ultrapure dialysis fluids, defined as <0.1 CFU/ml and <0.03 endotoxin units/ml ; maximal achievable convection volume in postdilution mode (proposed target 6 L/h ≈ 24 L/session) ; 9 % of HDF treatments were delivered as high flux hemodialysis : in one third of the study population the convective volume was only 18 L or less.
- β2 microglubulin (mg/dl) pre dialysis : in OL-HDF 26.4 (0.37), versus in low flux HD 35.4 (0.54) p<0.001

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High-efficiency postdilution OI-HDF reduces all-cause mortality in hemodialysis patients

Maduell F et al. J. Am Soc Nephrol 2013; 24:487-497

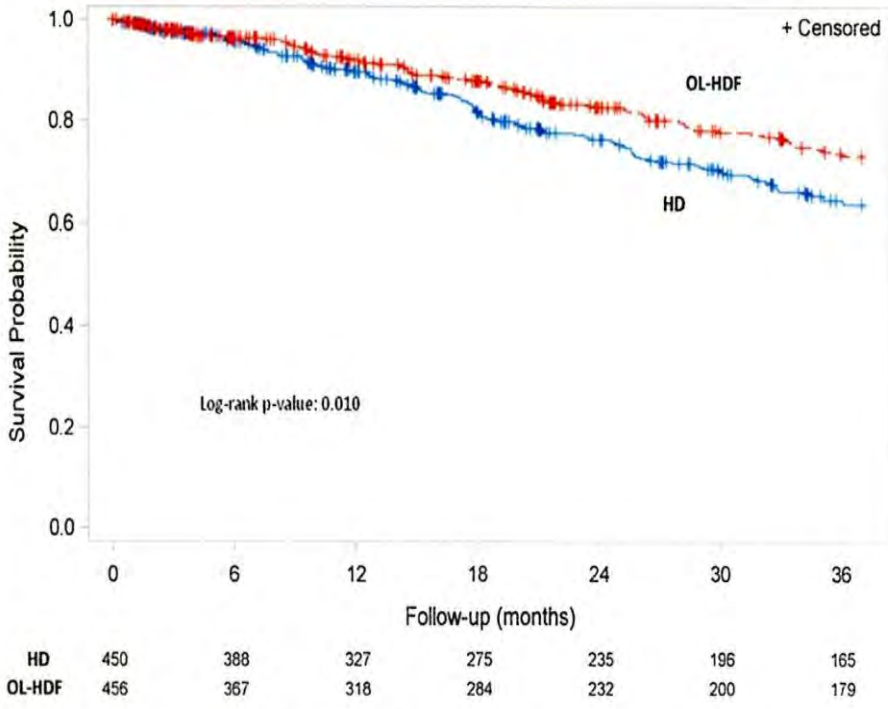

Figure 2. Kaplan–Meier curves for 36-month survival in the intention-to-treat population (P=0.01 by the log-rank test). HD, hemodialysis.

We found that high-efficiency OL-HDF (>24L) in patients with ESRD on hemodialysis was associated with a 30 % reduction in all-cause mortality compared with conventional high-flux hemodialysis

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Impact of high convective volume

Study name	Threshold volume for suvival benefit (observational studies)
DOPPS (Canaud) 2006	> 15 L
Riscarid (Panichi) 2008	> 23 L
Contrast (Grooteman) 2012	> 21.95 L
Purkush (Ok) 2012	> 17.4 L
ESHOL (Madrid/Maduell) 2013	> 23.1 L
Minimal convective volume, post dilution	? 3 L/m²/h or 12- 15L/m²/session
or predilution (easier to achieve)	?18-27 L/m²/session

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Impact of high convective volume

Study name	Threshold volume for suvival benefit	% patients not achieving target « postdilution » volume
DOPPS (Canaud) 2006	> 15 L	
Riscarid (Panichi) 2008	> 23 L	
Contrast (Grooteman) 2012	> 21.95 L	>30 %
Purkush (Ok) 2012	> 17.4 L	> 30 %
ESHOL (Madrid) 2013	> 23.1 L	10-15 %
Minimal convective volume ?	? 3 L/m²/h	**Autosub technology ?** **Pre/post mixed ?**

Daily OL HDF and high dialysis dose : combined outcomes in children

- Daily dialysis, reduced all the « uremic » peaks: urea and phosphate, overhydratation/dehydratation, and allowed a « free » diet, therefore induced « accepted »nutrition, all together+++conducting to
- A rescue therapy for cardiac impairement
- An EPO saver (?), a phosphate binder saver (phosphate clearance, and cellular shift)
- A well being factor with return to «feeling life» : no or only limited diet restrictions, no fatigue, no fighting for only «suboptimal» compliance, optimal social life immediately before and after a session (no recovery time)
- child compliance, team motivation : a «new start» with reduced cardiovascular risks….and growth impact ?…catch up growth

Daily on line hemodiafiltration : a pilot trial in children. Fischbach, J. Terzic, V. Laugel, C. Dheu, S. Menouer, P. Helms, A.Livolsi. Nephrol Dial Transplant 2004 ; 19 :2360-7

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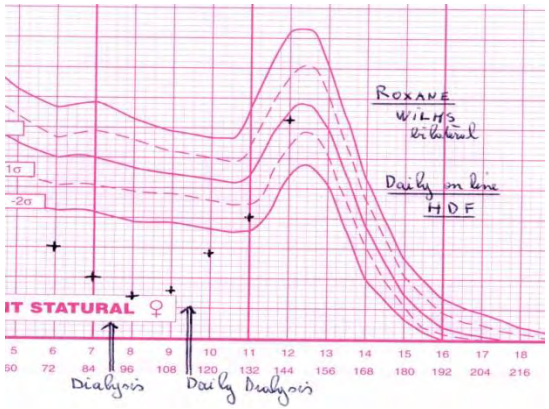
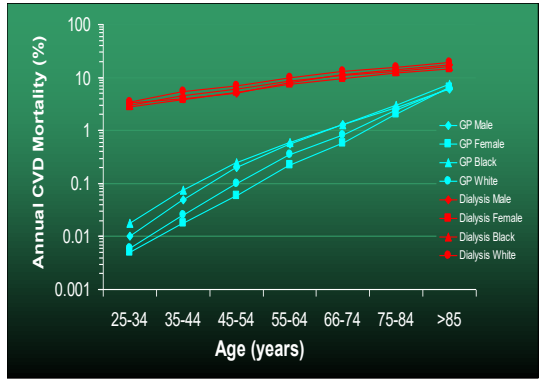
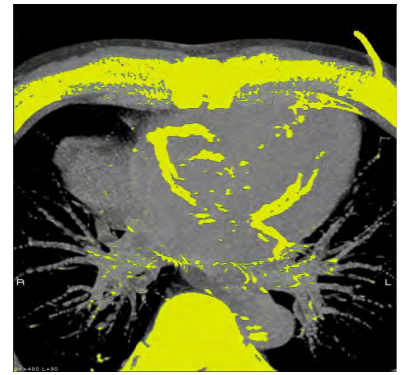
Intensive daily dialysis : pilot experiences

- A hope for catch up growth in children on chronic dialysis ?
- A hope for long term decreased cardiovascular risks ?
- A hope for residual renal diuresis preservation ???







Dialysis care should not compromise the future life for all the children waiting a too long time before kidney transplantation

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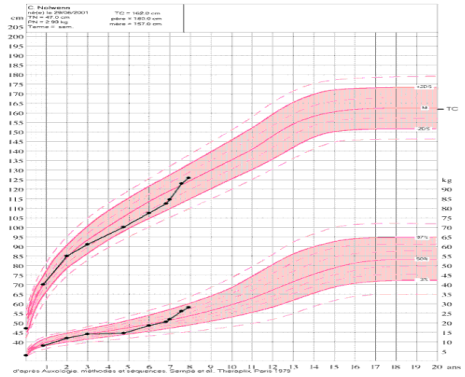
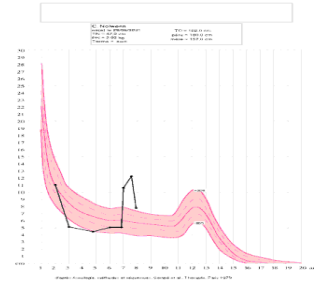
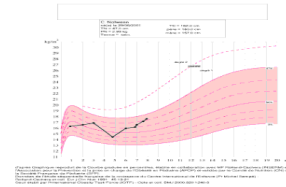
Daily on line HDF (high efficiency HDF) promotes catchup growth in children on chronic dialysis

FISCHBACH M, TERZIC J, MENOUER S, DHEU C, SEUGE L, ZALOSCZIC A.

Nephrol Dial Transplant 2010; 25: 867-73







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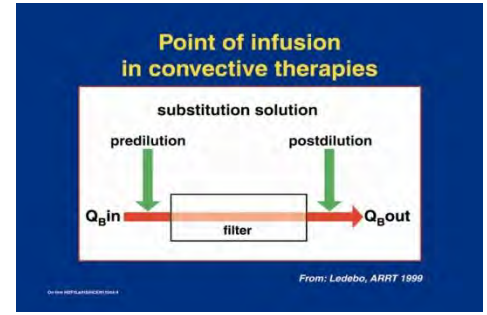
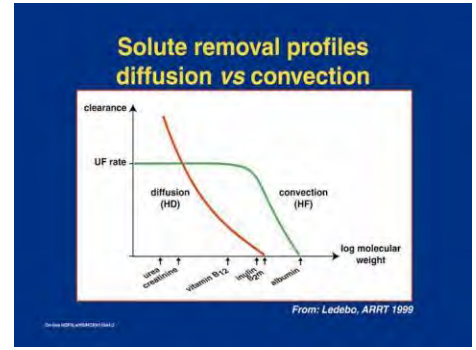
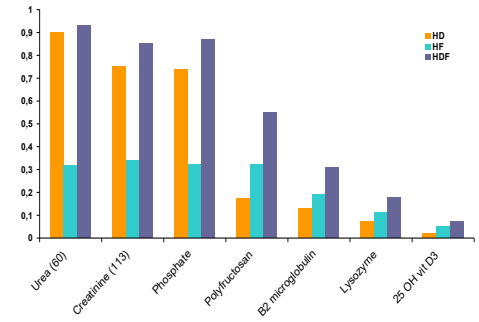
Dialysis regimen : in center daily on-line HDF

- In center daily on line HDF : since september 2002; N= 24
- 6 times 3 hour session (18h/week) treatments,
- Biocompatible, highly permeable dialysers (FX40 or FX60 polysulphone; age adapted), ultrapure dialysate, predilution hemofiltrate substitution
- Dialysis machines used were Fresenius 4008 (Fresenius Medical Care, Bad Homburg, Germany).
- The dialysis parameters (blood flow, dialysate flow, predilution reinfusion flow) were prescribed to achieve a Kt/Vurea of at least 1.4 per session;
  Kt/Vurea was assessed at each session by the on line clearance monitoring (OCM; Fresenius 4008 machine).







Intensified and Dialy Dialysis (OL-HDF) : less protein wasting, less cachexia

Increase in BMI (kg/m^2), pre 16.5+/-2.0 to post 18.0+/-2.4 ($p<0.01$) without any sign of overhydration : muscular mass increase ?

Change in growth velocity(cm/year),from 3.8+/-1.1 to 8.9+/-3.8 (peak 14.3+/-2.2)

Diet protein intake, mean 2.5+/-0.2

nPNA, mean 1.35+/-0.12

CRP in 13/15 <4mg/L but in two cases (chronic bronchitis, ciliopathy) 47 and 32

TAD urea 2.54+/-0.4

TAD bicar 0.65+/-0.13

less malnutrition (appetite , free diet)

less cachexia (proteasome ubiquitin system): growth, less protein wasting

Improved physical activity, less sleep disturbances

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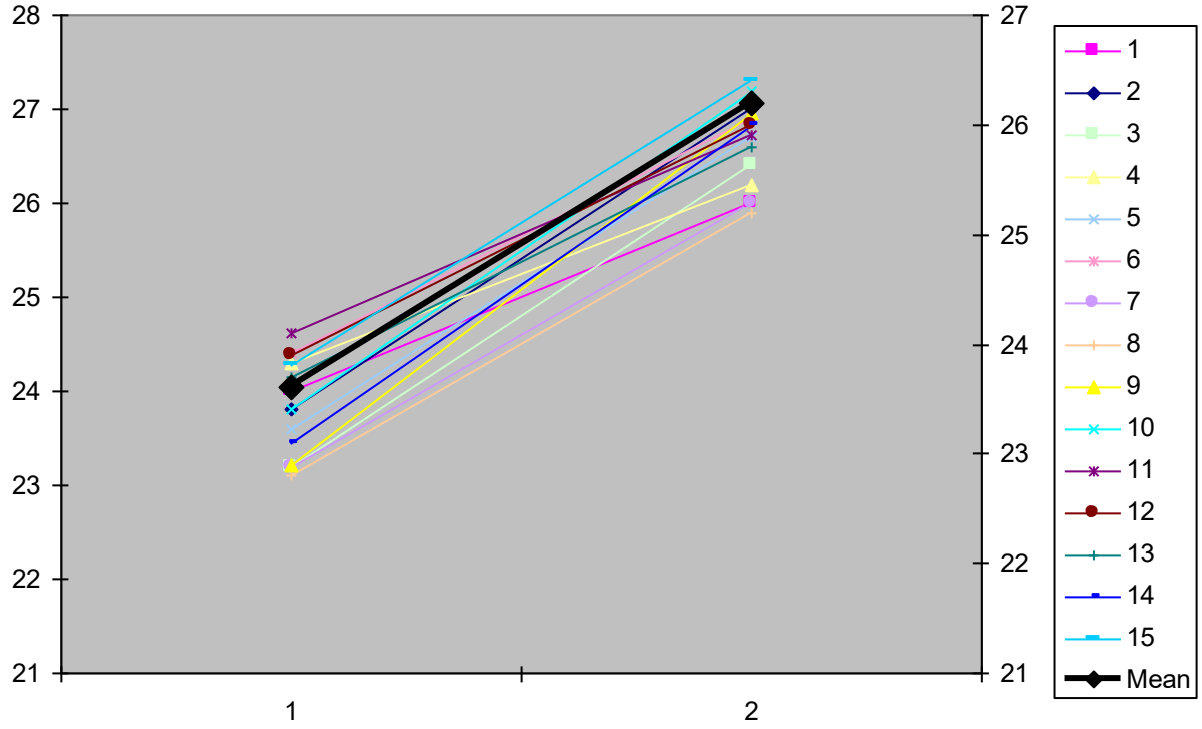
Fig. 1 : Bicarbonatemia, measured pre post dialysis session, mean of monthly determinations over the patient follow up on daily on line hemodiafiltration (dialysate bicarbonate 32mml/L)



Serum bicarbonate and mortality in stage 3 and stage 4 CKD

S.D. Navaneethan et al. Clin J Am Soc Nephrol 2011; 6:2395-2402

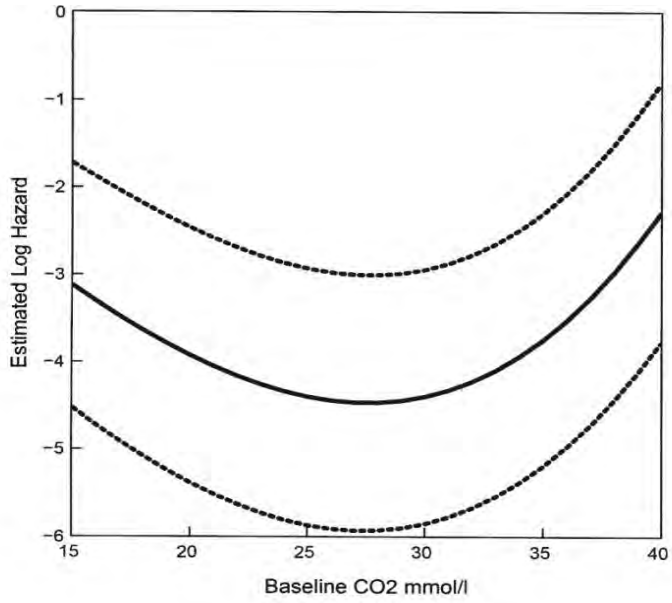


Figure 3. | Associations (log hazard and 95% confidence interval) between all-cause mortality and baseline serum bicarbonate levels. Model adjusted for age, gender, African-American race, body mass index, diabetes, hypertension, hyperlipidemia, malignancy, congestive heart failure, cerebrovascular disease, and coronary artery disease at chronic kidney disease diagnosis and estimated GFR, use of renin-angiotensin system blockers and diuretics, hemoglobin and albumin.

When serum bicarbonate was examined as a continuous variable, a J-shaped relationship was noted between serum bicarbonate and mortality

Results

- Mean time on daily OL-HDF (untill KTP): 20.5+/-8 months
- Growth velocity:

  the year before daily: 3.8+/-1.1 cm/y

  first year of daily: 14.3+/-3.8 cm/y

  mean over daily: 8.9+/-2.2

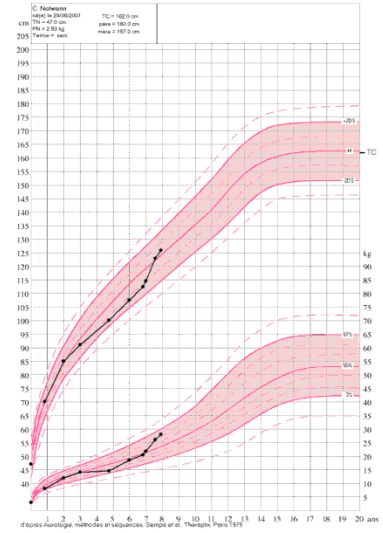
- Height (SDS)

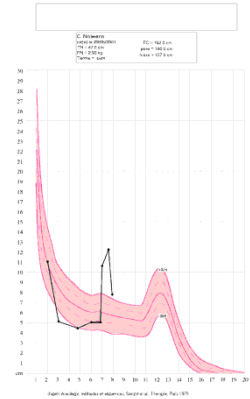
  start: -1.5+/-0.3

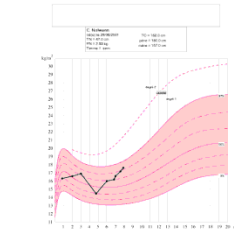
  end: +0.2+/1.1

  target parental height: -0.3

  end- target: +0.5

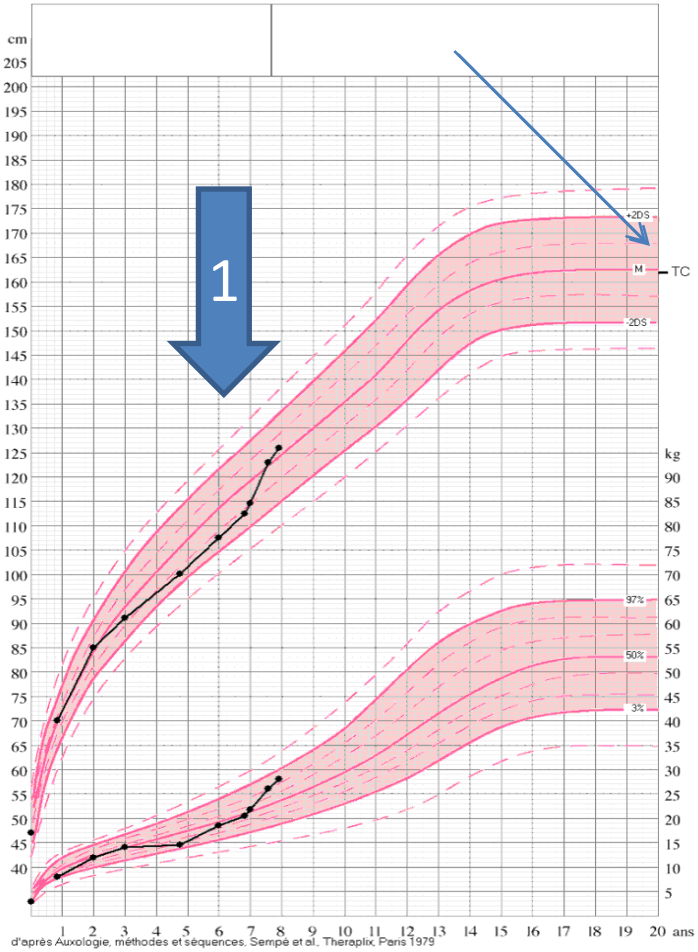


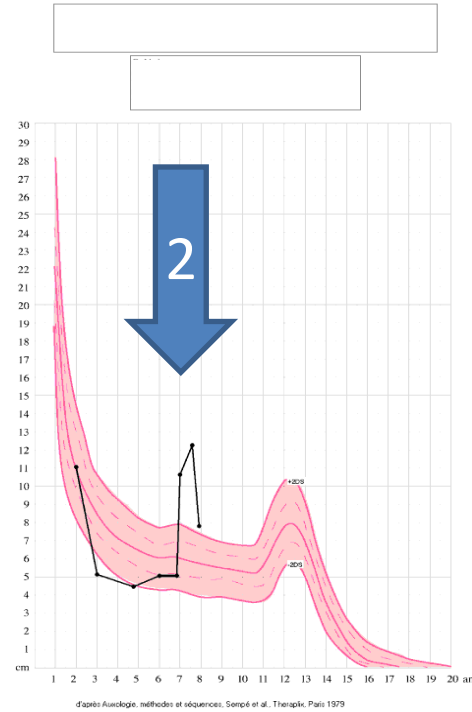


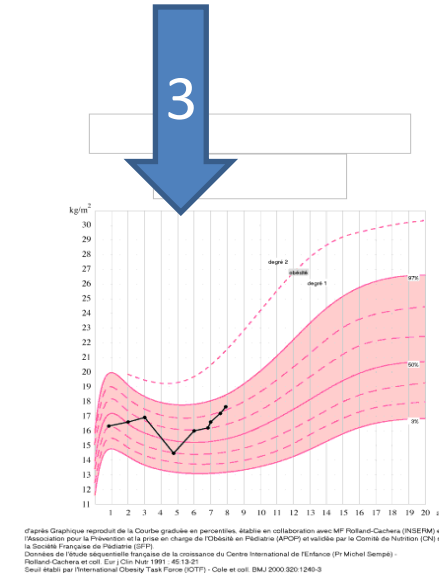


Patient 1 on daily OL-HDF

PDI (g/kg/d) : 2.7 ± 0.2
nPNA (g/kg/d) : 1.44 ± 0.15
Mean growth velocity (cm/year) : 10.4
Achieved height versus familial expected height (SDS) : +0.2







1 growth in SD 2 growth velocity 3 BMI

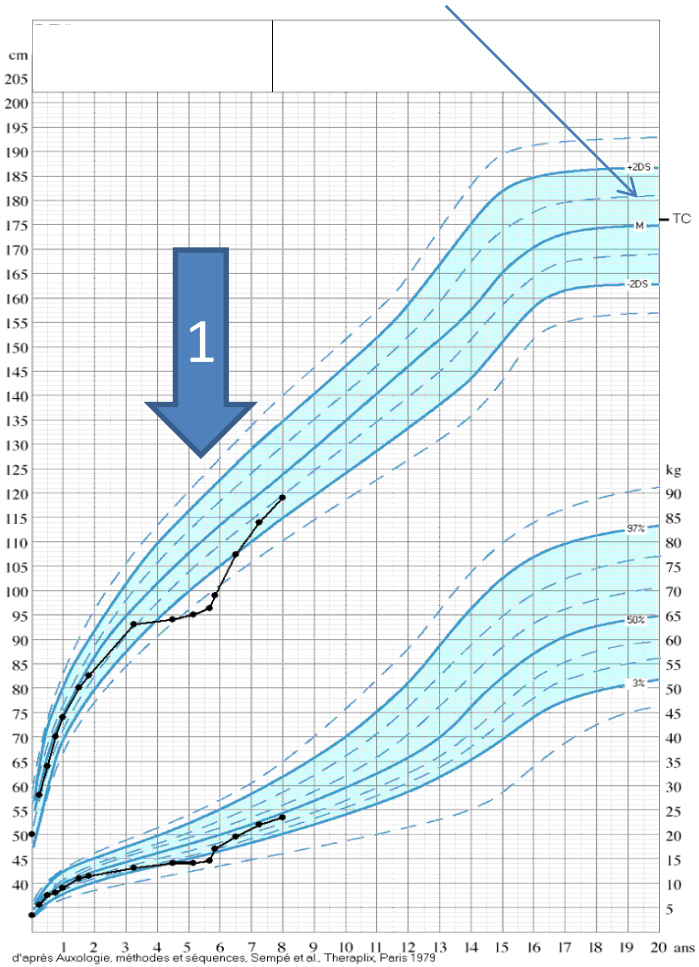
Patient 2 on daily OL-HDF

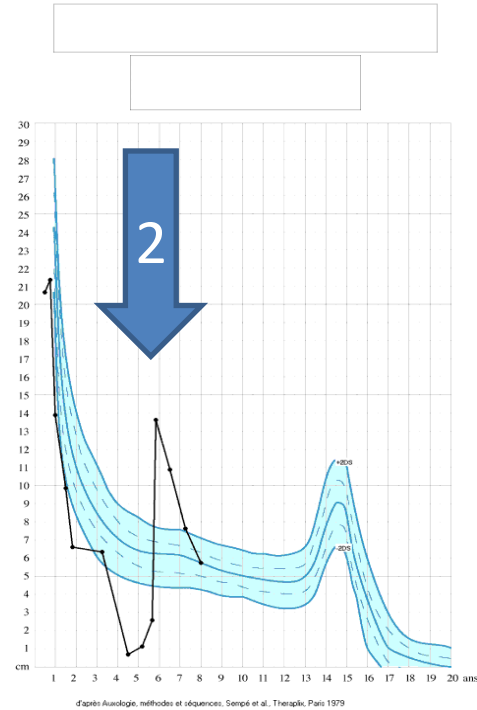
PDI (g/kg/d) : 2.9 ± 0.3

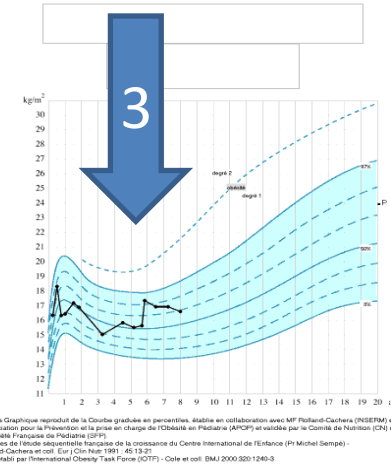
nPNA (g/kg/d) : 1.31 ± 0.11

Mean growth velocity (cm/year) : 8.1

Achieved height versus familial expected height (SDS) : -1.3

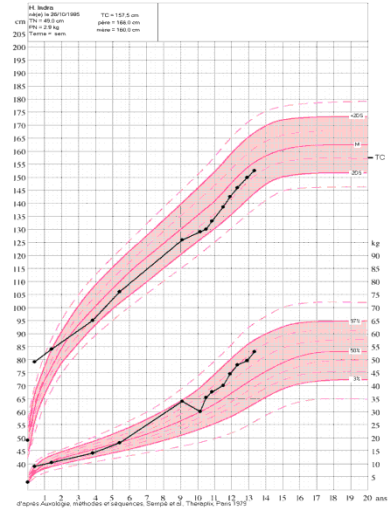


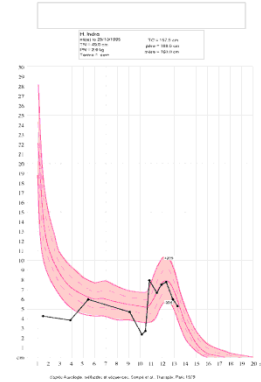


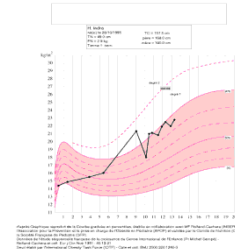


1 growth in SD 2 growth velocity 3 BMI

Results







- BMI kg/m^2 (%)

  start of daily 16.5±2.0 (48±24)

  end of daily 18.0±2.4 (65±26)

- Diet protein intake, mean 2.5+/-0.2 (g/kg/d)
- nPNA, mean 1.35+/-0.12 (g/kg/d)
- CRP in 13/15, <4mg/L but in two cases (chronic bronchitis, ciliopathy) 47 and 32mg/L
- β_2 microglobuline (predialysis) 15.3±3.3 mg/L
- TAD urea 2.4+/- 0.5; TAD bicar 0.65+/-0.13

Intensified and daily hemodialysis in children might improve statural growth. Fischbach M, Terzic J, Menouer S, Dheu C, Soskin S, Helmstetter A, Burger MC Pediatr Nephrol (2006) 21:1746-52

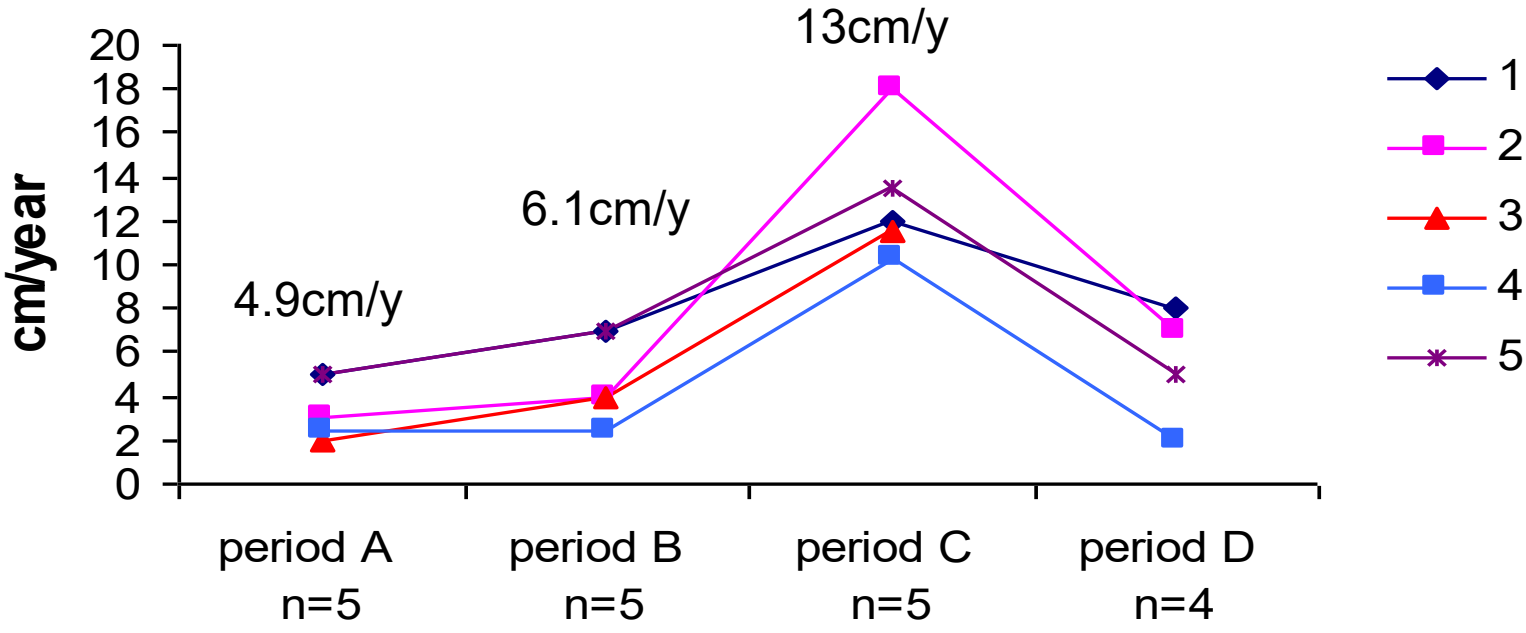


Fig. 3 Normalized individual median growth rate (cm/year) between the considered periods of treatment :
period A : conventional dialysis without rhGH ; period B : conventional dialysis under rhGH therapy ;
period C : intensified-daily dialysis ; period D : transplanted up to last follow up
* P< 0.001 : period C versus period A (and B)
**P<0.05 : period D versus period C
NS : not statistically different, period B versus period A
n : number of patients

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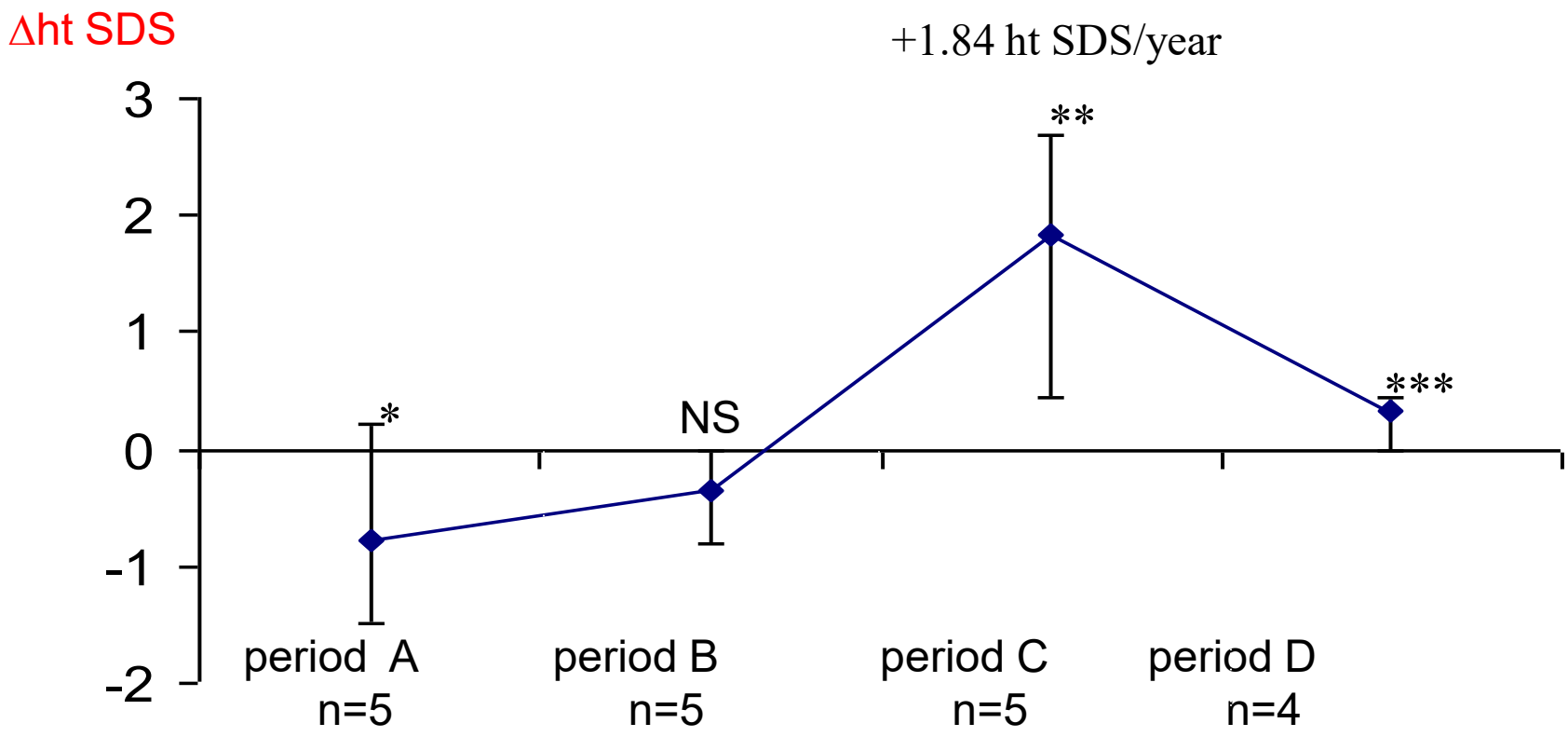

Fig. 2 Median (range) normalized height standard changes (Δ ht SDS per year) between the considered periods of treatment : period A :conventional dialysis without rhGH ; period B : conventional dialysis under rhGH therapy ; period C :intensified-daily dialysis ; period D : transplanted up to last follow up

* P<0.01 : period C versus period A and period C versus period B

**P<0.05 : period D versus period C, period D versus period A and period D versus period B

NS : not statistically different, period B versus period A

n : number of patients

Fischbach M et al Pediatr Nephrol (2006) 21:1746-52

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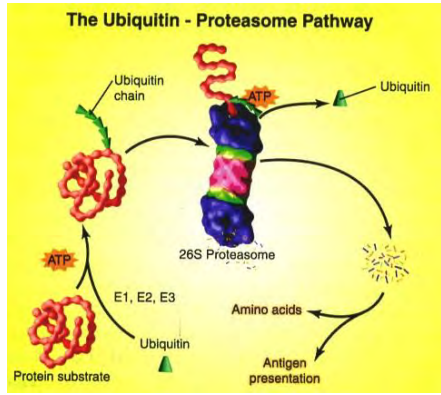
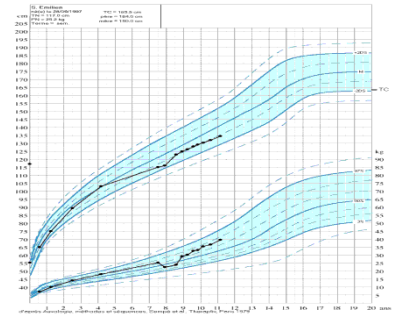
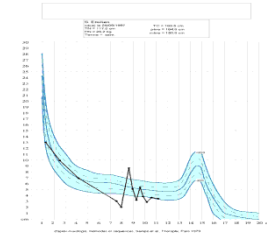
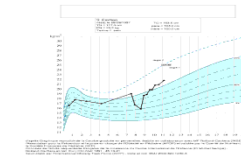
This anabolic impact of daily HDF (***intensified dialysis, large convective volume, high efficiency HDF***) is presumed to be secondary to many factors, like :

- *better cardiovascular control (BP, LVH)*
- *less acidosis, less inflammation*
- *improved nutririon : less malnutrition, less cachexia*
- *improved uremic toxins detoxification ($\beta_2$microglobuline)*
- *improved physical activity, less sleep disturbances*









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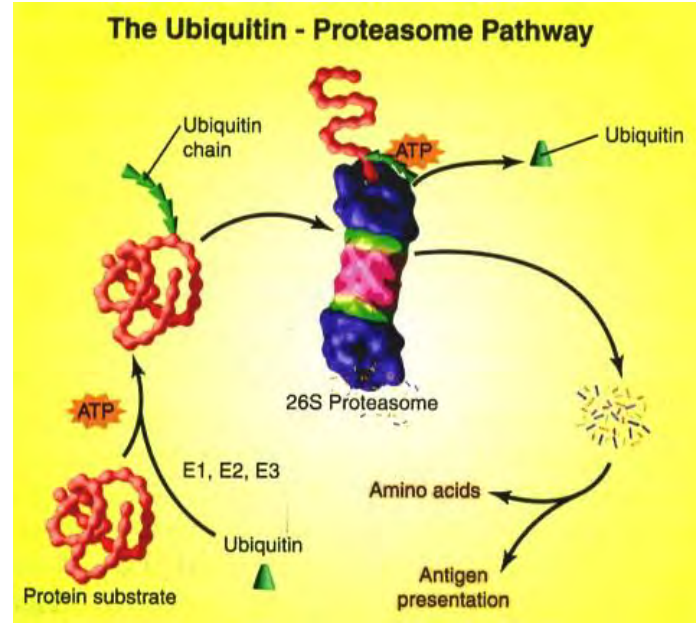
Cachexia in uremic patients : loss of protein stores,muscle wasting, growth impairment :

ATP-dependent, ubiquitin-proteasome system

- Metabolic acidosis+++
- Inflammation++
- Insuline resistance (PTH)
- GH-IGF1 axis anomalies
- Increased glucocorticoids production
- High levels of angiotensine II



Muscle wasting in chronic kidney disease : the role of the ubiquitine proteasome system and its clinical impact
VR Royan, WE Mitch. Pediatr Nephrol 2008; 23:527-35

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anabolism

catabolism

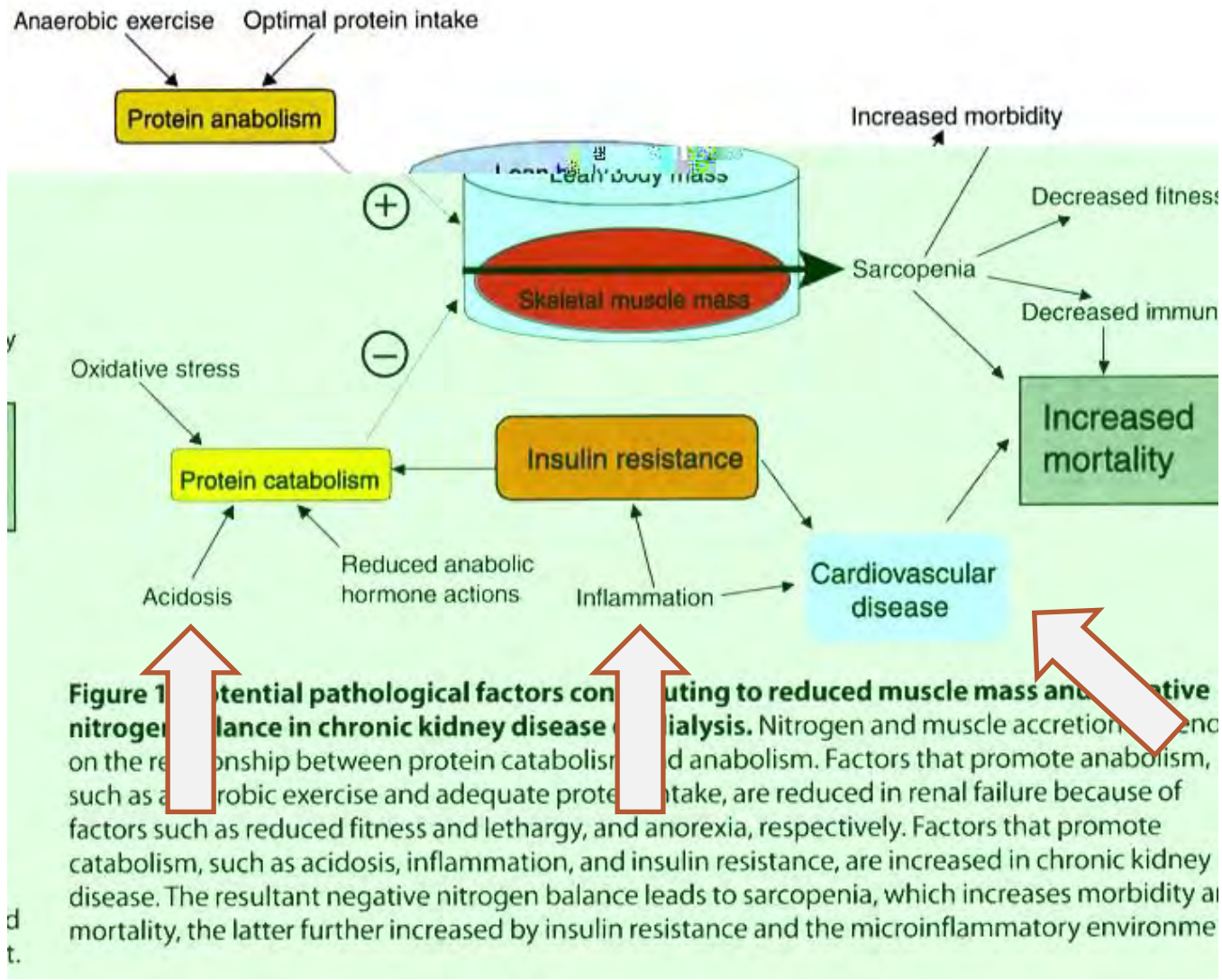

Figure 1 **…otential pathological factors con…uting to reduced muscle mass and …tive nitroge… …lance in chronic kidney disease (…ialysis.** Nitrogen and muscle accretion …enc on the re… …onship between protein catabolism … …d anabolism. Factors that promote anabolism, such as a… …robic exercise and adequate prote… …take, are reduced in renal failure because of factors such as reduced fitness and lethargy, and anorexia, respectively. Factors that promote catabolism, such as acidosis, inflammation, and insulin resistance, are increased in chronic kidney disease. The resultant negative nitrogen balance leads to sarcopenia, which increases morbidity a… mortality, the latter further increased by insulin resistance and the microinflammatory environme…

O'Sullivan AJ, Kelly JJ (2007) Insulin resistance and protein catabolism in non-diabetic hemodialysis patients. Kidney Int 71 :98-100

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OL-HDF in infants/children :

Extracorporeal fill volume : availability of lines for small children

Predilution/postdilution : HT, proteins, in practice easier in predilution mode (need for adapted substitution volume, $Q_{HF}=Q_B$)

Blood restitution : limit the amount of saline (air restitution? risks/benefits)

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OL-HDF in infants > 7/10 kg :

FX3 (30mL), baby lines postdilution (54mL),
children lines (75mL) predilution

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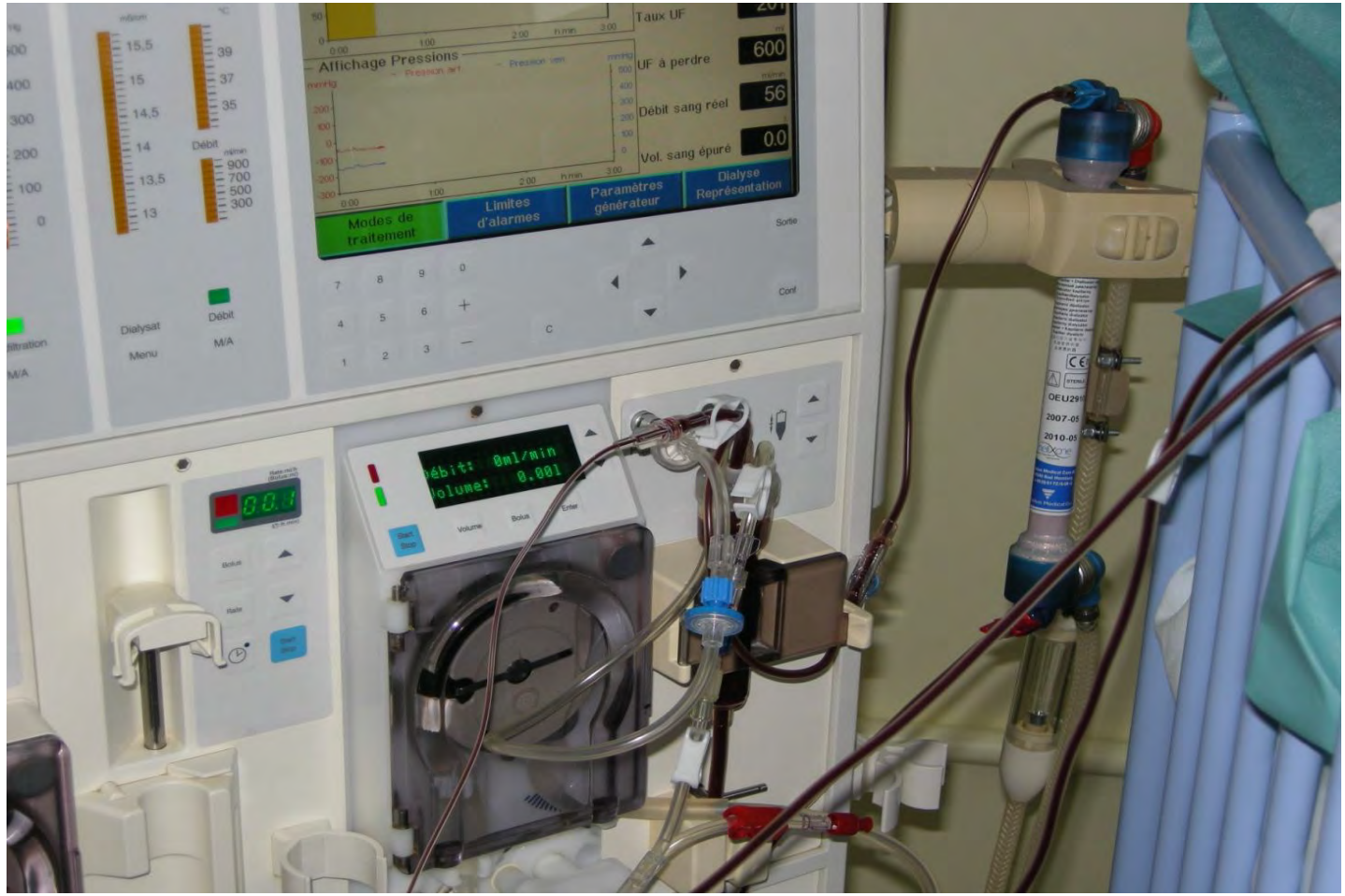
Baby arterial line and children veinous line



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OL-HDF in infants / children feasability and material availability

- « baby lines » 56mL, no arterial chamber, postdilution, « children lines » 78mL, arterial chamber, predilution, possibility to mix the lines
  babyArt +chlidrenVei=60/65mL
- dialyzers for HDF : F3 (0.6m2/32mL), FX40 (0.8m2/42mL)
- Thus HDF predilution in infants needs nearly 100mL extracorporeal fill volume(>8kg; without need for pre filling the tubes with blood)

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HDF versus HD : advantages

- Hemodynamic stability over the session : increased tolerance to weight loss and blood pression control improvement (**hemofiltration effect**) : osmotic stability, compartiment preservation, peripheral vascular resistances, myocardial contractility
- Optimal blood purification capacities both for urea and middle molecular weight compounds : high level dialysis dose easely achieved . A high dialysis dose usually induce a good nutrition status, especially with an increased caloric intake (apetite)

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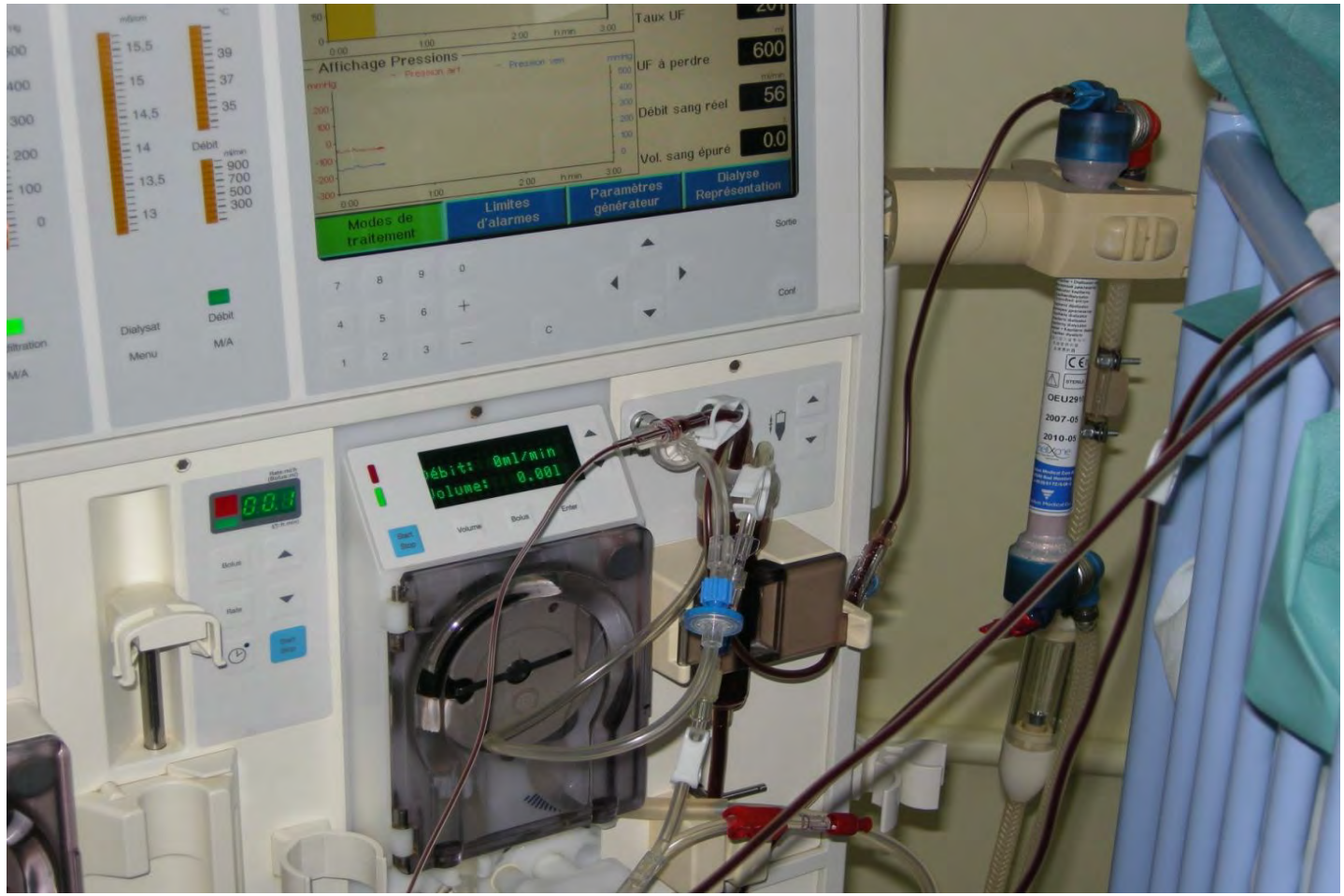
OL-HDF in infants :

FX3, baby lines


Affichage Pressions
Taux UF
UF à perdre
600
Débit sang réel
56
Vol. sang épuré
0.0
Modes de traitement
Limites d'alarmes
Paramètres générateur
Dialyse Représentation
Sortie
Conf
Dialysat
Menu
Débit
M/A
Débit
Volume
Bolus
Enter
Start Stop

Correction of metabolic acidosis in HD patients should be aimed for :

- to reduce the risk of mortality and morbidity
- to increase serum albumin levels and
- to reduce protein catabolism (nPNA)

Fouque D et al (2007) Guideline 6. Metabolic acidosis. Nephrol Dial Transplant 22(suppl 2):ii77-8

Fouque D et al (2008)
A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease.
Kidney Int 73:391-398

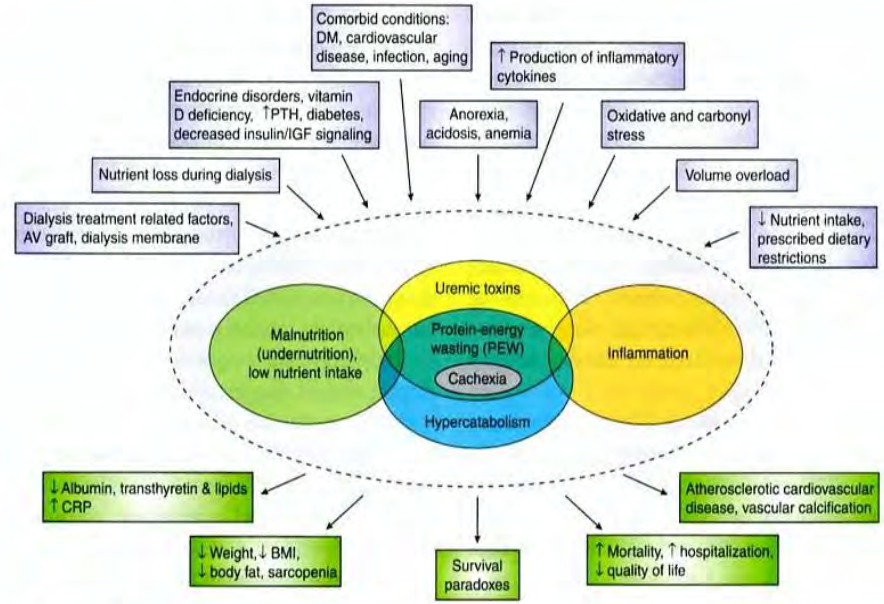


Figure 1 | Schematic representation of the causes and manifestations of the protein-energy wasting syndrome in kidney disease.

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Acidosis prevents growth hormone-induced growth in experimental uremia

C. Kleinknecht, S. Maniar, X. Zhou et al. Pediatr Nephrol 1996; 10:256-260

- The presence of severe metabolic acidosis blunts the response to GH in uremic and non-uremic rats : protein wasting
- Plasma IGF_1 was unrelated to pH or HCO_3-
- ESRF rats treated by rhGH:
  - Animals acidotic: mean bicar 11.5 mmol/l
  - Animals corrected for their acidosis : mean bicar 26 mmol/l
- Conclusion : there is a resistance to rhGH or IGF_1 in the presence of severe metabolic acidosis, conducting to weight and height loss (protein wasting, cachexia)

Effects of uremia and inflammation on growth hormone resistance in patients with CKD

G. Garibotto et al. Kidney Int 2008; 74:937-45

- Besides uremia per se, the effectiveness of GH might be attenuated by factors often found in CKD patietns, such as inflammation, metabolic acidosis, and low nutrient intake
- Uremia with inflammation, but no uremia per se, inhibits downstream growth hormone signaling contributing to muscle atrophy (in humans CKD) and blunts tissu potassium uptake

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Conclusions:

anabolic impact of daily high efficiency HDF

- Comfort, tolerance : reduced (suppressed?) dialysis morbidity; no/less recovery time, no/few medications
- Improved nutrition, more appetite, less diet restrictions, less fatigue , more physical activity
- Optimized uremic detoxification, better acidosis correction, limited inflammation : less protein wasting, less cachexia
- Cardiovascular protection : BP, hydration, inflammation
- Anabolisme, catch up growth

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Survival in pediatric dialysis and transplant patients

Samuel SM et al. and the Pediatric Renal Outcomes Canada Group.Clin J Am Nephrol 2011; 6:1094-1099

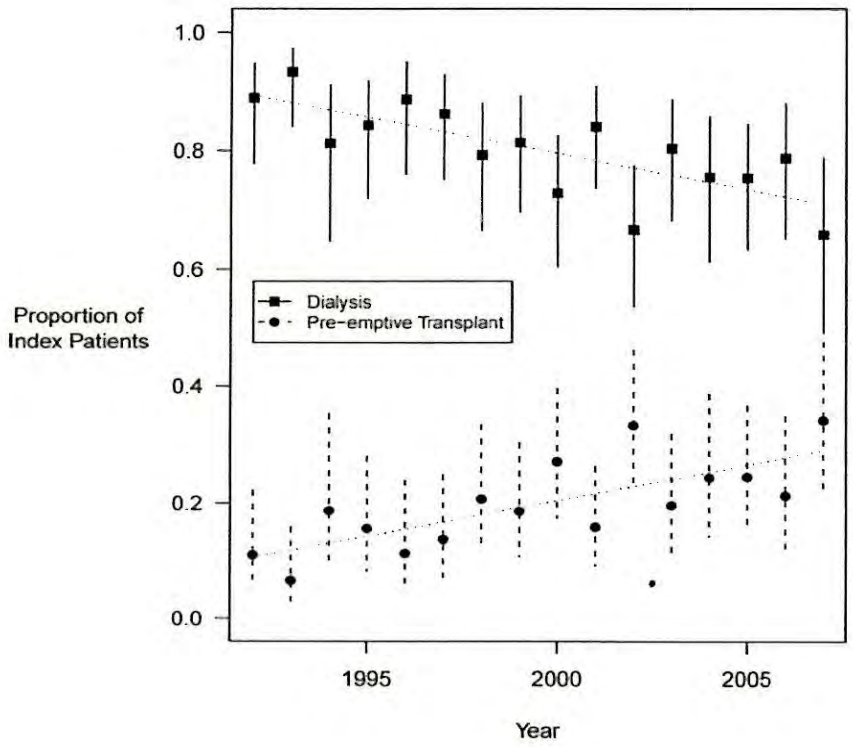

Figure 1. | Trends in initial renal replacement modality among pediatric ESRD patients in Canada. A chi-squared test was used to test for trends in proportions ($P < 0.001$).

We included 843 children (ages 0 to 18) initiating renal replacement therapy from 1992 to 2007 and followed them until death or date of last contact (median follow-up 6.8 years; interquartile range, 3.0 to 10.6)

During 5991 patients-years of follow-up 107 (12.7 %) patients died.

Pre-emptively transplanted patients did not demonstrate superior adjusted survival compared with those who spent>2 years on dialysis before transplant.

No significant improvements in survival were observed among ESRD patients over the study period.

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Hemodialysis Fluids Purity

Conventional dialysis fluid is defined as having a bacterial count of<100 CFU/ml and endotoxin count of <0.25 EU/ml.

Ultrapure dialysis fluid has a bacterial count of <0.1 CFU/ml and endotoxin count of <0.05 EU/ml.

The “purity” of on-line substitution fluid should be:
<1 CFU/500 ml and <0.05 EU/ml. (with the use of modern technology, a result of <0.005 EU/ml is now possible)

Note that the volume of the sample tested may vary, and hence the results should always be expressed per 500 ml of on-line substitution fluid tested

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Endotoxin level: not detectable
CHU Strasbourg 2012

N° Générateur : 00/00624

Dialysat		**Résultats**	**Niveau cible**
Flore aérobie revivifiable à 22°C	E 3921	< 1 UFC/100ml	< 10 UFC/100ml
Endotoxines bactériennes	E 3923	< 0,005 UI/ml	< 0,25 UI/ml

Solution de substitution		**Résultats**	**Niveau cible**
Flore aérobie revivifiable à 22°C	E 3922	< 1 UFC/500ml	< 1 UFC/500ml
Endotoxines bactériennes	E 3924	< 0,005 UI/ml	< 0,05 UI/ml

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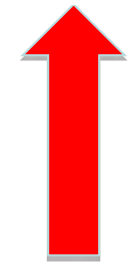
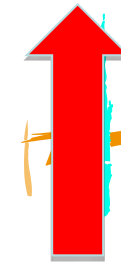
Endotoxin level: not detectable
CHU Strasbourg 2014

Dialysat :	N° analyse	Résultats	Niveau d'alerte*	Niveau d'action*
Flore aérobie revivifiable à 22°C	E 6813	< 1 UFC/100ml	< 5 UFC/100ml	< 10 UFC/100ml
Endotoxines bactériennes	E 6815	< 0,005 UI/ml	< 0.015 UI/ml	< 0.03 UI/ml

Solution de Substitution :	N°analyse	Résultats	Niveau d'alerte*	Niveau d'action*
Flore aérobie revivifiable à 22°C	E 6814	< 1 UFC/500ml	< 1 UFC/500ml	< 1 UFC/500ml
Endotoxines bactériennes	E 6816	< 0,005 UI/ml	< 0.015 UI/ml	< 0.03 UI/ml

* d'après la norme internationale ISO 23500:2011





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ISO 23500:2011/2014

Guidance for the preparation and quality management of fluids for haemodialysis and related therapies

Dialysat :	N° analyse	Résultats	Niveau d'alerte*	Niveau d'action*
Flore aérobie revivifiable à 22°C	E 6813	< 1 UFC/100ml	< 5 UFC/100ml	< 10 UFC/100ml
Endotoxines bactériennes	E 6815	< 0,005 UI/ml	< 0.015 UI/ml	< 0.03 UI/ml

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* d'après la norme internationale ISO 23500:2011

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water quality

- Adequate in terms of biochemical composition (Aluminium)
- The purity, in terms of microbial contaminants, measured as colony forming units (CFU) and endotoxin units (EU) are defined in the different fluids used for dialysis. *Nystrand R (2009) Official recommendations for quality of fluids in dialysis –the need for standardisation. Journal of Renal Care, 35: 74–81*
- *Standard quality dialysis fluid* (bacterial count <100 CFU/ml ; endotoxin <0.50 EU/ml) is not appropriate for use with high flux HD, due to the internal convective flow i.e. the back filtration. High flux dialysis needs *ultrapure dialysate* (bacterial count <10 CFU/100ml ; endotoxin <0. 25 EU/ml)
- *one line substitution fluid purity* (filtered ultrapure dialysate): sterile and non pyrogenic (germ free sterile : 0 UFC/liter; endotoxin free : < 0.05 UI/ml)

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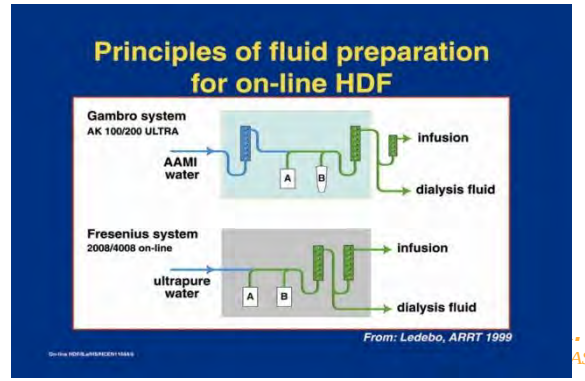
- But several important conditions must be fulfilled :
  - ultrapure water/dialysate,
  - high quality concentrate (powder cartridge),
  - designed on line machine, effective disinfection to prevent formation of biofilm during standstill ie heat disinfection (and chemical ?),
  - education for microbiological awareness ie **no machine movements** without without completely sterilizing both the water supply and the machine.
- The combination of ultrapure water and double filtered dialysate provides a sterile and non pyrogenic substitution fluid:
  - germ free sterile : 0 UFC/liter
  - endotoxin free : < 0.05 UI/ml



Purity : biochemically and microbiologically

- Choarcal filtration (0.2 µ)
- Reverse osmosis
- Dialysate filtration
- Filtered ultrapure dialysate : on line production of hemofiltration substitution fluid

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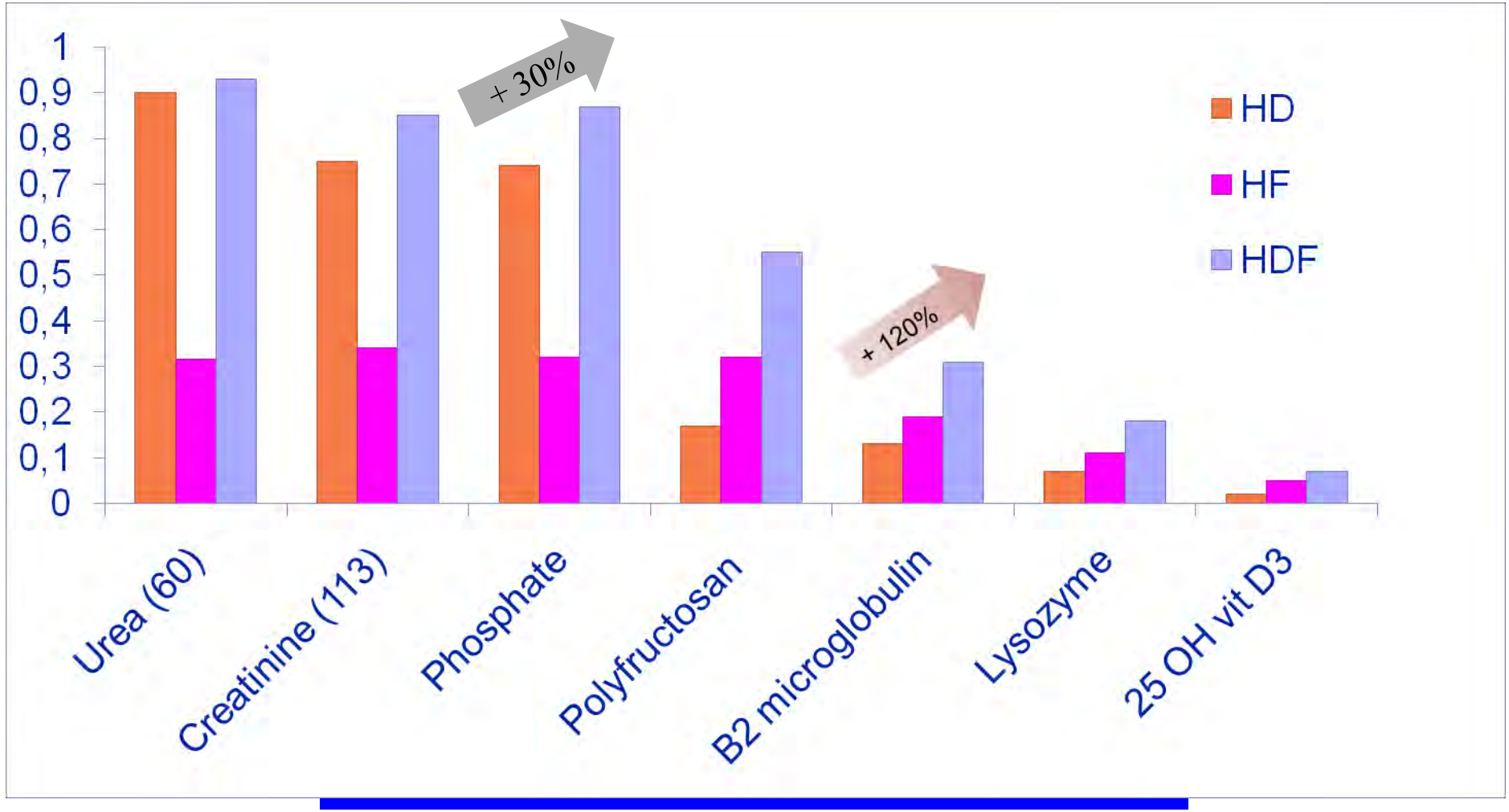

HDF allows an optimal blood purification not only for urea, but also for the middlemolecular weight compounds (Babb theory)

From M Fischbach et all .Contr Nephrol1985

Uremic toxins: which to dose?

Urea (Kt/V) as surrogate (diffusion) and β2 microglobulin or **the convective volume** (convection)?

Focusing on middle molecules...Convective dialysis dose

Small water soluble solutes
Asymmetric dimethylarginine
Benzylalcohol
ß-Guanidinopropionic acid
ß-Lipotropin
Creatinine
Cytidine
Guanidine
Guanidinoacetic acid
Guanidinosuccinic acid
Hypoxanthine
Malondialdehyde
Methylguanidine
Myoinositol
Orotic acid
Orotidine
Oxalate
Pseudouridine
Symmetric dimethylarginine
Urea
Uric acid
Xanthine

*CMPF is carboxy-methyl-propyl-furanpropionic acid

Protein-bound solutes
3-Deoxyglucosone
CMPF*
Fructoselysine
Glyoxal
Hippuric acid
Homocysteine
Hydroquinone
Indole-3-acetic acid
Indoxyl sulfate
Kinurenine
Kynurenic acid
Methylglyoxal
N-carboxymethyllysine
P-cresol
Pentosidine
Phenol
P-OHhippuric acid
Quinolinic acid
Spermidine
Spermine

Middle molecules
Adrenomedullin
Atrial natriuretic peptide
$ß_2$-Microglobulin
ß-Endorphin
Cholecystokinin
Clara cell protein
Complement factor D
Hyaluronic acid
Interleukin 1ß
Interleukin 6
Kappa-Ig light chain
Lambda-Ig light chain
Leptin
Methionine-enkepahlin
Neuropeptide Y
Parathyroid hormone
Retinol binding protein
Tumor necrosis factor alpha

Middle molecules

β2 - Microglobulin

EUTox European Uremic Toxin Work Group of the ESAO

Vanholder R. et al New insights in uremic toxins. *Kidney Int*, 2003, 63; 84: S6–S10

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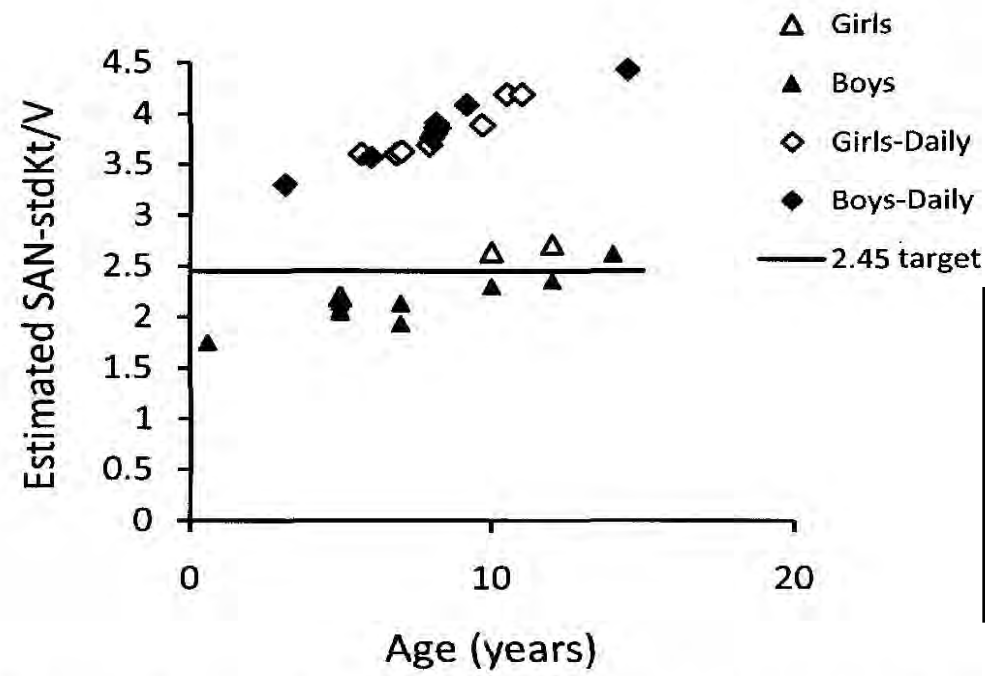
Dialysis dose and growth

(**Surface area normalized standard Kt/V: SAN**)

Daugirdas JT et al. Clin J Am So Nephro 2010, 5:821-827

Over 2.45



Fischbach et al.
NDT 2010

Could be Kt/Vurea a marker of dialysis adequacy? A surrogate+++

Figure 6. Estimated SAN-stdKt/V *versus* age in two studies in which increased growth rates were linked to intensified dialysis regimens, one with hemodialysis treatments given 3 times/wk by Tom *et al.* (10) and one using 6-times/wk hemodiafiltration by Fischbach *et al.* (11).

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Hemodiafiltration:
The addition of convective flow to hemodialysis:
"a complete dialysis dose".

M. Fischbach, H. Fothergill, A. Zaloszyc, L. Seuge Pediatr Nephrol 2012, 27: 351-6

HDF offers a complete dialysis dose: *not only an urea dialysis dose i.e. diffusive dose expressed as Kt/V urea, but also a convective dialysis dose i.e. convective volume per session.*

Hemodiafiltration is without doubt superior to HD with low flux membranes, although this is difficult to prove in prospective, randomized studies.

It is hoped that ongoing studies will definitively demonstrate the differences in patient outcome achieved with on-line HDF compared to high flux HD, only a non determined small convective volume with dialysate as substitution fluid (dialysate "purity"/endotoxins level).

When given on a daily basis, on-line HDF offers the "perfect stimulus package" for inducing catch up growth in children : no protein wasting.

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Impact of convective flow on phosphorus removal in maintenance haemodialysis patients

W.Lornoy et al. J. Ren Nutr 2006: 47-53

This study revealed a higher phosphorus removal and phosphorus reduction rate with postdilutional on-line HDF compared to high-flux HD. *Long-term use of on-line HDF therefore may have a positive impact on the cardiovascular status of the patients*

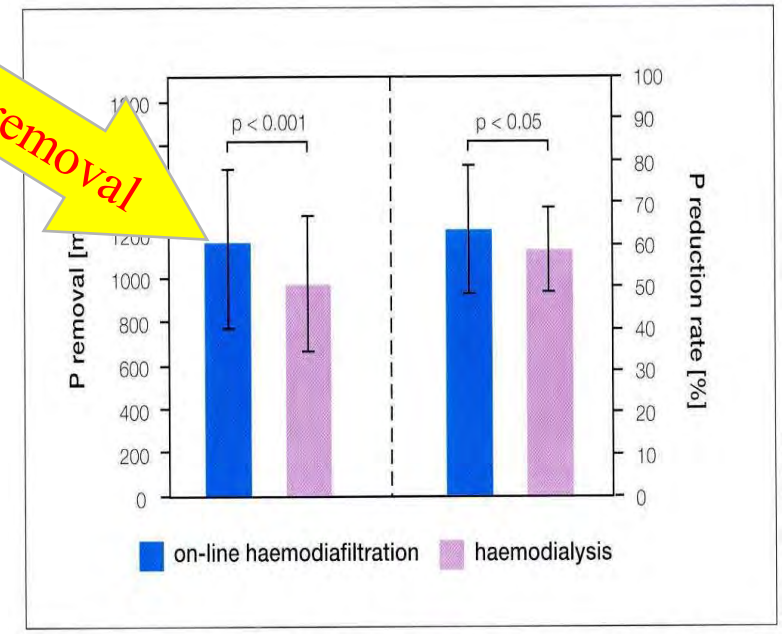

Fig. 4: *Phosphorus removal in total spent dialysate and ultrafiltrate and phosphorus reduction rate in oHDF and HD*

Phosphate should be considered as a MMW uremic toxin in terms of dialysis purification : water molecular environment; importance of the convection (HDF)

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The effect of dialysis modality on phosphate control : HD compared to HDF.

The Pan Thames Renal Audit

A. Davenport et al. Nephrol Dial Transplant 2010; 25:897-901

- HDF offers improved phosphate control compared to standard intermittent HD

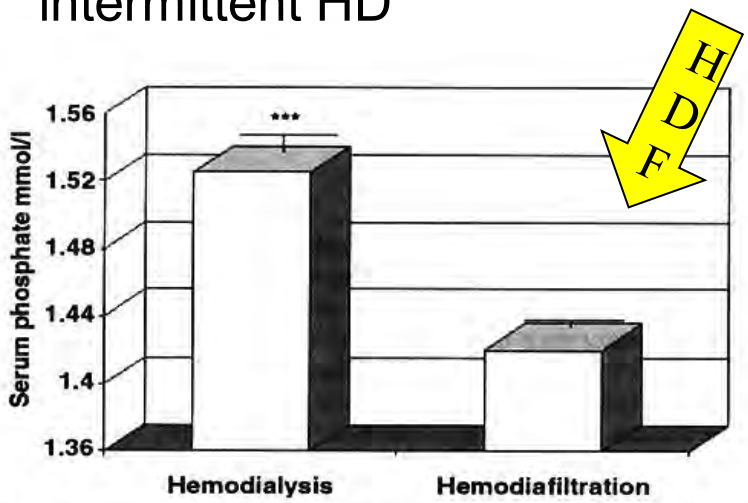

Fig. 1. Serum phosphate in hemodialysis and hemodiafiltration cohorts. Data expressed as mean (SEM). ***$P < 0.001$.

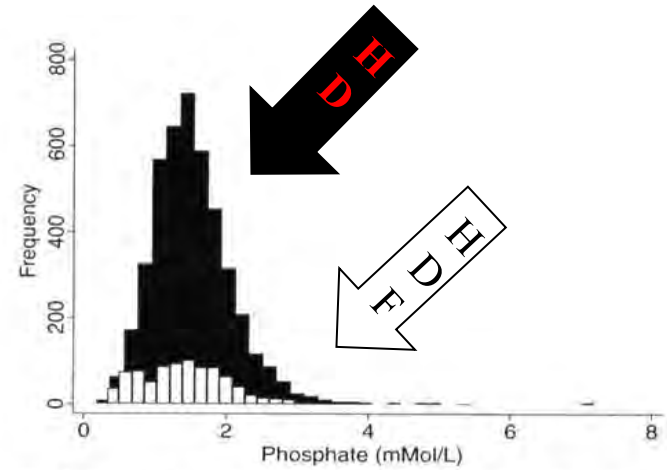

Fig. 2. Frequency distribution curves of the pre-dialysis midweek serum phosphate concentrations in the haemodialysis patients (black bars) and haemodiafiltration patients (white bars).

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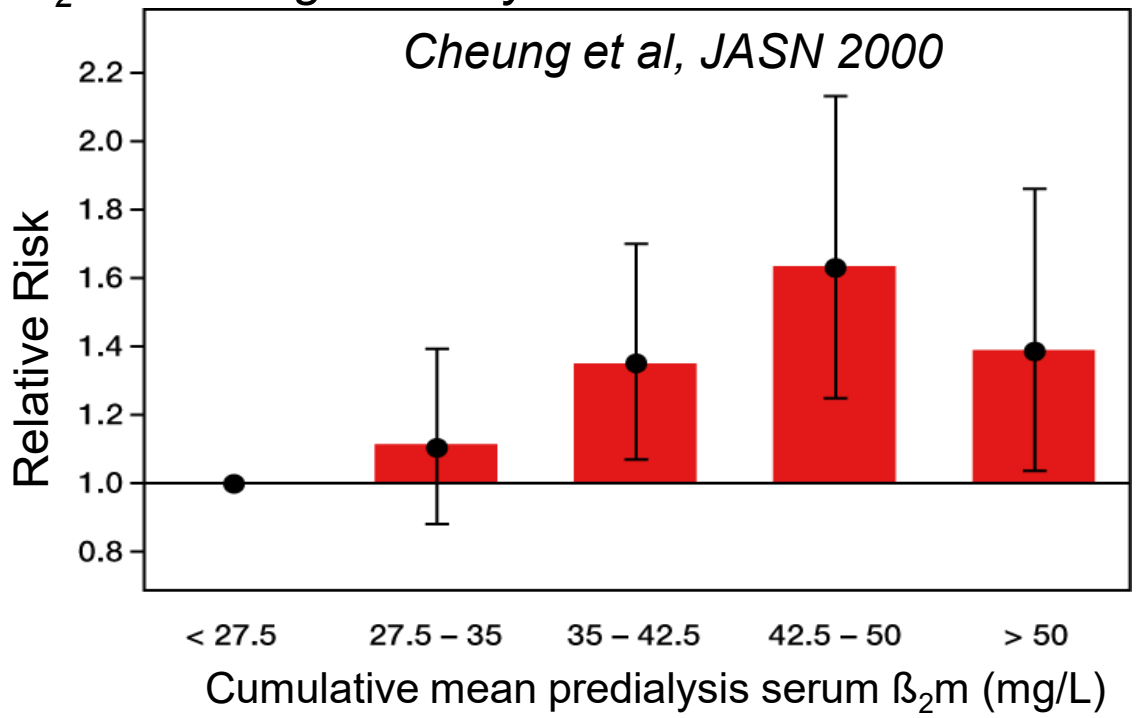
Serum β_2m levels and mortality in the HEMO study : less than 27.5 is ”better”

Predialysis ß$_2$m level significantly correlated with all-cause mortality (p= 0.001)



n =1 813

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Optimal Hemodialysis Prescription: Do children need more than a urea dialysis dose? the importance of the convective volume

M Fischbach et al. Inter J Nephrol 2011

1) Dialysis: diffusion (HD), convection (HF) and combination therapy (HDF) : uremic toxins removal
2) Kt/V urea: diffusive dialysis dose (HD)
3) Convective volume (HF, HDF): **β_2 microglobulin, phosphate**
4) A complete dialysis dose : Kt/V urea (>1.4) and the convective volume (?, >14L postdilution /adult; impact on β_2 microglobulin, phosphate)

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Impact of treatment time :

Longer treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality in the DOPPS. Saran R et all Kidney Int. 2006;69(7):1222-8.

1) UF rate /session time/ ECV control : a UF over 10mL/h/kg BW is a mortality risk factor
2) Phosphate, the “sillent killer” : phosphate dialytic removal is time and clearance dependent
3) Nutrition and phosphate diet intake versus kelators medication acceptance/compliance
4) Effect of « all the middle molecular weight uremic toxins »
5) In conclusion, increased treatment time :
   - Increased patient survival
   - Is synergic with Kt/V
   - No ideal, unique treatment time, but at least adjusted to : UF rate, Phosphatemia, weight (uremic toxins are produced by the viscera/muscles, but not by TBW)

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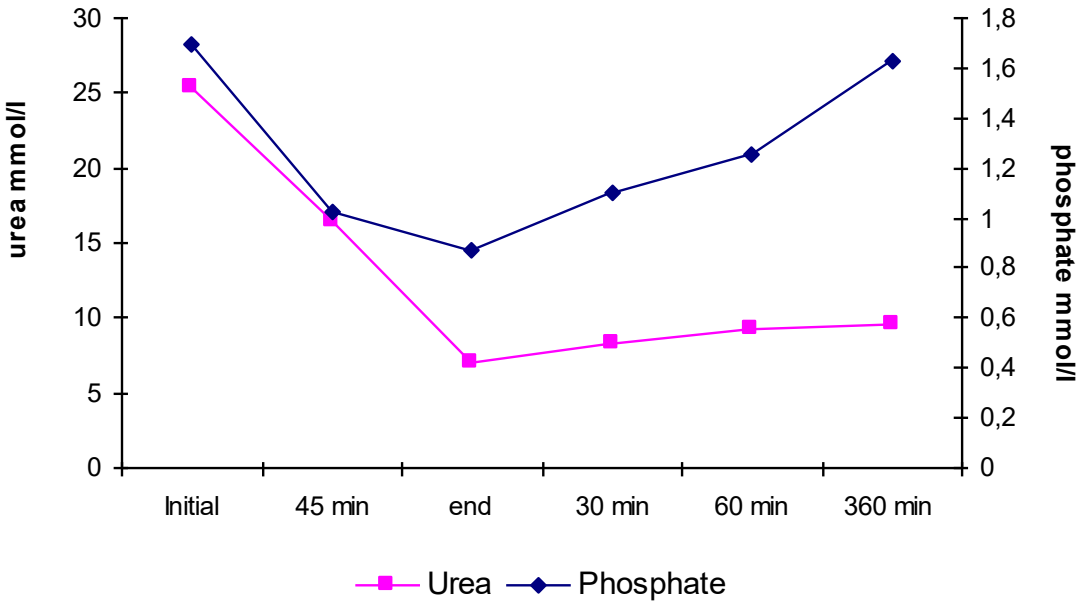
Phosphate end dialysis value : a misleading parameter of hemodialysis efficiency

M. Fischbach, B. Boudailliez, M. Foulard, and the French Society for Pediatric Nephrology Ped Nephrol 1997; 11:193-195

Urea and phosphate serum levels over dialysis and postdialysis time in the studied children population(n : number of dialysis sessions)



Postdialytic phosphate rebound

- End + 60 min : 45±19 %
- End + 360 min : 89±23 %
- Longer duration than for urea
- Importance of the rebound
- False value of the end session phosphate level

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Introduction

- If dialysis is a need, the best available modality of treatment should be proposed to provide an excellent dialysis comfort despite assuring an optimal high dialysis dose over an acceptable, short dialysis session duration time …more than high flux membranes, that is HDF….and over all daily on-line HDF
- Hemodiafiltration (HDF) reflects most the relevant progresses acquired in the last 20/25 years for hemodialysis (HD) management :
  - dialysate purity and membrane biocompatibility (chronic inflamation /cachexia),
  - global purification capacity: « a complete dialysis dose », a determined diffusive dose (Kt/Vurea) and a determined convective dose (convective volume/phosphate/ $ß_2$-microglobulin) , and
  - optimal hemodynamic tolerance (HF)

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- In our center we used HDF for mostly all children on chronic HD since July 1981, treating a total of 129 new patients (2002)
- Initially, we have choosen HDF in children for :
  - the potential impact of combined dialysis therapies during the same session time, both convective therapy ie hemofiltration (HF) and diffusive therapy ie hemodialysis (HD) , and for
  - the hemofiltration specific impact on blood pressure control capacity , tolerance of weight loss/control of hypertension
  - And for dialysate/membrane biocompatibility/purity : beta2microglubulin storry (amyloidosis, marker of purification/outcome)

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High convective volume : need for a change of the dialysis composition (Na_D) ?

- We learned the need fo Na_D decrease to avoid sodium positive dialysis balance even conducting to « dialysis induced hypertension »
- Ali R, 3 years old, on daily HDF, was converted to Autosub + HDF. With the same blood flow (80 ml/min) the predilution flow rate increased from 80 to 280-300 ml/min. He became hypertensive after 4 weeks. Decreasing Na_D from 140 to 134 was suffisant to restaure normal blood pressure.

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OL-HDF in children/infants

- Bicarbonate, NaD, Ca++ in dialysate and in substitution fluid (adapt the concentrations to the enhanced exchanges, diffusion and convective volume)
- predilution modality without increased cost:
  - Feasability with « low » blood flows
  - In case of normal high Ht, less need for anticoagulation
  - Limitation of dialytic albumin loss
  - Enhanced dialysis purification capacity ?
  - Need for a blood thermic monitoring ?

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The International Journal Of Pediatric Nephrology / Vol. 5 no. 3, 1984 / p.p. 151-154

Hemodiafiltration versus hemodialysis in children

M. Fischbach, Y. Attal, J. Geisert

Service de Nephrologie et d'Hemodialyse
Service de Pediatrie 3
Hopital de Hautepierre
Strasbourg, France

TABLE I - PARAMETERS USED FOR THE STUDY

HD (12 months)	HDF (12 months)
plate (0.92 m2) cuprophane	capillary (1 m2) PAN
Q_B 120-160 ml/min	Q_B 120-160 ml/min
Q_D 500 ml/min	Q_D 500 ml/min
3 X 5 h/week	3 X 3 h/week
	substitution fluid 7-9 (lactate)
	TMP less than 300 mmHg

TABLE II - RELATIONSHIP IN 6 CHILDREN BETWEEN SERUM LEVELS OF UREA, CREATININE, PHOSPHATE IN HD AND HDF (AT START AND END OF TREATMENT SESSION)

	HD (15 h/week)		HDF (7.5 - 9 h/week)	
	start	end	start	end
urea mmol/l	40±6	16±3	32±4	6±2
creatinine µmol/l	1,080±256	410±167	810±280	240±123
phosphate mmol/l	1.65±0.28	0.9±0.19	1.34±0.15	0.5±0.08

TAC urea :

HD : 28 mmol/l
HDF :18 mmol/l

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Hemodiafiltration advantages

- Optimized hemobiocompatibility : bicarbonate dialysate, synthetic membrane, retrofiltration control
- Better anemia control

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Hemodiafiltration versus hemodialysis in children

M Fischbach, Y Attal, J Geisert, J of Pediatr Nephrol 1984; 5:151-4

Hemoglobine values and need for transfusions		
	HD (12 months)	**HDF (12 months)**
Hb g/dl	7.4	8.3
Number of transfusions for the whole group	32 (mean 5)	12 (mean 2)
Membrane	Cuprophane	Polyacrylonitrile
Duration (sessions)	3x5 h	3x3 h

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Hemodiafiltration with high permeable membranes in children

M Fischbach, G Hamel, E Tarral, J Geisert. Blood purification 1984; 2:203

	HDF PAN	HDF Polysulfone
Hb g/dl	8.3±0.3	8.9±0 .2
Need of transfusion (ml/kg)	20	10
Duration	3x3 h	3x3 h

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Hémofiltration, volume échangé (litre/séance), clairance (extraction moléculaire)

$Cl_{HF} = Q_{HF} \times Ct$

$Q_{HF} \leq 1/3\ Q_{sg}$ (post dilution)

$Q_{HF} > 1/3\ (>1/1)\ Q_{sg}$ (predilution)

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Hemodiafiltration (1)

Maduell F. Hemodialysis International 2005 ; 9:47-55

- A blood purification method must be chosen that removes the same range of uremic toxins as the native kidney
- It may be desirable to use daily dialysis treatment schedules
- Potential clinical advantages result from a combination of :
  - improved blood purification,
  - use of ultrapure dialysate and
  - more frequent treatment schedules : daily on line hemodiafiltration

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Choice of modality with the use of High-Performance Membrane and evaluation for clinical effects

Ikuo Masakane. Saito A, Kawanishita H, Yamashita AC, Mineshima M (eds):High-Performance Membrane Dialyzers. In Contrib Nephrol. Basel, Karger; 2011, vol 173, pp 84-94.

- The golden target for dialysis therapy should be to guarantee longer survival and to give a higher quality of life without dialysis-related complications.
- Generally, we choose a dialysis modality for better solute removal and better biocompatibility. In this issue we would like to propose that the patients preference for dialysis therapy is a useful parameter in prescribing the dialysis modality.
- *In our recent experience chronic dialysis patients have had preferences on a dialysis modality and membrane, and* ***pre dilution online HDF.***

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High convective volume : need for a change of the dialysate composition (Na_D) ?

At bedside, we learned the need to decrease the Na_D of the substitution fluid applying Autosub+.

We believe on the need to redefine dialysate/substitution fluid composition in case of high convective volume prescription.

Almost all children on high convective volume need of lowered Na_D, between 134 and 138 mmol/L.

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High efficiency OL-HDF : (re)consider the Na_D

Ali, 3 years old, congenital nephrotic syndrom, anuric, 14 kg BW, 0.75 m² BSA, central catheter :

On pre dilution HDF, 4008

- Blood flow 80 ml/min,
- Substitution flow 80 ml/min
- Na_D 140 mmol/L
- BP 95/47 mmHg
- CorDiax 60 (large surface area of the membrane, to achieve pre dilution flow and hope for enhanced phophate removal

Converted on HDF 5008 Autosub +

- Blood flow 80 ml/min,
- Pre dilution flow 280-300 mL/min
- Na_D 140 mmol/L
- CorDiax 60
- After 4 weeks, volume overloaded with high blood pressure 145/95 mmHg, after decreasing Na_D to 134 mmol/L : normalization of BP (95/45)

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