How to improve HD outcome in children
more convection, more time, more sessions
daily intensive hemodiafiltration

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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 hemodialysis regime still have:

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

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

- ✓ From HD to HDF (the addition of HF to HD, that is HDF, a complete dialysis dose) to OL-HDF (purity of the dialysis fluids),
- ✓ high efficiency HDF (hydraulic permeability of the membranes "Cordiax"; autosub+: viscosity control) : impact of the achieved convective volume, "high efficiency HDF"
- ✓ 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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Long term consequences of pediatric patients with end stage renal disease. LERIC (n=249)

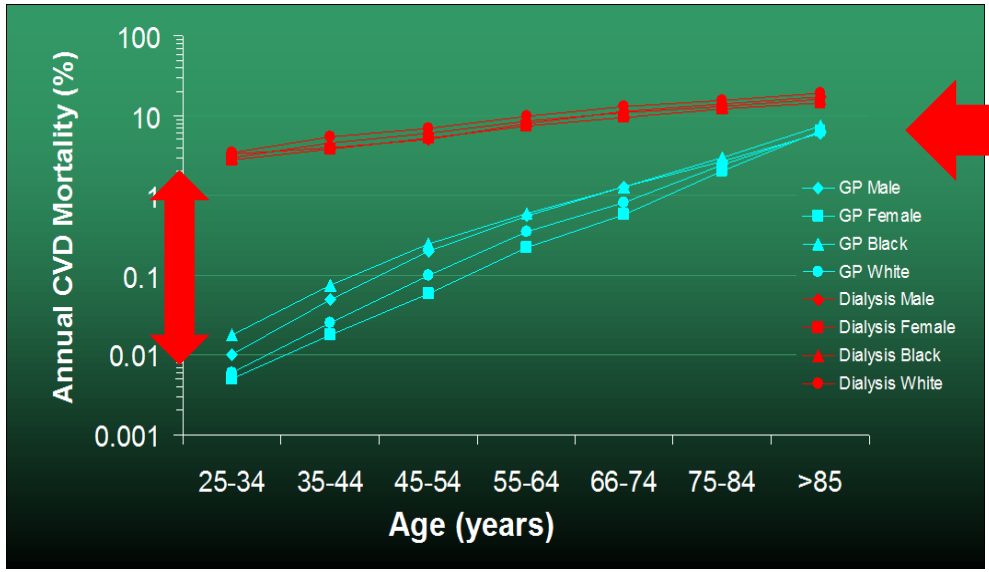
Jopp W Groothoff (Amsterdam) APN 2007

- *Higher mortality risk, especially cardiovascular death* (40 to 50 % of the deaths)
- Metabolic bone disease (osteopenia 81,6 %)
- *Growth retardation less than –2,3 DS in 2/3 of them (mean « adult » Ht : male 164 cm ; female 156 cm)*
- Malignancies (25 % of the deaths)
- Cognitive impairment, full scale IQ –10,4 (difference patients-controls)

Groothoff JW, Lihen MR, Van de Kar NCAJ, Wolff ED, Davin JC (2005) Cardiovascular disease as a late complication of end stage renal disease in children. Pediatr Nephrol 20: 374-379

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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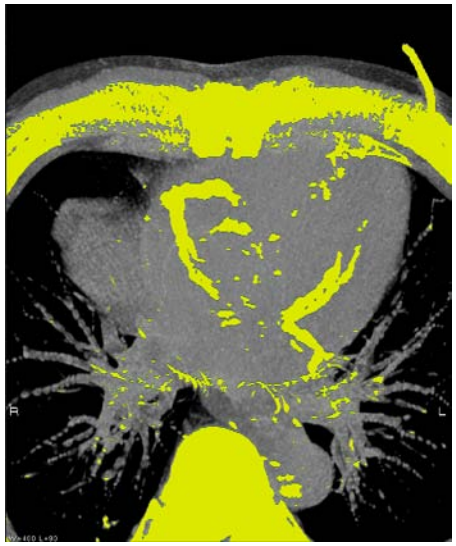
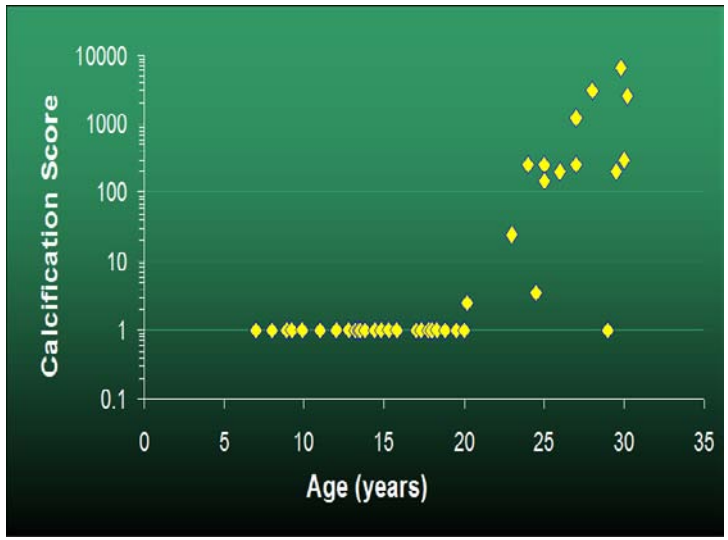
Hyperphosphatemia, a « silent killer »

(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

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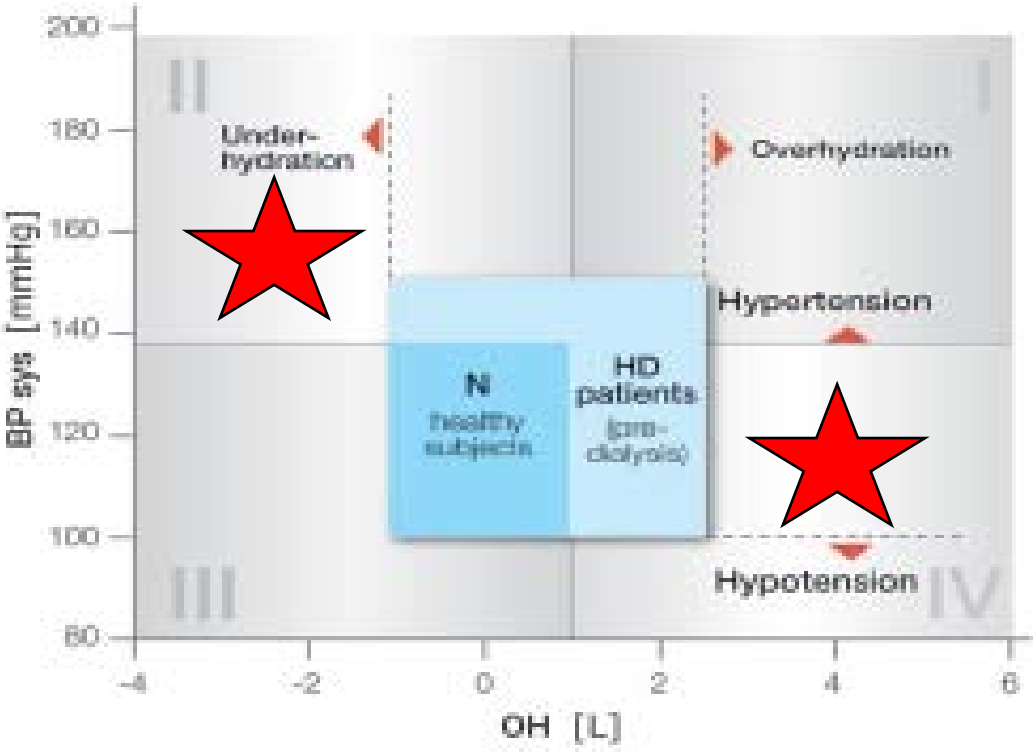
Blood Pressure versus hydration in patients on dialysis : « box plot », importance of the BCM evaluation



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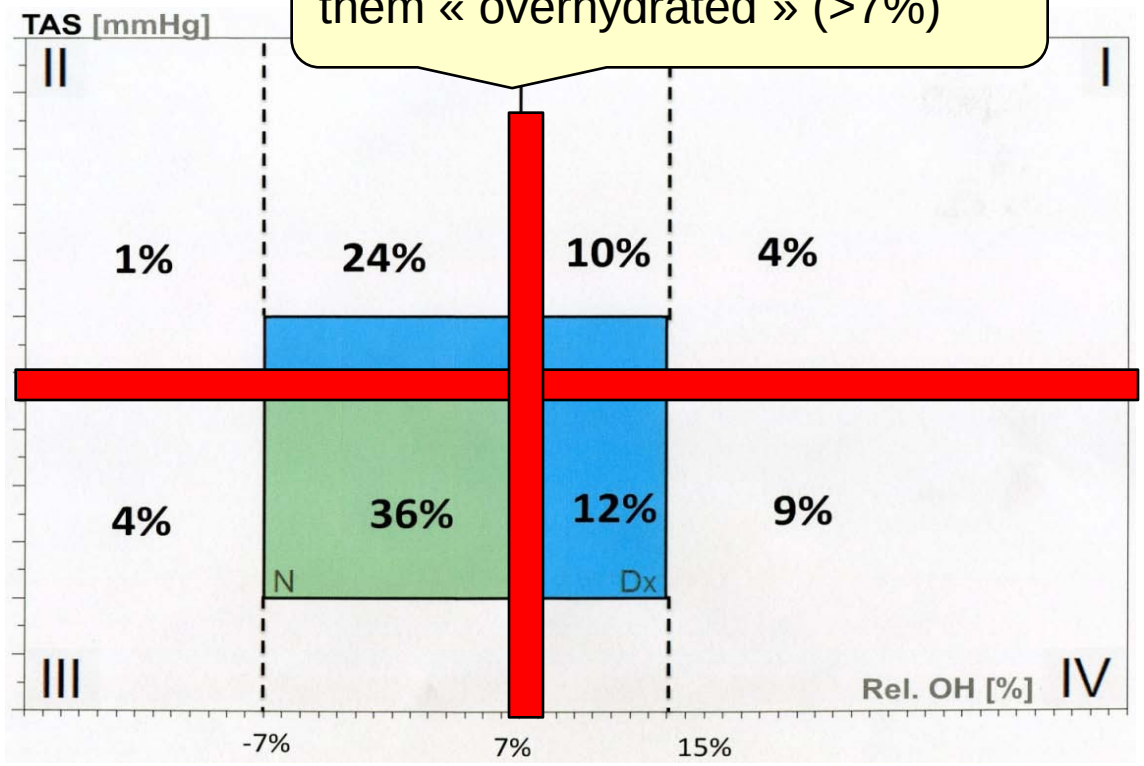
Hydration measurement by bioimpedance spectroscopy and blood pressure management in children on hemodialysis.

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*

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

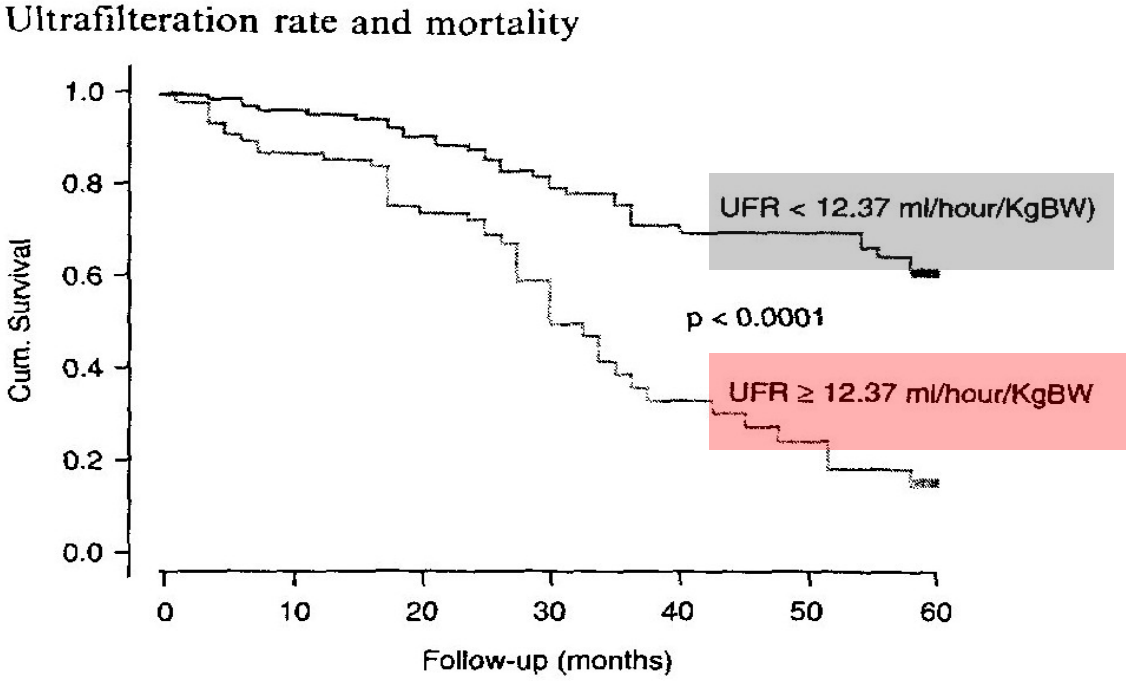

Fig. 3. Survival curves adjusted for significant predictors at Cox regression analysis by using UFR as categorical variable defined according to the receiver operating characteristic (ROC) derived UFR threshold of 12.37 ml/h/kg BW.

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 hour/session

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 the body composition assessment (BCM, bioimpedance)

Only probing a lower 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)

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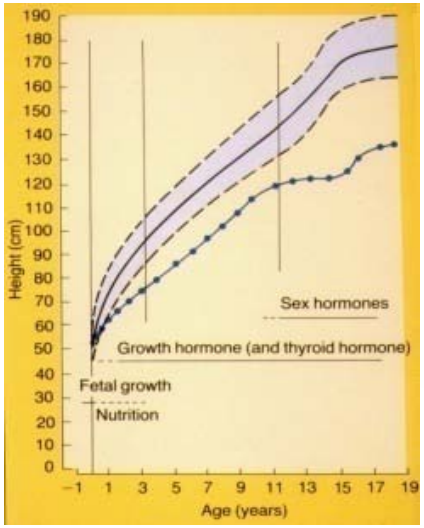
Major progress of final adult height have been made during the past decades for dialysed children, nevertheless ongoing improvement is necessary



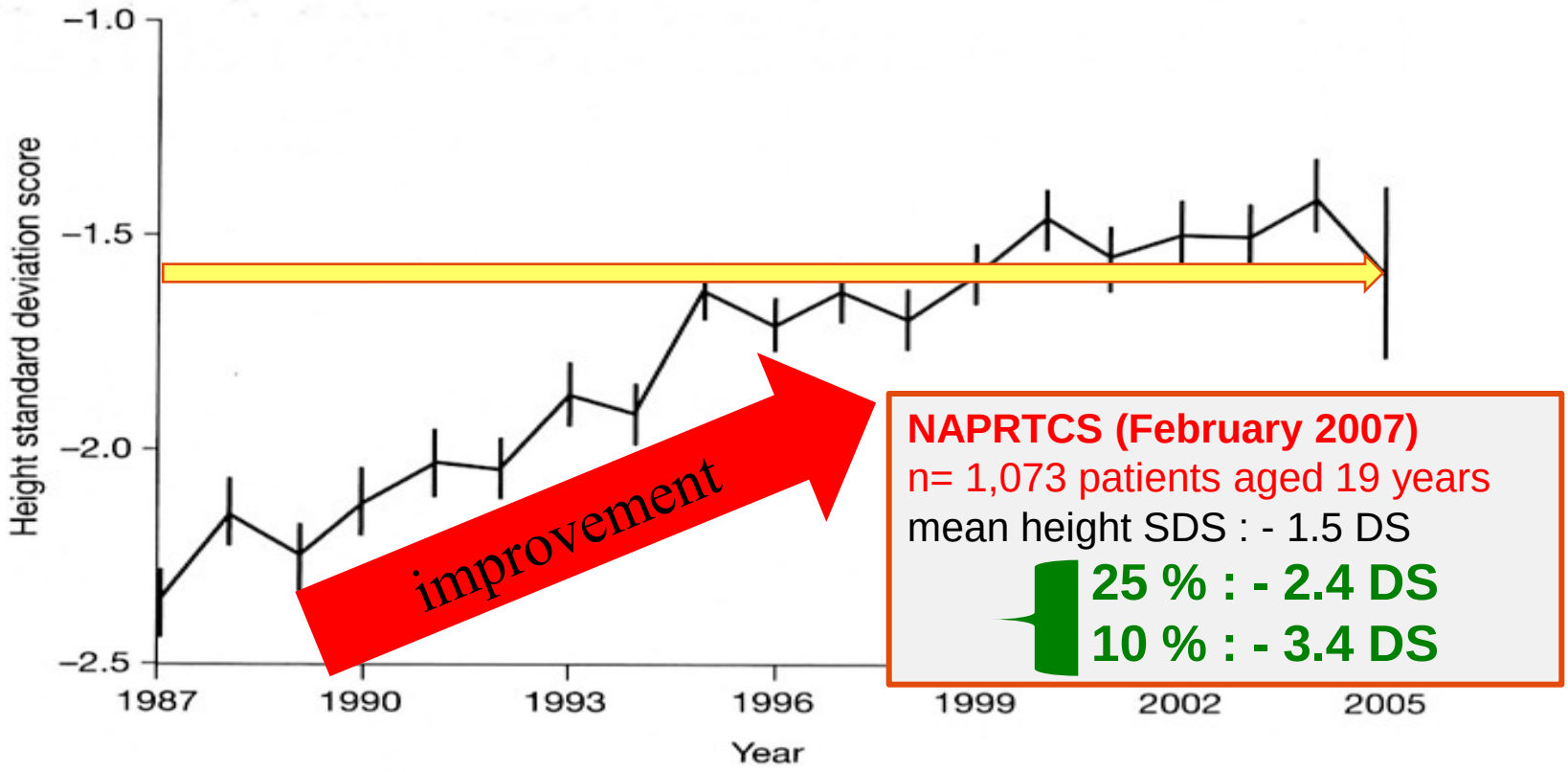


Figure 1 In the past two decades, there has been a steady improvement in the height standard deviation scores of pediatric renal allograft recipients at the time of transplantation. Data from the North American Pediatric Renal Trials and Collaborative Studies.[3]

Fine R. Nature Clinical Practice. Nephrology 2007; vol 3, n° 6:318-24

Longitudinal growth in children following kidney transplantation from conservative to pharmacological strategies

T. Ulinski, P. Cochat. Pediatr Nephrol 2006. 21:903-9

- At the time of Tx children with CRF are significantly shorter than their peers
- ***The final adult height correlated with the height deficit at the time of kidney Tx : need to optimyze growth during dialysis time***
- Spontaneous catch-up growth remains often insufficient after pediatric kidney transplantation despite satisfactory GFR function
- As long as corticosteroids are believed to be essential after renal Tx, rhGH should be considered to optimize longitudinal growth in children

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Nutritional status in dialyzed children

- Malnutrition due to poor appetite and restrictive diet, could be cured by dietary replacement, supplementation : nasogastric and gastrostomy feeds (PD) and intradialytic feeding (HD)
- Cachexia is due to loss of protein stores despite no inadequate diet : bioincompatibility of the dialysis (inflammation); adequate or optimal (urmia toxicity:acidosis, purification, loss of substrates in the dialysate/convective volume)
- All together impacting on final outcome :
  - statural growth retardatation : rhGH « resistance » , morbidity
  - uremic cardiomyopathy and vasculopathy : mortality (CKD/MBD)

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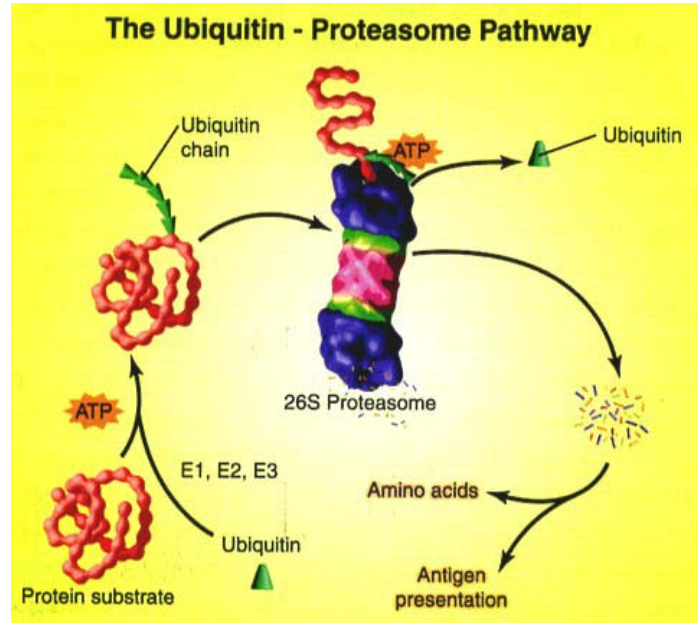
Muscle wasting in chronic kidney disease : the role of the ubiquitine proteasome system and its clinical impact

VR Royan, WE Mitch. Pediatr Nephrol 2008; 23:527-35

- **Malnutrition**
- **Volume overload**
- **Metabolic acidosis**
- **Inflammation**
- **Uremic toxins**
- Insuline resistance (PTH)
- GH-IGF1 axis anomalies



Cachexia in uremic patients : loss of protein stores, muscle wasting, growth impairment : ***ATP-dependent, ubiquitin-proteasome system***

How to improve conventional hemodialysis

- Consider not only urea removal (diffusive process) but also middle molecular weight compounds toxicity (convective flow) :

  HDF is superior to HD,

  HDF adds a convective dialysis dose to HD

- Use/exploit biocompatible and highly permeable membrane (molecular permeability, water permeability) : ultrapure dialysate, convective flow, on line substitution fluid production
- Hemodialysis on line monitoring : Kt/V, BVM, modelling (sodium, ultrafiltration, ultrafiltrate, dialysate temperature)
- Dialysis time ***: from intermittent (and some « rescue sessions ») to daily dialysis (dialysis without stress)***

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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 blood purification as well as the highest possible convective clearance.
- The following points should be considered when writing an HDF prescription for children:
- HDF requires an optimal arterial blood flow of 5 to 8 ml/min/kg body weight or 150 to 240 ml/m² body surface area. This can be achieved through either a fistula or a central venous line.

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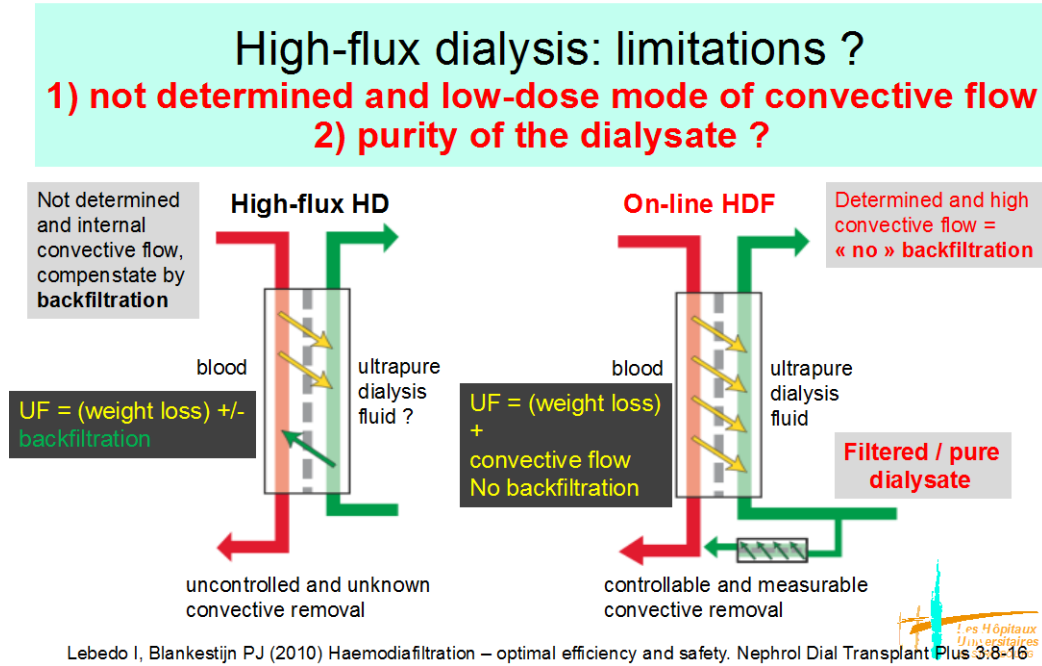
- A high flux membrane with surface area equal to the child's body surface area is used.
- Dialysate flow of 1.5 times the blood flow is sufficient and adequate to optimize the diffusive blood purification process using highly permeable membranes for HDF
- Convective flow is equal to total ultrafiltration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



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

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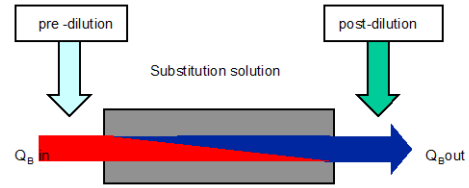
- Post-dilution HDF - the convective flow is ≤1/3 of the blood flow, and limited by the risk of filter clotting. It typically decreases over the dialysis session (TMP should be limited less than 300 mm Hg)
- Pre-dilution HDF - the convective flow is set at ≥ 50% of blood flow, but optimally can be increased 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 a *convective flow 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

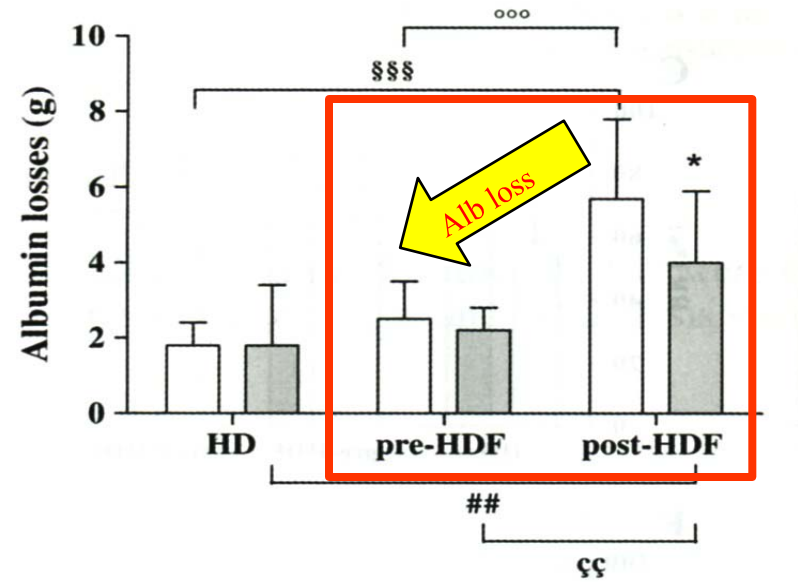

Fig. 3 : when comparing strategies, post dilution HDF induced more albumin losses (5.7±2.1 g/session) than the two other modalities (1.8±0.6 g/session)

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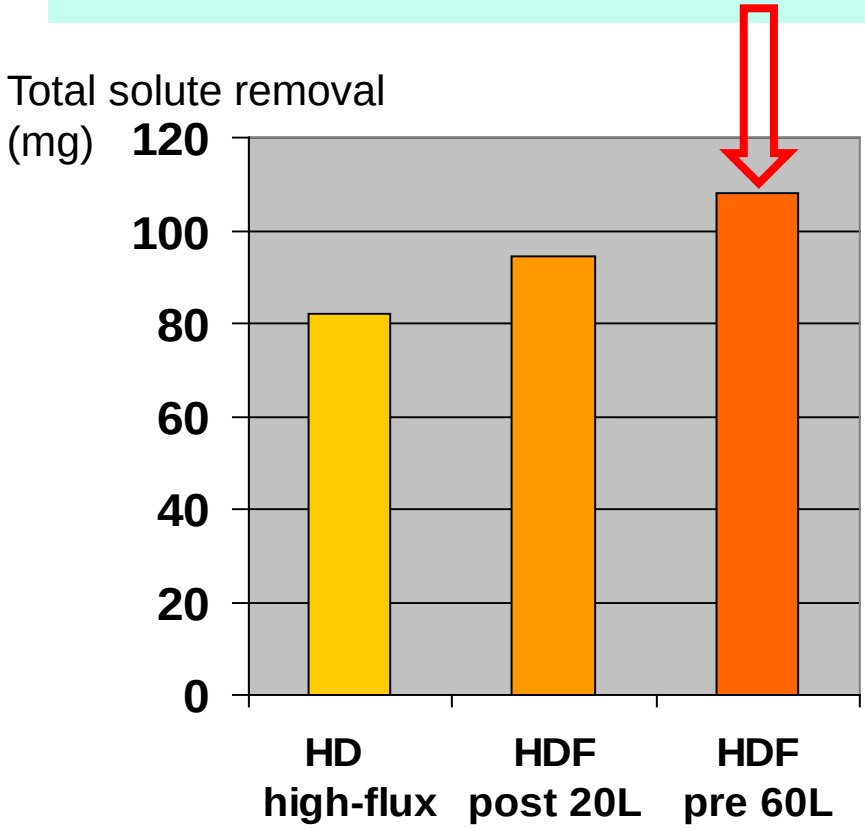
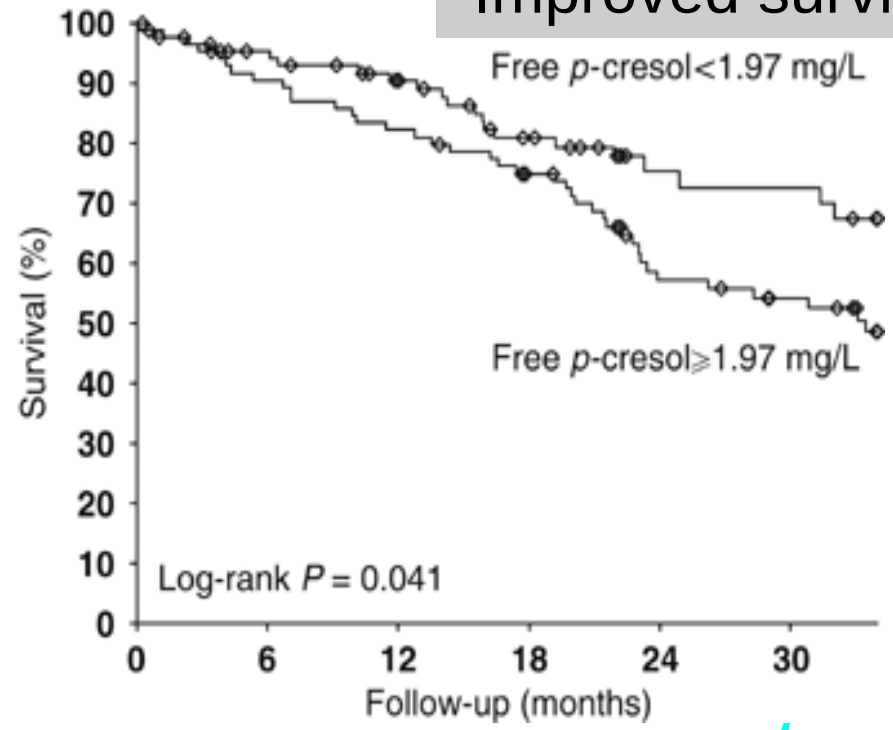
P-cresol , a protein-bound uremic toxin impact on survival

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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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

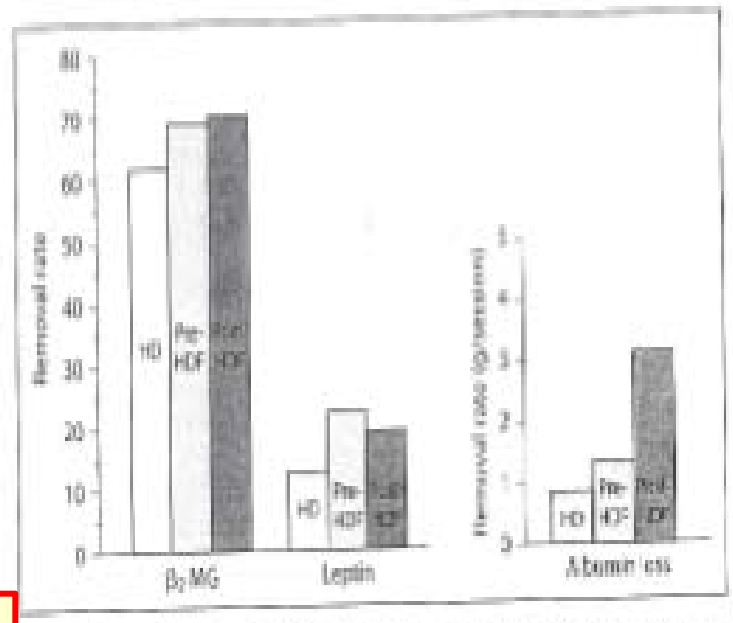

Fig. 2. Removal rates of β_2MG and leptin, and albumin loss. Pre-dilution HDF mode has higher removability of β_2MG or leptin than HD mode, and less albumin loss than post-dilution HDF mode.

Predilution HV-HDF with AutoSub plus

Removal of protein-bound uremic-toxins

(Indoxyl-Sulfate;IS)

Free-Fraction *f* as a function of
Albumin concentration C_{alb} and bonding affinity K_A:

$$f = \frac{C_{free}}{C_{free} + C_{bound}} = \frac{1}{1 + K_A * C_{alb}}$$

With IS free fraction *f* =10% we got $K_A * C_{alb} = 9$.

Diluting Albumin concentration results in higher free fractions f_{pre} of IS:

$$f_{pre} = \frac{1}{1 + K_A * C_{alb} / \left(1 + Q_{inf,pre} / Q_{PW}\right)}$$

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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%

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

Protein-bound uremic-toxins removal rises with increasing Qsub (convective flow)

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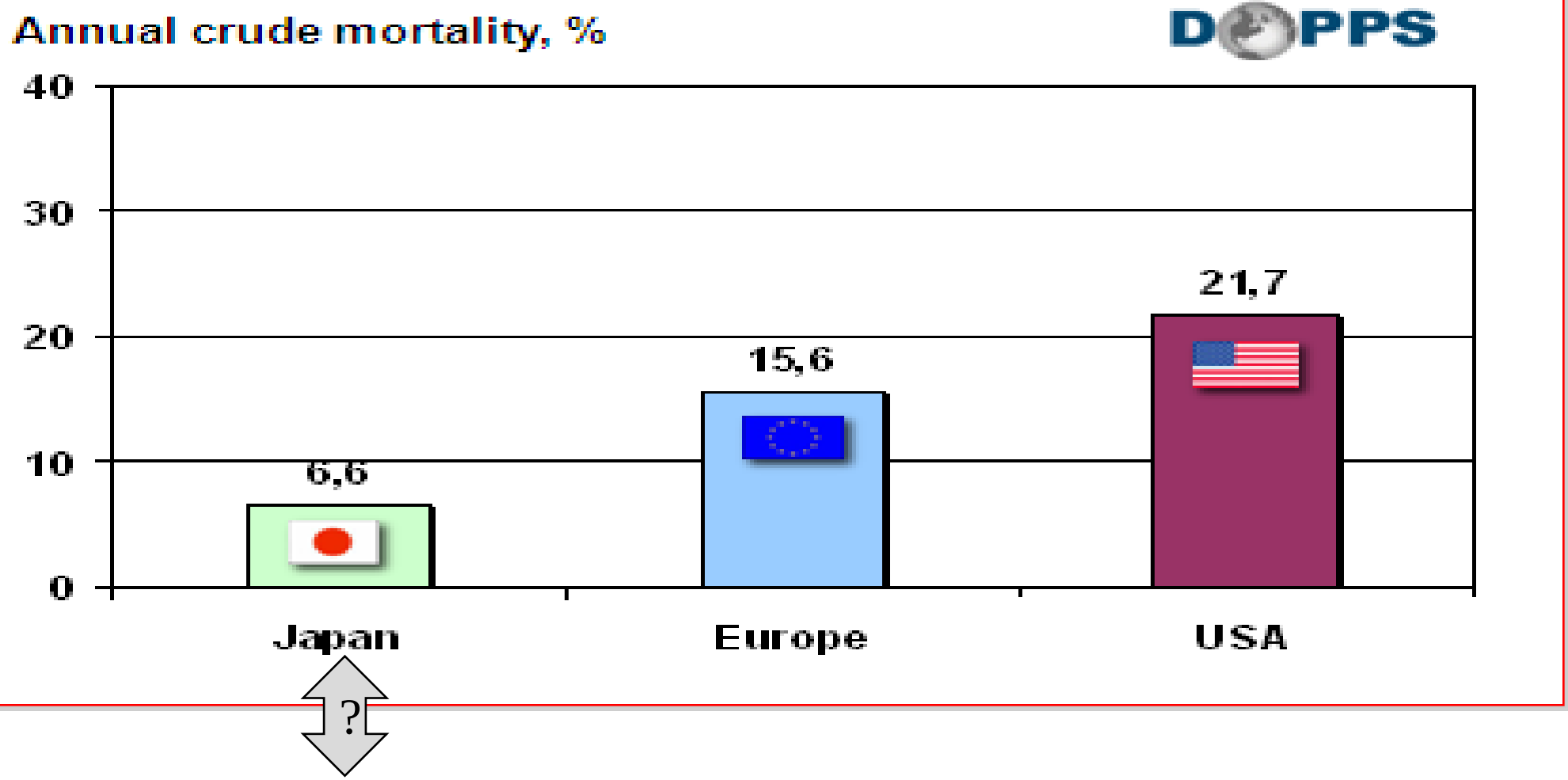

mortality risk:

dialysis fluids purity ?

HDF predilution ?

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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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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)
- Cost ?

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Adequate HDF prescription: « quality » of a high convective volume

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

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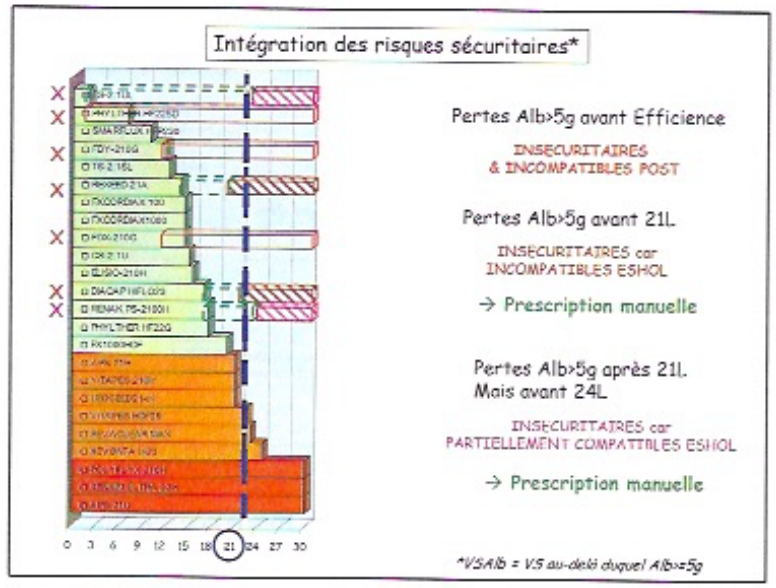

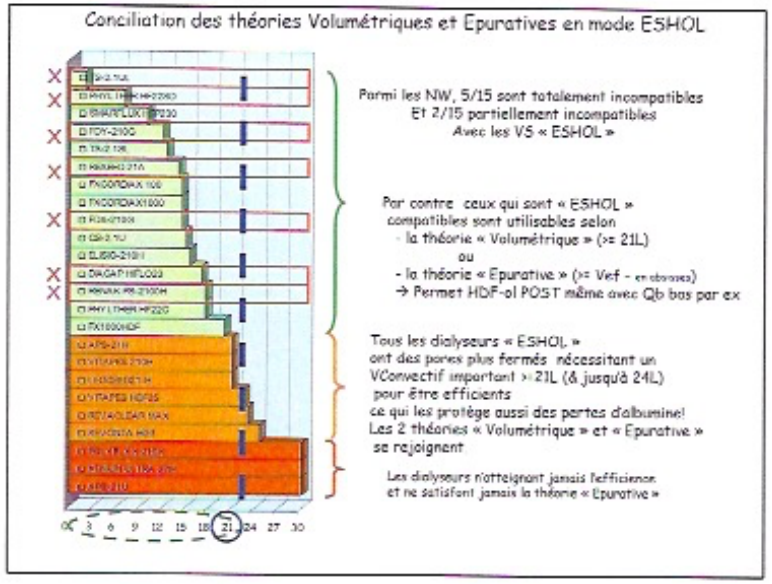

J Potier
Journées Experts HDF
FMC- Paris Novembre 2014

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

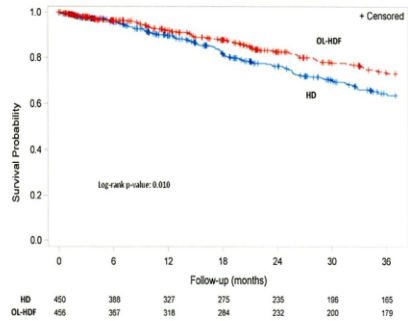

Figure 2. Kaplan–Meier curves for 36-month survival in the intention-to-treat population (P=0.01 by the log-rank test). HD, hemodialysis.

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

- Need for adapted Na_D in case of very 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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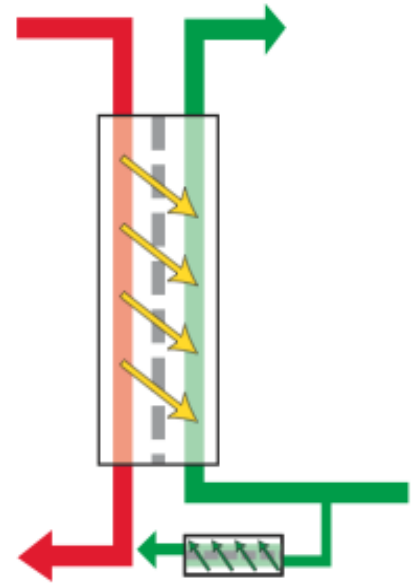
Hemodiafiltration on line : purity

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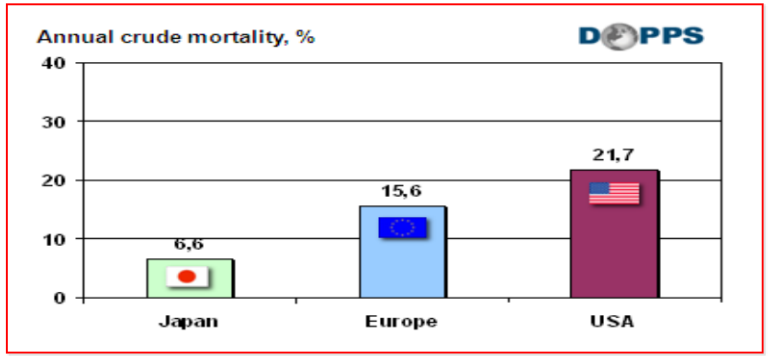
- Replacement fluid that is generated on-line from the dialysate must be ‘ultra-pure’ as discussed above. The microbiological purity (bacterial count and endotoxin level) should be determined regularly at 1-3 monthly intervals.

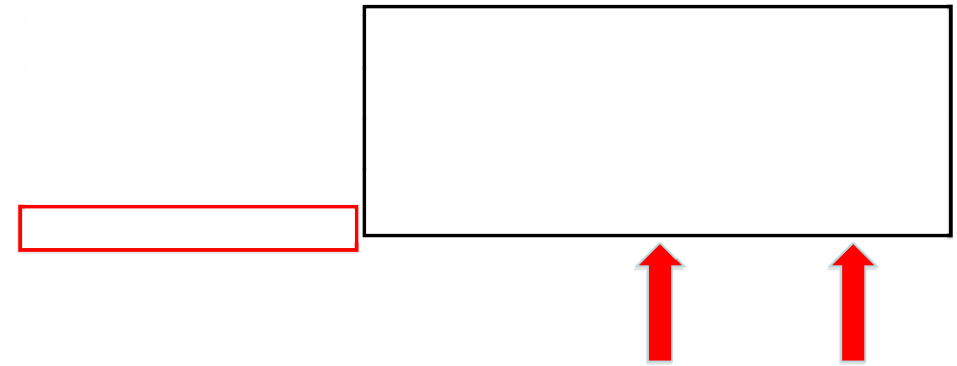


Masakane Ikuto ASN 2008:
mortality risk and dialysis fluids purity

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



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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 need for a volume of « good quality » (impact of the membrane) :
  - beta-2-microglobulin extraction coefficient >80%
  - myoglobin>65%
- Risk of « loss » in the dialysate and high convective volume (check for albumin; quality of the membrane)
- Dialysis fluids : purity, temperature control (« cooling »; BTM), NaD (on-line diffusive sodium), Ca++, HCO_3^-
- More than purification, importance of the volume control (UF and sodium balance): BCM, BP, IDWG…

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From adequate to optimal dialysis

- « adequacy » assessment : outcome (morbidity/mortality/growth/development/) or surrogates like urea kinetics (diffusion process) and more (β2 microglobuline or convective volume?),

- How to improve conventional HD:

✓ high flux membrane for « all »

✓ biocompatibility/purity of the dialysis fluids (endotoxin's level),

✓ volume control (dry weight/BP/LVH): interest of an objective assessment (bioimpedancemetry, BCM), reduction in UF demands per dialysis session

✓ should HDF become the standard for in center dialysis ?

- More dialysis, more frequent/longer sessions: « daily » dialysis, daily in center high efficiency hemodiafiltration

dialysis dose and outcome in children:
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
Longer or more frequent sessions ?

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Intensified hemodialysis regimens :
neglected treatment options for children and adolescents

Muller D. et al. Pediatr Nephrol 2008; 23:1729-36

Table 1 Summary of the different modalities of current intensified hemodialysis regimens and their major benefits and disadvantages

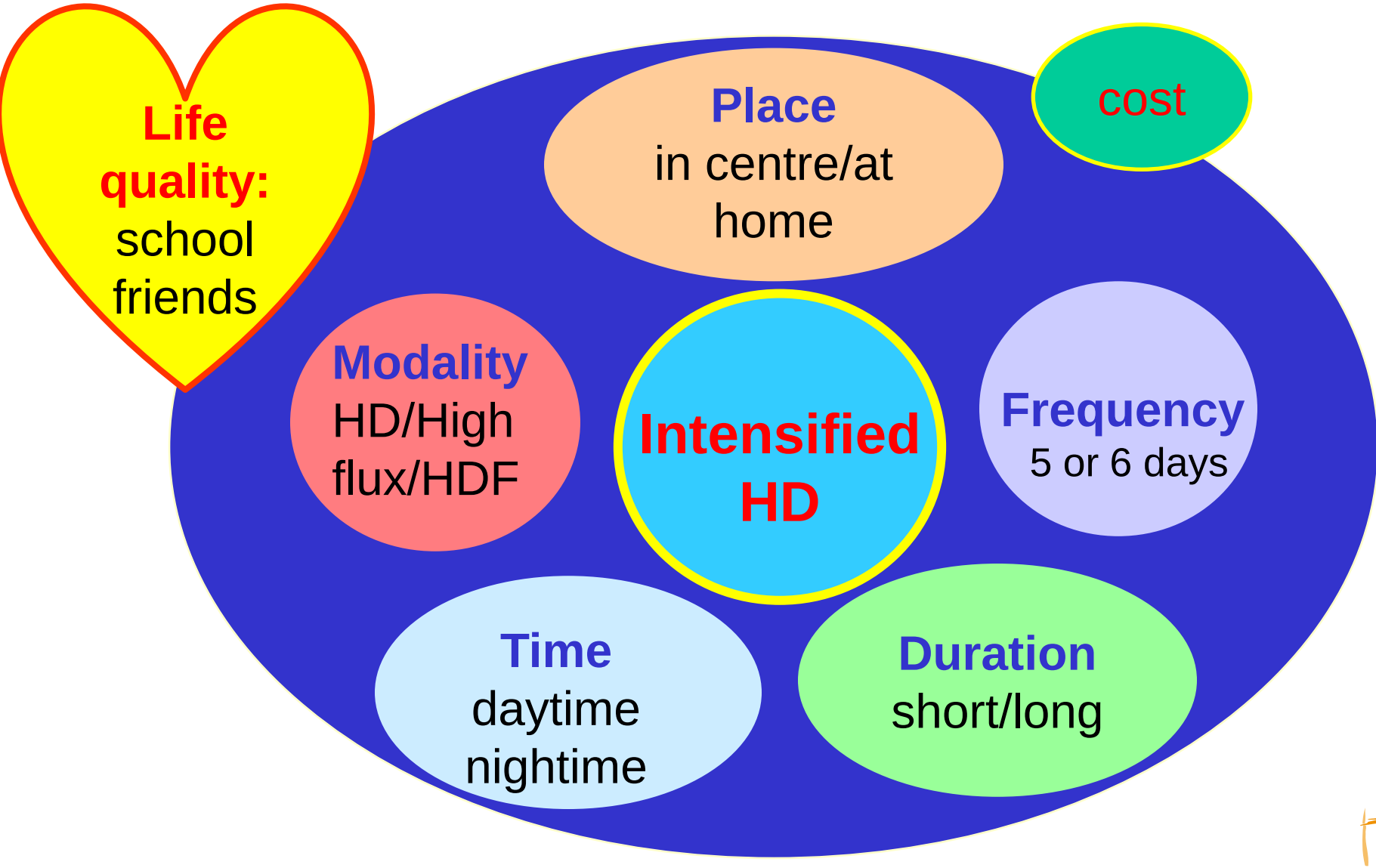
Method	Sessions per week	Duration per session (h)	Major advantages	Major disadvantages
Conventional	3	4–5	Standardized and most widespread procedure	Poor phosphate removal and volume control, poor social rehabilitation
Short daily	5–6	2–3	Superior phosphate removal and volume control	Poor social rehabilitation
Intermittent long nocturnal	3	8	Good phosphate removal and volume control, superior social rehabilitation	Intermittent procedure with restrictions of fluid intake for patient
Quotidian nocturnal	5–6	8	Excellent removal of phosphate, excellent volume control, social rehabilitation	Frequent dialysis, high costs for dialysis

Recent advances in pediatric dialysis, a review of selected articles

Mahan JD, Patel HP. Pediatr Nephrol 2008; 23:1737-7

Intensified HD may improve growth and LVH in children

Cost is of importance, but the highest standard should be offered to children waiting for TX



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

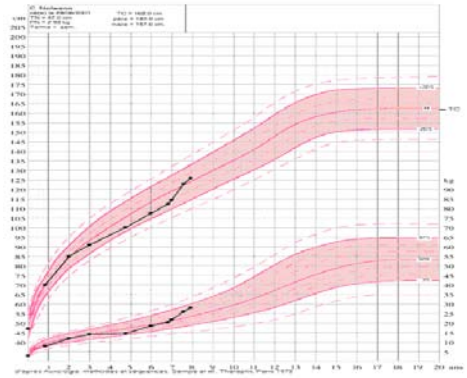
F. Schaefer. Editorial comments. Nephrol Dial Transplant 2010; 25:658-660

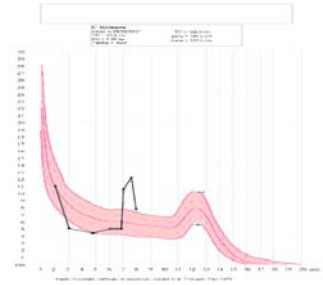
- 35 % to 50 % of children with ESRD still grow up to became small adults with a final height below the third percentile of the general population
- Growth failure is a common end point of a variety of abnormalities associated with CKD :
  - Protein energy malnutrition due to anorexia and chronic inflammation (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+++)

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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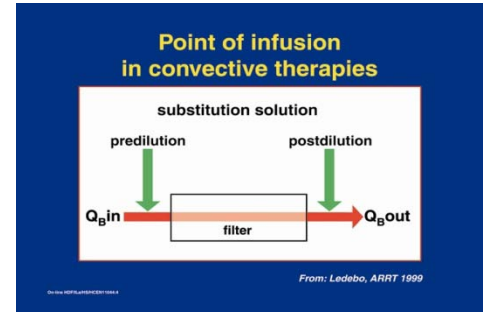
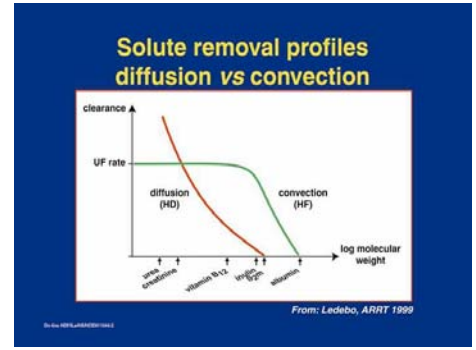
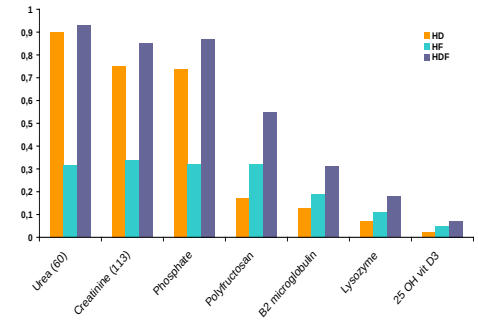
Dialysis regimen : in center daily on-line HDF

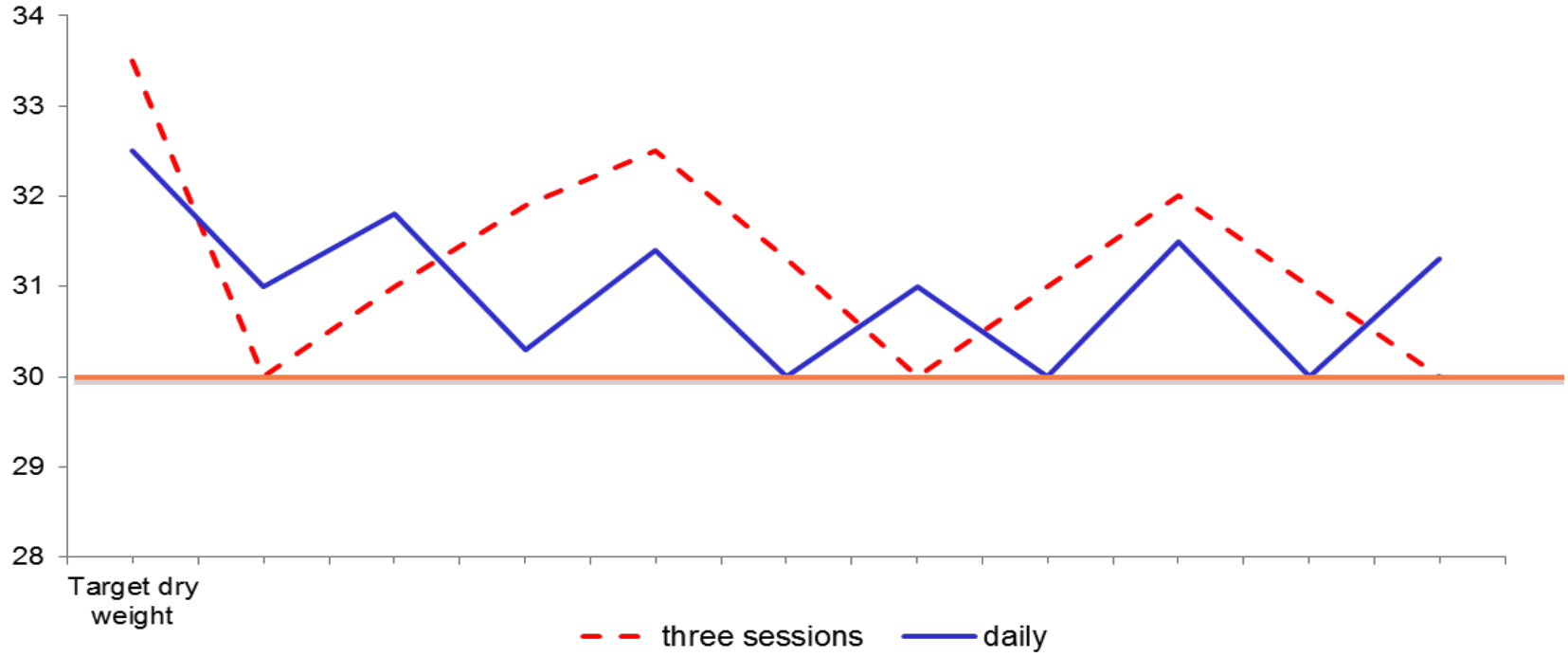
- In center daily on line/high efficiency HDF (since september 2002)
- 6 times per week (18h/week; 3 hour session)
- “floating” dry weight
- ultrapure dialysate, highly permeable membrane (polysulphone),
- Kt/Urea of at least 1.4 per session; Kt/Urea assessed at each session by the on line clearance monitoring, quality tool
- Convective volume 27 L/m^2/session, predilution reinfusion (equivalency of 9 to 12 L/m^2/session in postdilution)







Floating dry weight : daily versus three times dialysis



« safe » UF ≤ 1.5 % BW loss/hour , dry weight 30 kg, UF ≤ 450 mL/h

- Daily dialysis : floating dry weight , dry weight reached over the week
- Three times dialysis a week : « no safe UF »

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Dialysis tolerance :

- During the sessions : no symptoms of intolerance, no dyscomfort, optimal UF tolerance and dry weight easely reached over the weekly dialysis procedure, adhesion to school working during the sessions (no « fatigue »)
- Post dialysis : no recovery time, less sleep disturbances, normal feeling out of the dialysis center, « natural » compliance to whole therapy (dialysis, diet and medications in attempt to be kidney transplanted)

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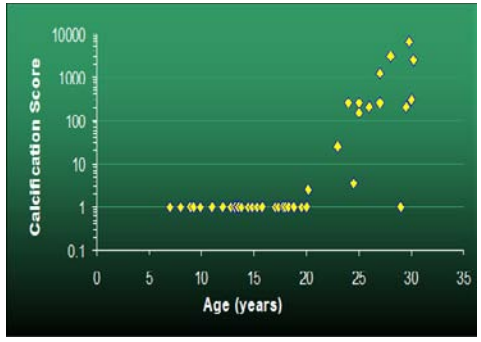
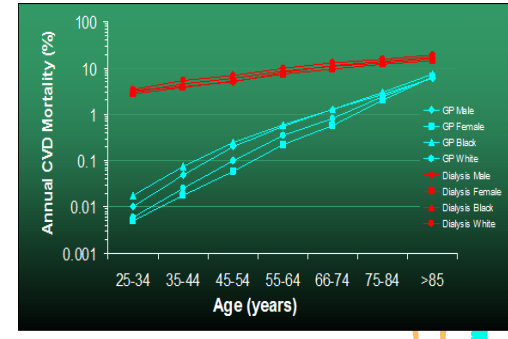
Dialysis purification capacities : DIH

- Weekly Kt/V_{urea} around 10 (SAN Kt/V over 2.45) : high dialysis dosis , equivalency of 35% GFR (from CKD5 to CKD3)
- Predialytic phosphate values : median 1.39 mmol/l (range 1.65 to 0.63), despite high protein intake (more than 2 g/kg/day) and only 2/15 child on chelators (normal Ca x P)



normal {Ca x P} product

Less vascular risk ???



In center daily on line hemodiafiltration: a five years children experience.

Fischbach M, Dheu C, Seuge L, Menouer S, Terzic J (2008) Clinical Nephrology 69,4: 279-84

	Start of DIH (n= 12)	End of DIH (n=12)
Diet	Restricted	Free (water, salt, proteins)
Antihypertensive drugs	10/12 (at least two drugs/patient)	2/12 (one drug/patient)
Potassium chelators	12/12	4/12 (only on « Sunday », the dialysis free day)
Phosphate chelators	12/12	1/12
Post dialysis recovery time*	6 to 15 min	No perception to be dialysed

1

* Minutes to recovery after a hemodialysis session : a simple health-related quality of life question thas is reliable, valid, and sensitive to change. Lindsay R. et al. Clin J Am Soc Nephrol 2006; 1:952-9

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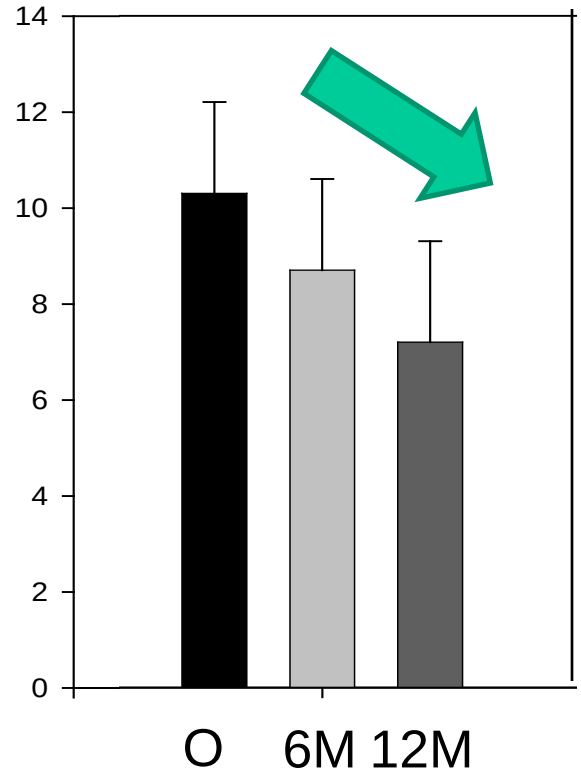
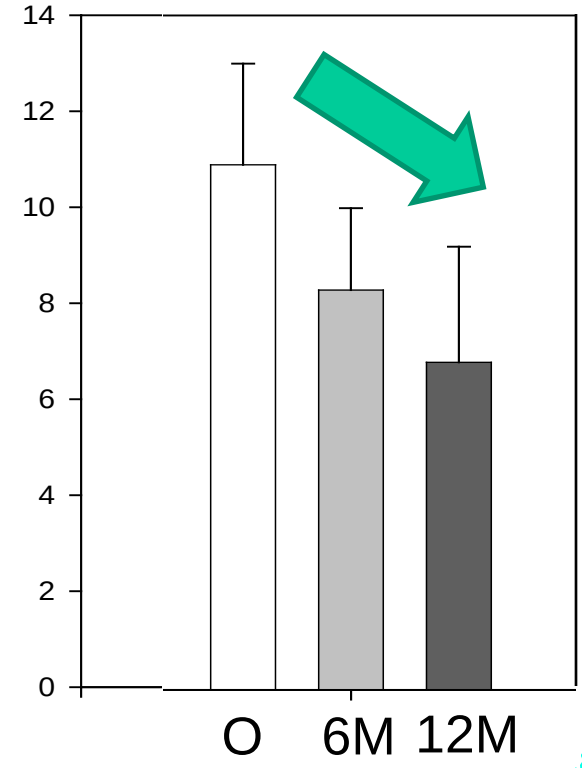
Switch from HDF (3 times/week) to daily HDF: regression of LVH

Posterior Wall thickness



Interventricular Septum



Fischbach M, Terzic J, Laugel V, Dheu C, Menouer S, Helms P, Livolsi. A (2004) Daily on line hemodiafiltration : a pilot trial in children. Nephrol Dial Transplant 19: 2360-67

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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 m^2 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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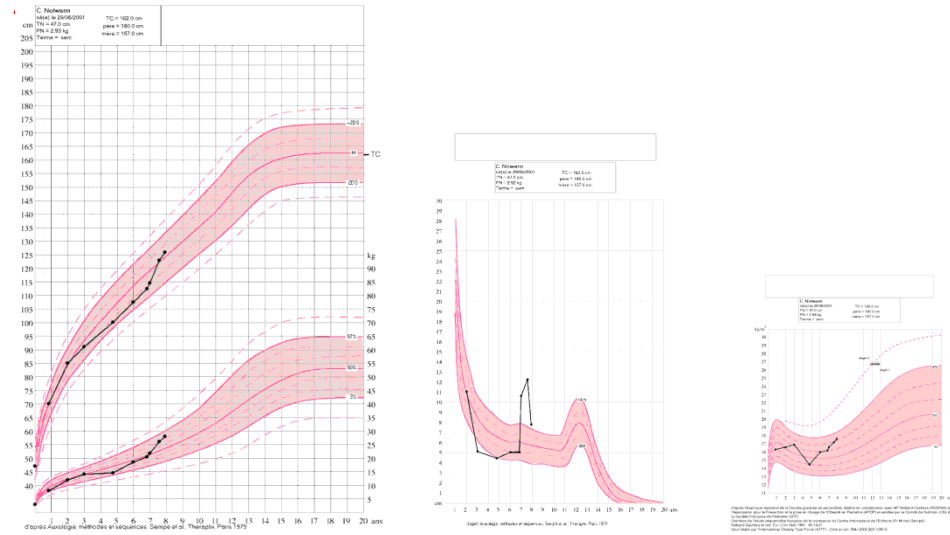
Results

- 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

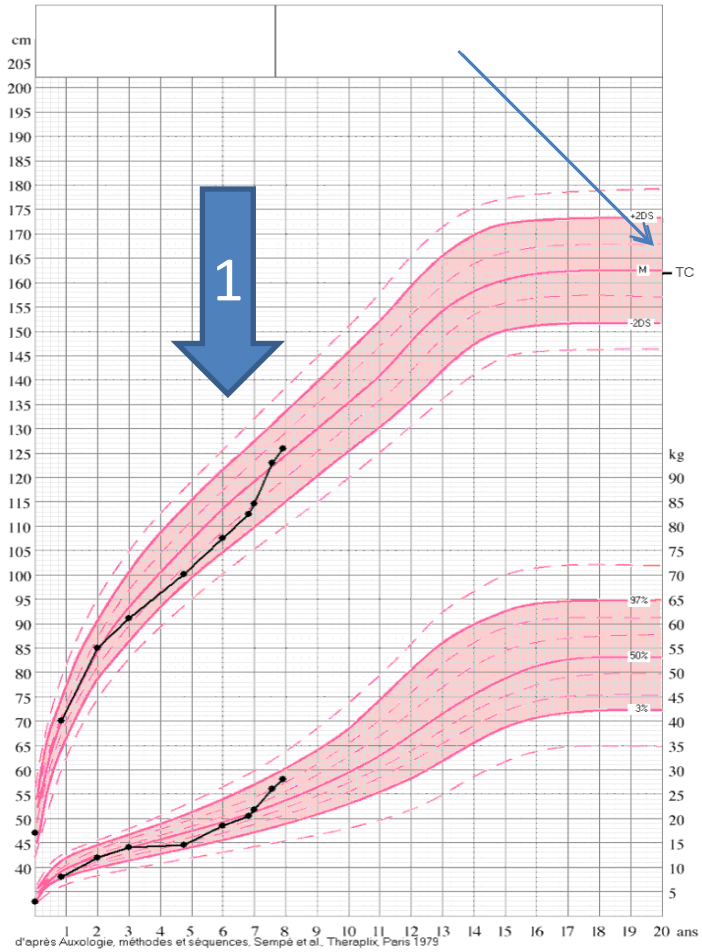
  end: +0.2+/1.1

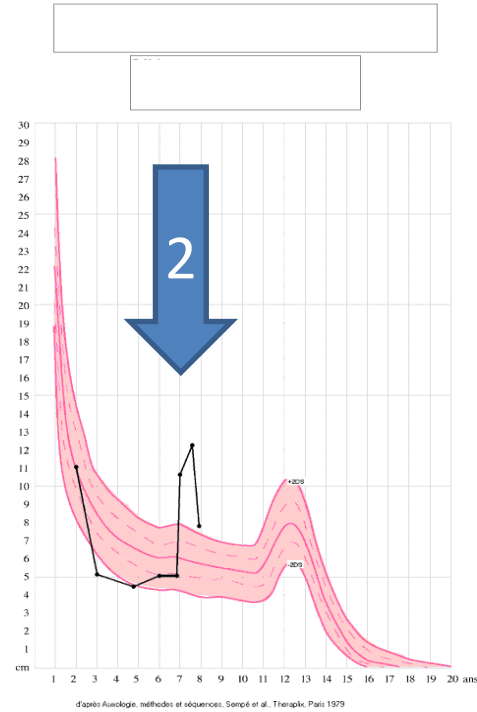
  target parental height: -0.3

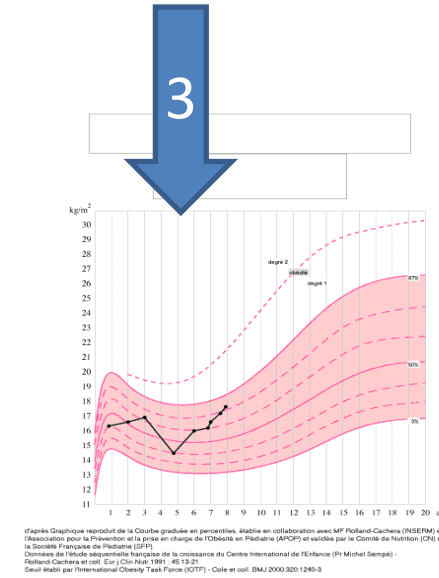
  end- target: +0.5

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



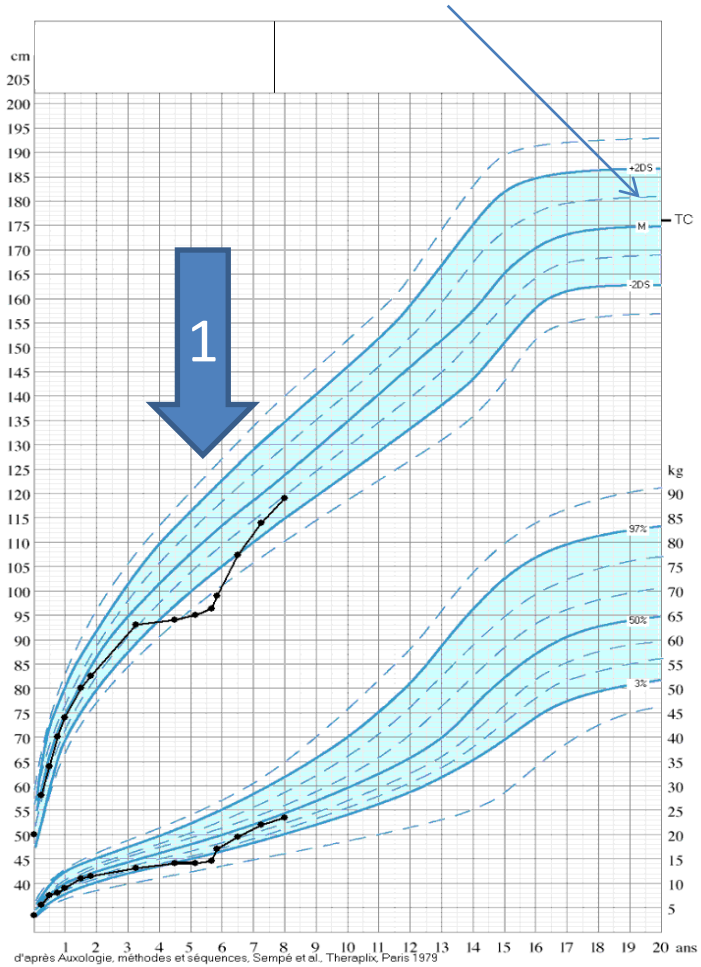


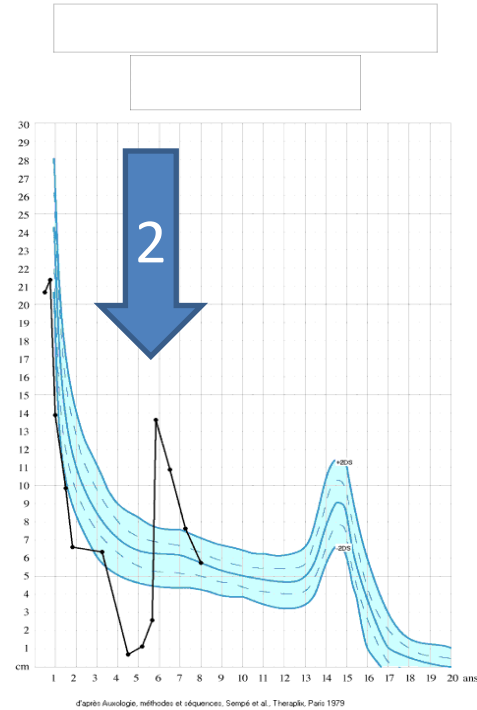


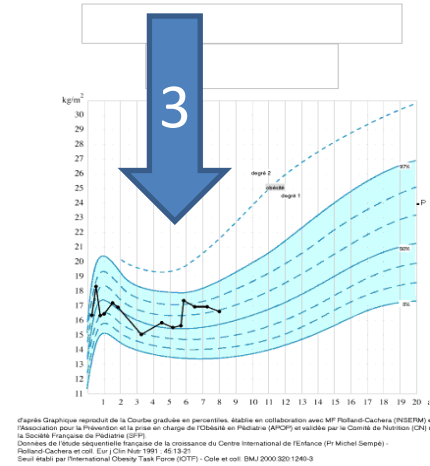
1 growth in SD 2 growth velocity 3 BMI

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

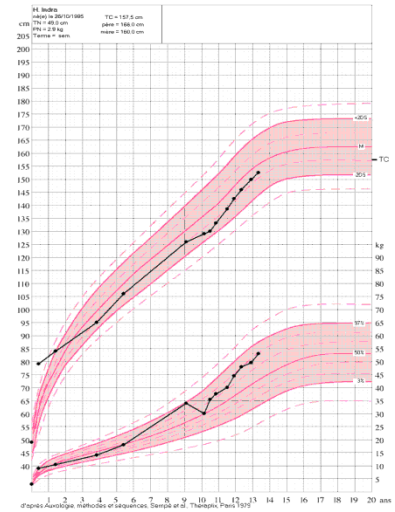


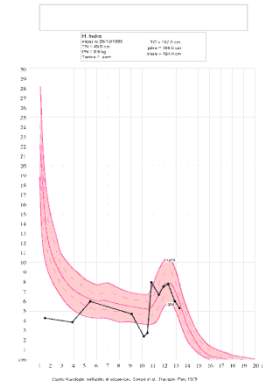


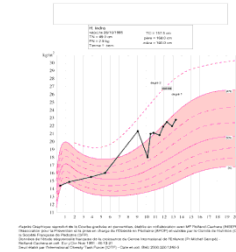


1 growth in SD 2 growth velocity 3 BMI

Results







- BMI kg/m^2 (%)

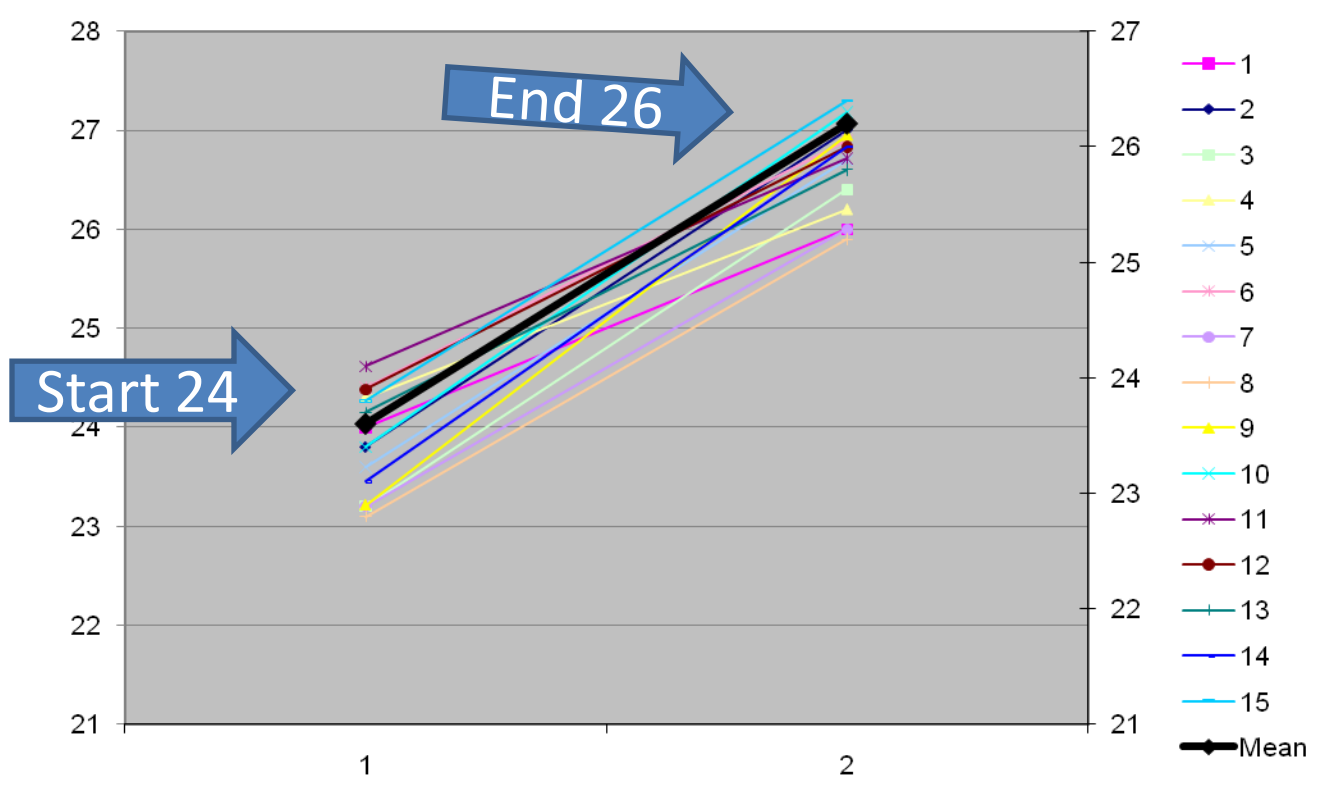
  start of daily 16.5±2.0 (48±24)

  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

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

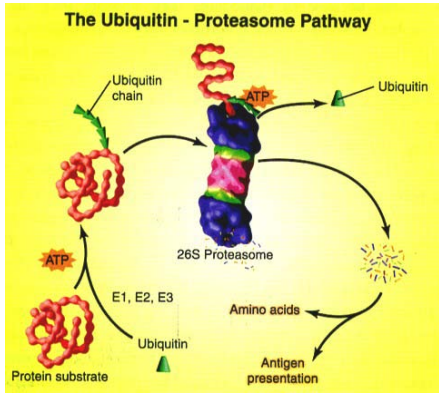
TAD bicar 0.65+/-0.13

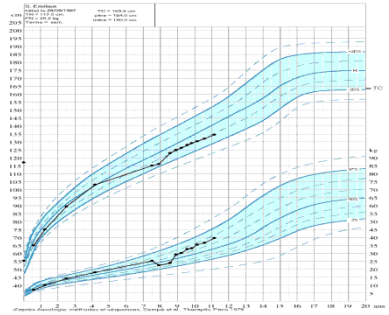


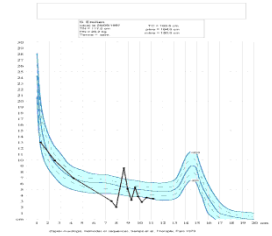
Reduced « acidosis / alcalosis dialytic » waves

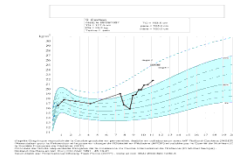
This anabolic impact of daily HDF, intensified dialysis, (*large convective volume, high efficiency HDF*) is presumed to be secondary to a « stimulus package » :

- *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*









Daily hemodiafiltration in children in center, from CKD5 to CKD3

- Normal diet ; no add of « unprogrammed » session
- No intradialytic symptoms; no recovery time
- BP, LVH : improved, nearly disappeared
- Ph: « no » need for chelators despite PCRn>2gr/kg BW
- K, potassium: day off dialysis, chelators ?
- B_2 m, CRP: reduced inflammation, despite frequent dialysis
- « never » acidosis, $TAD_{bicarbonate}$
- **Cardiovascular preservation**
- **No cachexia, no protein wasting, catch up growth**

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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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Adequate/optimal dialysis:

daily high efficiency HDF

High flux membranes (for « all »; a « good » membrane)

Purity of dialysis fluids (endotoxins< 0.001 UI / ml)

Volume control (BP, LVH…) UF rate ≤ 10/15mL/kg/h

Determined convective volume : HDF

Efficient convective volume; dialytic albumine loss

Phosphate control « without » phosphate binder

Inflammation control (beta2 micro)

Anabolisme, growth, preservation of life chance

More dialysis time (daily <u>and</u> intensive)

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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 (OL-HDF/high convective volume):
  GFR equivalency :30 to 40%

it is time to change a 25/30 years old dialysis strategy and not to only use « daily » as a rescue modality

« first class » therapy: in center daily high efficiency hemodiafiltration

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