Dialysis practice: how to write an HDF prescription

high efficiency HDF: convective volume
OL-HDF (purity); membrane quality
volume control (BCM, UF and NaD)

Fischbach Michel
Pediatric Dialysis Unit
University hospital Strasbourg France
HDF started
1981 July
Strasbourg
France

High technology, 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 »
Hemodiafiltration in children, a history

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

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

3) daily OL-HDF, Sept 2002: \textit{more dialysis time, catch up growth}

4) high efficiency HDF (\textit{autosub + technology=high convective volume, « tools not toys »}) (BCM/BVM/BTM and on-line diffusive plasmatic sodium) and daily HDF: \textit{volume control (floating dry weight), cardiovascular preservation, normal growth}
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.
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 \( (\text{TMP} ; \text{mmHg}) \)
- Sieving coefficient \( (S)^* \)
- Molecular permeability \( (\text{MW}) : <1 \)

\[ *S = \frac{2 \times C_{UF}}{c_i + c_o} \]

\( \text{UF} \) : ultrafiltrate solute concentration

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

\[ Q_{UF} < \frac{1}{3} Q_B \] (in practice often 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

\[ K_{HDF} = K_{HD} + x Q_{UF} x 0.46 \]
\[ K_{HDF} = K_{HD} (1 - Q_{UF} x S/Q_{B}) + K_{HF} \text{ (Granger)} \]

with \( Q_{UF} x S = K_{HF} \) and \( Q_{B} = K_{max} \)

\[ K_{HDF} = K_{HD} + K_{HF} \quad -- \quad \frac{K_{HD} x K_{HF}}{K_{max}} \]

If \( K_{HD} \) is equal to \( K_{max} \), then \( Q_{HDF} = K_{HD} \)
HDF allows an optimal blood purification not only for urea, but also for the middlemolecular weight compounds (Babb theory)

*From M Fischbach et al. Contr Nephrol 1985*
Hyperphosphatemia, a « silent killer »
(FGF23;Klotho) of patients with renal failure

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
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**

• 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/m²/session or per week).

High-flux dialysis: limitations?
1) not determined and low-dose mode of convective flow
2) purity of the dialysate?
• **Post-dilution HDF** - the convective flow is $\leq 1/3$ 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 $\geq 50\%$ 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, $\beta_2$ 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 **pre-dilution** mode, after the filter, **post-dilution** mode, or mixed.
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.
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

<table>
<thead>
<tr>
<th></th>
<th>Pre HDF</th>
<th>Post HDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qb eff (mL/min)</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>Q_D (mL/min)</td>
<td>800</td>
<td>800</td>
</tr>
<tr>
<td>Q_inf (mL/min)</td>
<td>145</td>
<td>70</td>
</tr>
</tbody>
</table>

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)
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

Small water soluble solutes
- Asymmetric dimethylarginine
- Benzylalcohol
- β-Guanidinopropionic acid
- β-Lipoic acid
- Creatinine
- Cytidine
- Guanidine
- Guanidinoacetic acid
- Guanidinosuccinic acid
- Hypoxanthine
- Maionialdehyde
- Methyguanidine
- Myoinositol
- Orotic acid
- Orotidine
- Oxalate
- Pyruvouridine
- Symmetric dimethylarginine
- Urea
- Urine acid
- Xanthine

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

Middle molecules
- Adrenomedullin
- Atrial natriuretic peptide
- β2-Microglobulin
- β-Endorphin
- Cholecystokinin
- Clara cell protein
- Complement factor D
- β2 - Microglobulin
- Hysterionic acid
- Interleukin 1β
- Interleukin 6
- Kappa-lg light chain
- Lambda-lg light chain
- Leptin
- Methionine-enkephalin
- Neuropeptide Y
- Parathyroid hormone
- Retinol binding protein
- Tumor necrosis factor alpha

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)
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

N= 175 HD patients, prosp. obs. study
### Predilution HV-HDF with AutoSub plus

<table>
<thead>
<tr>
<th>$Q_{\text{inf}} / Q_b$</th>
<th>$Q_{\text{inf}} / Q_{\text{pw}}$</th>
<th>Indoxyl-Sulfate free-fraction $f_{\text{pre}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0,0</td>
<td>0,0</td>
<td>10%</td>
</tr>
<tr>
<td>0,7</td>
<td>1,0</td>
<td>18%</td>
</tr>
<tr>
<td>1,0</td>
<td>1,5</td>
<td>22%</td>
</tr>
<tr>
<td>4,0</td>
<td>6,0</td>
<td>44%</td>
</tr>
</tbody>
</table>

Protein-bound uremic-toxins removal rises with increasing $Q_{\text{sub}}$.

$Q_{\text{inf}}$ : Infusion rate  
$Q_b$ : blood flow rate  
$Q_{\text{pw}}$ : plasma flow rate
How to prescribe hemodialysis or hemodiafiltration in order to ameliorate dialysis-related symptoms and complications


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
### Recommandations for a « standard » dialysate

<table>
<thead>
<tr>
<th></th>
<th>Endotoxines</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRANCE</td>
<td>&lt; 0,25 UI / ml</td>
</tr>
<tr>
<td>ISO 23500</td>
<td>&lt; 0,5 UI / ml</td>
</tr>
<tr>
<td>JAPON</td>
<td>&lt; 0,05 UI / ml</td>
</tr>
</tbody>
</table>

### Recommandations for an « ultrapur » dialysate

<table>
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<tr>
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<tbody>
<tr>
<td>FRANCE</td>
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</tr>
<tr>
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<td>&lt; 0,03 UI / ml</td>
</tr>
<tr>
<td>JAPON</td>
<td>&lt; 0,001 UI / ml</td>
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### Recommandations for the substitution fluid (convective volume)

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<tr>
<td>FRANCE</td>
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<tr>
<td>JAPON</td>
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</table>

mortality risk: dialysis fluids purity? HDF predilution?
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+)
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.
On line HDF is not a self-fulfillly prophecy: it must be used *wisely*

(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* (fistula quality, session time, membrane, dialysate)
Dialysis membranes: practical parameters

• **Capillary membrane**, biocompatible (EO free), high flux (polysulfone, PAN); area= BSA in m²
• 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/m²); back filtration risk if applied 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)
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, compensate by backfiltration

UF = (weight loss) +/- backfiltration

Determined and high convective flow = «no» backfiltration

Filtered / pure dialysate

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 β₂ m 80 %)
- Loss of albumine (< 5 gr in adults)
- Purity of the dialysis fluids
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)
• **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.

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.

• 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

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

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)…
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
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)
HDF and Na<sub>D</sub> (sodium in dialysate)

- The substitution fluids (convective volume/dose) have the same sodium concentration as the dialysate (Na<sub>D</sub>): « on-line »
- Napl : the diffusible sodium
- Na<sub>D</sub> versus Napl, BCM®, BVM®, on line « Na diffusable »
  - In predilution Na<sub>D</sub> 134 – 138 mmol/L
  - In postdilution Na<sub>D</sub> 138 – 142 mmol/L
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)
Restrict the UF demand to 1.25% BW loss per hour, apply “cooling” technology (\( T_D = 36° \)) to preserve from cardiac and cerebral ischemia (Chris W. McIntyre)
Limit the IDWG<4%: more sessions
UF rate< 1.25%/h BW (floating dry weight)
IDWG<4% ? Euvolemia ? Cooling T_D=36°
M Fischbach et al Pediatr Nephrol 2015

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.

- 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.
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 modality.

• On line substitution fluid could be obtained by cold sterilization that is ultrafiltered ultrapure dialysate.
The effect of on-line hemodiafiltration on improving the cardiovascular function parameters in children on regular dialysis

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
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++, HCO₃⁻
- Volume control (BCM), BP, IDWG…
# Impact of high convective volume high efficiency hemodiafiltration

<table>
<thead>
<tr>
<th>Study name</th>
<th>Threshold volume for survival benefit (observational studies)</th>
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</thead>
<tbody>
<tr>
<td>DOPPS (Canaud) 2006</td>
<td>&gt; 15 L</td>
</tr>
<tr>
<td>Riscarid (Panichi) 2008</td>
<td>&gt; 23 L</td>
</tr>
<tr>
<td>Contrast (Grooteman) 2012</td>
<td>&gt; 21.95 L</td>
</tr>
<tr>
<td>Purkush (Ok) 2012</td>
<td>&gt; 17.4 L</td>
</tr>
<tr>
<td>ESHOL (Madrid) 2013</td>
<td>&gt; 23.1 L</td>
</tr>
<tr>
<td><strong>Children: convective volume</strong>, post dilution</td>
<td>? 3 L/m²/h or 12-15L/m²/session</td>
</tr>
<tr>
<td><strong>or predilution (easier to achieve?)</strong></td>
<td>? 18-27 L/m²/session</td>
</tr>
</tbody>
</table>
Optimal convection volume for improving patient outcomes in an international incident dialysis cohort treated with online hemodiafiltration

Bernard Canaud\textsuperscript{1,2}, Carlo Barbieri\textsuperscript{2}, Daniele Marcelli\textsuperscript{2,3}, Francesco Belloccchio\textsuperscript{2}, Sudhir Bowry\textsuperscript{2}, Flavio Mari\textsuperscript{2}, Claudia Amato\textsuperscript{2} and Emanuele Gatti\textsuperscript{2,3}

\textsuperscript{1}Montpellier University I, UFR Medicine, Montpellier, France; \textsuperscript{2}Fresenius Medical Care, Bad Homburg, Germany and \textsuperscript{3}Danube University, Krems, Austria

Improvement becomes 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/3 times per week)
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 \( T_D=36^\circ \); Euvolemia ?)
✓ daily “optimyzed” dialysis (floating dry weight; BCM®; diffusible Napl on-line; Kt/V on-line; BVM®; BTM®)
Cardiovascular benefits of daily haemodialysis: peeling the onion

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


- 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, ZALOSZCZIC A.
Nephrol Dial Transplant 2010; 25: 867-73
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 4/5 hours)

• 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
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
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/m² (%)**
  
  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**

- **β2 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 nutrition: less malnutrition, less cachexia
- improved uremic toxins detoxification ($\beta_2$ microglobuline)
- improved physical activity, less sleep disturbances
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 $T_D=36^\circ$; Euvolemia ? )
- **daily “optimyzed” dialysis** (floating dry weight; BCM®; diffusible Napl on-line; Kt/V on-line; BVM®; BTM®)
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
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
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
Daily on line hemodiafiltration : the perfect « stimulus package » to induce growth.

- 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+++))
HDF: extracorporeal blood circulation, vascular access, lines, filter

- Vascular access: fistula (double/single puncture), central line
- Blood flow: 150mL/min/m²; dialysate flow $Q_D \geq 1$ to 1.5 $Q_B$
- 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)
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 ($\text{ureaKt/V and a determined convective volume}$)
- volume control, dry weight ($\text{BCM®; on-line plasma diffusive sodium}$)
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), charcoal 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
Different forms of HDF: internal HDF, classical HDF (with bags), on-line HDF

- Classical HDF (with bags)
- High-flux dialysis
- On-line HDF (ultrapure dialysate)

From: Ledebo, ARRT 1999
**On line HDF**, a determined dose of convective flow

**Highflux HD** = internal, ”uncontrolled” HDF, i.e. low efficiency HDF, at risks/dialysate quality?

<table>
<thead>
<tr>
<th></th>
<th>on-line HDF</th>
<th>high-flux HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>membrane</td>
<td>high-flux, synthetic</td>
<td>high-flux, synthetic</td>
</tr>
<tr>
<td>dialysis fluid quality</td>
<td>ultrapure</td>
<td>ultrapure</td>
</tr>
<tr>
<td>Diffusive process</td>
<td>determined by QB, QD, K0A</td>
<td>determined by QB, QD, K0A</td>
</tr>
<tr>
<td>Convective flow</td>
<td>measurable, determined by operator</td>
<td>not possible to measure or to control; internal filtration determined by KUF, delta P</td>
</tr>
<tr>
<td>Dialysis fluid quality (substitution fluid)</td>
<td>sterile, non-pyrogenic</td>
<td>dialysate backfiltered through dialyzer membrane</td>
</tr>
</tbody>
</table>
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 - 3.2 mg/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)
The effect of on-line hemodiafiltration on improving the cardiovascular function parameters in children on regular dialysis

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
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
### Recommandations pour un dialysat « standard »

<table>
<thead>
<tr>
<th></th>
<th>Endotoxines</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRANCE</td>
<td>&lt; 0,25 UI / ml</td>
</tr>
<tr>
<td>ISO 23500</td>
<td>&lt; 0,5 UI / ml</td>
</tr>
<tr>
<td>JAPON</td>
<td>&lt; 0,05 UI / ml</td>
</tr>
</tbody>
</table>

### Recommandations pour un dialysat « ultrapur »

<table>
<thead>
<tr>
<th></th>
<th>Endotoxines</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRANCE (2007)</td>
<td>&lt; 0,25 UI / ml</td>
</tr>
<tr>
<td>ISO 23500</td>
<td>&lt; 0,03 UI / ml</td>
</tr>
<tr>
<td>JAPON</td>
<td>&lt; 0,001 UI / ml</td>
</tr>
</tbody>
</table>

### Recommandations pour un liquide de substitution

<table>
<thead>
<tr>
<th></th>
<th>Endotoxines</th>
</tr>
</thead>
<tbody>
<tr>
<td>France (2007)</td>
<td>&lt; 0,05 UI / ml</td>
</tr>
<tr>
<td>ISO 23500</td>
<td>&lt; 0,03 UI / ml</td>
</tr>
<tr>
<td>JAPON</td>
<td>&lt; 0,001 UI / ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dialysat</th>
<th>N° analyse</th>
<th>Résultats</th>
<th>Niveau d’alerte*</th>
<th>Niveau d’action*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flore aérobie revivable à 22°C</td>
<td>E 6813</td>
<td>&lt; 1 UFC/100ml</td>
<td>&lt; 5 UFC/100ml</td>
<td>&lt; 10 UFC/100ml</td>
</tr>
<tr>
<td>Endotoxines bactériennes</td>
<td>E 6815</td>
<td>&lt; 0.005 Ul/ml</td>
<td>&lt; 0.015 Ul/ml</td>
<td>&lt; 0.03 Ul/ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Solution de Substitution :</th>
<th>N° analyse</th>
<th>Résultats</th>
<th>Niveau d’alerte*</th>
<th>Niveau d’action*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flore aérobie revivable à 22°C</td>
<td>E 6814</td>
<td>&lt; 1 UFC/500ml</td>
<td>&lt; 1 UFC/500ml</td>
<td>&lt; 1 UFC/500ml</td>
</tr>
<tr>
<td>Endotoxines bactériennes</td>
<td>E 6816</td>
<td>&lt; 0.005 Ul/ml</td>
<td>&lt; 0.015 Ul/ml</td>
<td>&lt; 0.03 Ul/ml</td>
</tr>
</tbody>
</table>

* d’après la norme internationale ISO 23500:2011

Endotoxin level: not detectable
CHU Strasbourg 2014
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 processes) 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
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)
Beta-2-Microglobulin in Hemodiafiltered Children: Long-Term Efficiency Follow-Up

M. Fischbach, G. Hamel, C. Koehl, J. Geisert

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

Fig. 1. β₂M serum level variations in HDF with different membranes (mean = SEM, n = 30 sessions).

Fig. 2. β₂M Serum level variations with a polysulfone membrane versus condition of dialysis management: HF, HD or HDF (mean ± SEM; n = 30 sessions).
Beta-2-Microglobulin in Hemodiafiltered Children: Long-Term Efficiency Follow-Up

M. Fischbach\textsuperscript{a}, G. Hamel\textsuperscript{b}, C. Koehl\textsuperscript{c}, J. Geisert\textsuperscript{a}

\textsuperscript{a}Service de Pédiatrie 3 – Néphrologie – Dialyse – Transplantation, Hôpital de Hautepierre, \textsuperscript{b}Laboratoire de Biochimie (Pr. J. Mark), Hôpital de Hautepierre et \textsuperscript{c}Laboratoire d’Analyse, Institut de Chimie biologique (Pr. J. Vincendon), Strasbourg, France

\textbf{Table 2.} \(\beta_2\)M serum levels with the same polysulfone membrane in HD, HF or HDF (n = 30 sessions), versus pooled dialysate and/or filtrate extraction (mean ± SE)

\begin{tabular}{llllll}
 & Pooled dialysate and/or filtrate & Serum, mg/l & \\
 & volume l & \(\beta_2\)M & mg/l & mg & pre & post \\
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 \\
\end{tabular}

\textbf{Table 4.} HDF treatment in the 5 children described in table 3

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HDF PAN 150</th>
<th>HDF polysulfone</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 x 3 h/week</td>
<td>1.5 years</td>
<td>3 x 3 h/week</td>
</tr>
<tr>
<td>(\beta_2)M sieving coefficient</td>
<td>0.015 ± 0.001</td>
<td>0.504 ± 0.029</td>
</tr>
<tr>
<td>(\beta_2)M removal per HDF session, mg</td>
<td>3 ± 0.5</td>
<td>75 ± 4</td>
</tr>
</tbody>
</table>

\(\beta_2\)M sieving coefficient from ref. 8.

\textbf{Table 3.} Evolution of \(\beta_2\)M serum levels in 5 anuric children under HDF treatment

<table>
<thead>
<tr>
<th></th>
<th>Jan 83</th>
<th>Jan 84</th>
<th>Jan 85</th>
<th>Jan 86</th>
<th>Jan 87</th>
<th>Jan 88</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean weight, kg</td>
<td>22 ± 1</td>
<td>23 ± 1.3</td>
<td>24 ± 0.8</td>
<td>25 ± 1.4</td>
<td>26.5 ± 1.5</td>
<td>27.4 ± 1.2</td>
</tr>
<tr>
<td>(\beta_2)M serum mg/l</td>
<td>35 ± 7.5</td>
<td>42 ± 8</td>
<td>39 ± 4.8</td>
<td>42 ± 6.3</td>
<td>39.6 ± 4.5</td>
<td>41.3 ± 8.2</td>
</tr>
</tbody>
</table>
### « Practical » conditions for On-Line fluid preparation

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

**no machine movements**
High convective volume: need for a change of the dialysate composition (NaD)?

• Since 1981, we perform HDF in children, mainly pre-dilution (EPO; blood flow 80-200 ml/min)

• For many years, our standard NaD 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+).
High convective volume: need for a change of the dialysate composition ($\text{Na}_D$)?

At bedside, we learned the need to decrease the $\text{Na}_D$ 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 $\text{Na}_D$, between 134 and 138 mmol/L.
High efficiency OL-HDF : (re)consider the Na\textsubscript{D}

Ali, 3 years old, congenital nephrotic syndrome, anuric, 14 kg BW, 0.75 m\textsuperscript{2} BSA, central catheter:

**On pre dilution HDF, 4008**
- Blood flow 80 ml/min,
- Substitution flow 80 ml/min
- Na\textsubscript{D} 140 mmol/L
- BP 95/47 mmHg
- CorDix 60 (large surface area of the membrane, to achieve pre dilution flow and hope for enhanced phosphate removal

**Converted on HDF 5008 Autosub +**
- Blood flow 80 ml/min,
- Pre dilution flow 280-300 mL/min
- Na\textsubscript{D} 140 mmol/L
- CorDix 60
- After 4 weeks, volume overloaded with high blood pressure 145/95 mmHg, after decreasing Na\textsubscript{D} to 134 mmol/L : normalization of BP (95/45)
High efficiency HDF: reconsider the dialysis fluids composition, at least $\text{Na}_D$

- Need for adapted $\text{Na}_D$ in case of high convective volume
- Ca balance? Bicarbonate concentration?
- Thermic control (cooling)
HDF and Na\textsubscript{D} (sodium in dialysate)

- The substitution fluids (convective volume/dose) have the same sodium concentration as the dialysate (Na\textsubscript{D}): « on-line »
- Napl: the diffusible sodium
- Na\textsubscript{D} versus Napl, BCM\textsuperscript{®}, BVM\textsuperscript{®}, on line « Na diffusable »
- In predilution Na\textsubscript{D} 134 – 138 mmol/L
- In postdilution Na\textsubscript{D} 138 – 142 mmol/L
HDF: extracorporeal blood circulation, vascular access, lines, filter

- Vascular access: fistula (double/single puncture), central line
- Blood flow: 150mL/min/m²; dialysate flow $Q_D \geq 1$ to $1.5 \ Q_B$
- 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)
Hemodiafiltration versus hemodialysis in children

HDF with bags "lactate"

Dialysate: acetate, no endotoxins control

TABLE 1 - PARAMETERS USED FOR THE STUDY

<table>
<thead>
<tr>
<th>HD (12 months)</th>
<th>HDF (12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>plate (0.92 m2) cuprophane</td>
<td>capillary (1 m2) PAN</td>
</tr>
<tr>
<td>QB 120-160 ml/min</td>
<td>QB 120-160 ml/min</td>
</tr>
<tr>
<td>QD 500 ml/min</td>
<td>QD 500 ml/min</td>
</tr>
<tr>
<td>3 X 5 h/week</td>
<td>3 X 3 h/week</td>
</tr>
<tr>
<td>substitution fluid 7-9 (lactate)</td>
<td>substitution fluid</td>
</tr>
<tr>
<td>TMP less than 300 mmHg</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1 Hemodiafiltration schema.
Hemodiafiltration versus hemodialysis in children

M. Fischbach, Y. Attal, J. Geisert
Service de Nephrologie et d’Hemodialyse
Service de Pedriatre 3
Hopital de Hautepierre
Strasbourg, France

Increased « osmotic » tolerance

**TABLE IV - RELATIONSHIP BETWEEN UREA, CREATININE CLEARANCE IN HD (KHD) AND IN HDF (KHDF)**

<table>
<thead>
<tr>
<th></th>
<th>Urea</th>
<th>Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ml/min/kg body weight</td>
<td>ml/min</td>
</tr>
<tr>
<td>KHD</td>
<td>90 ± 2</td>
<td>4.3</td>
</tr>
<tr>
<td>KHDF</td>
<td>131 ± 9</td>
<td>6.3</td>
</tr>
</tbody>
</table>

**TABLE I - PARAMETERS USED FOR THE STUDY**

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<td>3 X 5 h/week</td>
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<tr>
<td>substitution fluid 7-9 (lactate)</td>
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</tr>
<tr>
<td>TMP less than 300 mmHg</td>
<td>TMP less than 300 mmHg</td>
</tr>
</tbody>
</table>
HDF versus HD: advantages

- Optimal blood purification capacities, both for urea and « middle molecular weight compounds » (Ph): high level dialysis dose easily 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 pressure control improvement (hemofiltration effect): osmotic stability, compartment preservation, peripheral vascular resistances, myocardial contractility.
**Hemodiafiltration with high permeable membranes in children**


<table>
<thead>
<tr>
<th>Method</th>
<th>TAc urea mmol/L</th>
<th>PCRn g/kg/j</th>
<th>Phosphate mmol/L</th>
<th>Aluminium prescription g/day</th>
<th>Hemoglobin g/dl</th>
<th>Need of transfusion per year</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD (15 h/week)</td>
<td>28±4</td>
<td>0.7±0.2</td>
<td>1.65±0.28</td>
<td>3</td>
<td>7.4</td>
<td>5</td>
<td>1981</td>
</tr>
<tr>
<td>HDF (9 h/week)</td>
<td>18±3</td>
<td>1±0.1</td>
<td>1.34±0.15</td>
<td>1.5</td>
<td>8.3</td>
<td>2</td>
<td>1982</td>
</tr>
<tr>
<td>HDF (9 h/week)</td>
<td>20±2</td>
<td>1.8±0.3</td>
<td>1.15±0.18</td>
<td>0.5</td>
<td>8.9</td>
<td>1</td>
<td>1983</td>
</tr>
</tbody>
</table>
Hemodiafiltration with high permeable membranes in children


<table>
<thead>
<tr>
<th></th>
<th>HD</th>
<th>HDF</th>
<th>HDF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 h/week</td>
<td>9 h/week</td>
<td>9 h/week</td>
</tr>
<tr>
<td></td>
<td>cuprophane</td>
<td>PAN</td>
<td>polysulfone</td>
</tr>
<tr>
<td></td>
<td>12 months</td>
<td>12 months</td>
<td>12 months</td>
</tr>
<tr>
<td>TAc urea mmol/L</td>
<td>28±4</td>
<td>18±3</td>
<td>20±2</td>
</tr>
<tr>
<td>PCRn g/kg/j</td>
<td>0.7±0.2</td>
<td>1±0.1</td>
<td>1.8±0.3</td>
</tr>
<tr>
<td>Phosphate mmol/L</td>
<td>1.65±0.28</td>
<td>1.34±0.15</td>
<td>1.15±0.18</td>
</tr>
<tr>
<td>Aluminium prescription g/day</td>
<td>3</td>
<td>1.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Hemoglobin g/dl</td>
<td>7.4</td>
<td>8.3</td>
<td>8.9</td>
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<tr>
<td>Need of transfusion per year</td>
<td>5</td>
<td>2</td>
<td>1</td>
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<td>Date</td>
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HDF versus HD : advantages

- Hemodynamic stability over the session: increased tolerance to weight loss and blood pressure control improvement (hemofiltration effect): osmotic stability, compartment preservation, peripheral vascular resistances, myocardial contractility.

- Optimal blood purification capacities, both for urea and «middle molecular weight compounds» (Ph): high level dialysis dose easily achieved.

- A high dialysis dose usually induce a good nutrition status, especially with an increased caloric intake (apetite).
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).
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
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
Dialysis membranes: practical parameters

- Type of membrane: biocompatibility, high flux
- Initial blood volume need, i.e., area related, quality of restitution
- Molecular permeability: maximal clearance for urea and the other uremic toxins, i.e., 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
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)
Adequate HDF prescription:

*importance of the membrane*

- Hydraulic permeability: high convective volume
  (> 25 L in postdilution; > 60 L in predilution)
- Molecular permeability: extraction coefficient
  (phosphate and $\beta_2$ m 80 %)
- Loss of albumine (< 5 gr)
- Purity of the dialysis fluids (backfiltration/convective flow)
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 \((\text{TMP} ; \text{mmHg})\)
- Sieving coefficient \((S)\) * Molecular permeability

\[ *S = \frac{2 \cdot C_{UF}}{c_i + c_o} \]

\( C_{UF} \): ultrafiltrate solute concentration

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

\[ Q_{UF} < \frac{1}{3} Q_B \] (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**

\[
K_{\text{HDF}} = K_{\text{HD}} + x Q_{\text{UF}} x 0.46
\]

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

with  \( Q_{\text{UF}} x S = K_{\text{HF}} \) and  \( Q_B = K_{\text{max}} \)

\[
K_{\text{HDF}} = K_{\text{HD}} + K_{\text{HF}} - \frac{K_{\text{HD}} x K_{\text{HF}}}{K_{\text{max}}}
\]

If  \( K_{\text{HD}} \) is equal to  \( K_{\text{max}} \) then  \( Q_{\text{HDF}} = K_{\text{HD}} \)
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.

![Diagram showing pre-dilution and post-dilution modes of substitution solution addition.]

In HDF addition of substitution solution can be made before the filter called *predilution* mode, after the filter, *postdilution* mode, or mixed.
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…
Hct\textsubscript{outlet} at which fractional filtration of plasma water is 0.50 for any level of Hct\textsubscript{a}. This relationship is independent of Qb\textsubscript{a}.

For an Hct\textsubscript{a} less than 0.35, Hct\textsubscript{0} « could allow » a higher FF (until 0.50) resulting in membrane fouling (high protein concentration).

For an Hct\textsubscript{a} a higher than 0.35, a FF of 0.5 results in an Hct\textsubscript{0} over 0.5; not safe, use Hct\textsubscript{outlet}.

**Conclusions**: the safest use for Q\textsubscript{UF} should be based on:

- Hct\textsubscript{outlet} ≤ 0.5 if Hct\textsubscript{a} > 0.35
- FF < 0.5 if Hct\textsubscript{a} < 0.35
Choice of modality with the use of High-Performance Membrane and evaluation for clinical effects


- 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.
mortality risk: dialysis fluids purity? HDF predilution?
Adequate HDF prescription: *importance of the membrane*

- Hydraulic permeability: high convective volume
  (> 25 L in postdilution; > 60 L in predilution)
- Molecular permeability: extraction coefficient
  (phosphate and $\beta_2$ m 80%)
- Loss of albumine (< 5 gr)
- Purity of the dialysis fluids (backfiltration/convective flow)
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
Hemodiafiltration in children 1981-2002

• Reduced intradialytic symptoms (tolerance to weight loss, hemodynamic stability, rapid osmotic clearance tolerance)

• Lowered $\text{TAC}_{\text{urea}}$ (Ku ml/min/kg increased)

• Phosphate management improved, less phosphate chelators

• Transfusions rate decreased, anemia control
HDF: volume control, dry weight

- Clinically and clinical team experience
- Blood pressure assessment (accuracy) and hydration evaluation (BCM)
- On-line relative plasma volume change (hematocrit 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
Dialysis adequacy today, a European perspective: morbidity, mortality, 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.
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

From 65% to less than 20% survival at 5 years
if BW loss per hour (UF rate) was over 1.25%

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.
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

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)
Blood Pressure versus hydration: weight loss and NaD
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.
UF rate $< 1.25\% / h \text{ BW}$ (floating dry weight) 
IDWG $< 4\%$ ? Euvolemia ? Cooling $T_D = 36^{\circ}$

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

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

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

The relation BP versus hydration in children on chronic hemodialysis: « far from clear »
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.
Dry-weight: A concept revisited in an effort to avoid medication-directed approaches for blood pressure control in hemodialysis patients

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

(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 (fistula quality, session time, membrane, dialysate)
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.

- 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+++)}
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)₂D₃, and phosphate as CKD progresses. When Klotho expression first decreases, FGF-23 increases, lowering circulating 1,25(OH)₂D₃, which depresses Klotho expression further and increases PTH expression. Increased PTH induces further FGF-23 increases, causing large decreases in 1,25(OH)₂D₃ 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.
The phosphate renal aging process: an independent pathogenic role

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


- Patients whose protein intake raises while their serum P declined over time showed the greatest survival (optimal nutrition/anabolism)

- Otherwise, the decline in phosphate 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)
The gut-kidney axis: indoxyl sulfate, \textit{p}-cresyl sulfate, endotoxins and CKD progression


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

- Uremic toxins production
- “leaky” gut (endotoxins)
P-cresyl sulfate and indoxyl sulfate in hemodialysis patients

• 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
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.
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
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.
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

High BP not always overhydrated
Low BP not always underhydrated
Dry-weight: A concept revisited in an effort to avoid medication-directed approaches for blood pressure control in hemodialysis patients

• 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.
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.
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.
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


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

37% patients hypertensive
« only » 40% of them on overhydration
dialysis dose and outcome:
more intensive, more frequent, a « complete » dialysis dose

*Kt/Vurea reassessment, addition of a convective volume*


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

<table>
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<tr>
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<td><strong>Distance from center</strong></td>
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<td>HD or HDF</td>
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</tbody>
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**Social life**

- **Night**
  - At home
  - At home
- **Dialysis center**
  - 3 h
  - 8 h
  - 8 h
- **“Night life”**
  - Possible
  - Restricted
  - Restricted
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)
HDF : mise en place

• Traitement de l’eau : pureté, désinfection (stérilisation thermique, thermo chimique)
• Membrane d’HDF : « autocontrol » pre, post, mixed
• Membrane d’HDF :
  – Volume convectif (perméabilité hydraulique)
  – Coefficient d’extraction (perméabilité moléculaire, $\beta_2$ 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 ($\beta_2$ m 80 %)
- Perte d’albumine (< 5 gr)
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): $\beta_2$ microglobulin, phosphate

4) A complete dialysis dose: Kt/V urea (>1.4) and the convective volume (? >14L postdilution /adult; impact on $\beta_2$ microglobulin, phosphate)
Long ± term effects of high efficiency on-line hemodiafiltration on uremic toxicity; a multicentre prospective randomized study


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


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- **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**
Hemodiafiltration: The addition of convective flow to hemodialysis: “a complete dialysis dose”.

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.
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
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

- **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 ($\beta_2$ microglobulin
  - regulation of calcification inhibitors, like: fetuin-A, matrixGLA protein, osteoprotegrin
DOPPS study – HDF vs HD: “clear effect of the amount of the convectif volume”

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
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


Fig. 3. Overall (A) and cardiovascular survival (B) among the treatment groups.
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 analysis, 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.
Mortality and cardiovascular events in online haemofiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study

• 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).
In general, no impact, but 30% did not reach the end point, a « high convective volume »
Effect of on line HDF on all case mortality and cardiovascular outcome

Grootemann MPD et al. for the CONTRAST investigators.

- 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 microglobulin (mg/dl) pre dialysis: in OL-HDF 26.4 (0.37), versus in low flux HD 35.4 (0.54) p<0.001
High-efficiency postdilution OL-HDF reduces all-cause mortality in hemodialysis patients


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.
## Impact of high convective volume

<table>
<thead>
<tr>
<th>Study name</th>
<th>Threshold volume for survival benefit (observational studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOPPS (Canaud) 2006</td>
<td>&gt; 15 L</td>
</tr>
<tr>
<td>Riscarid (Panichi) 2008</td>
<td>&gt; 23 L</td>
</tr>
<tr>
<td>Contrast (Grooteman) 2012</td>
<td>&gt; 21.95 L</td>
</tr>
<tr>
<td>Purkush (Ok) 2012</td>
<td>&gt; 17.4 L</td>
</tr>
<tr>
<td>ESHOL (Madrid/Maduell) 2013</td>
<td>&gt; 23.1 L</td>
</tr>
<tr>
<td><strong>Minimal convective volume</strong>, post dilution</td>
<td>? 3 L/m²/h or 12-15 L/m²/session</td>
</tr>
<tr>
<td>or predilution (easier to achieve)</td>
<td>?18-27 L/m²/session</td>
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## Impact of high convective volume

<table>
<thead>
<tr>
<th>Study name</th>
<th>Threshold volume for survival benefit</th>
<th>% patients not achieving target « postdilution » volume</th>
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<td>DOPPS (Canaud) 2006</td>
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<td>&gt; 30 %</td>
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<tr>
<td>ESHOL (Madrid) 2013</td>
<td>&gt; 23.1 L</td>
<td>10-15 %</td>
</tr>
<tr>
<td>Minimal convective volume ?</td>
<td>? 3 L/m²/h</td>
<td></td>
</tr>
</tbody>
</table>

**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, overhydration/dehydration, and allowed a «free» diet, therefore induced «accepted» nutrition, all together+++conducting to

- A rescue therapy for cardiac impairment

- 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

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

FISCHBACH M, TERZIC J, MENOUER S, DHEU C, SEUGE L, ZALOSSZIC A.
Nephrol Dial Transplant 2010; 25: 867-73
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/m²), 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
Fig. 1: Bicarbonatemia, measured pre post dialysis session, mean of monthly determinations over the patient follow up on daily on line hemodiafiltration (dialysate bicarbonate 32mM/L)
Serum bicarbonate and mortality in stage 3 and stage 4 CKD


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

- $\beta_2$ microglobuline (predialysis) 15.3±3.3 mg/L

- TAD urea 2.4+/− 0.5; TAD bicar 0.65+/−0.13
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

Fig. 2  Median (range) normalized height standard changes ($\Delta$ h 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

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 nutrition: less malnutrition, less cachexia*
– *improved uremic toxins detoxification (β₂microglobuline)*
– *improved physical activity, less sleep disturbances*
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
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)
OL-HDF in infants > 7/10 kg:
FX3 (30mL), baby lines postdilution (54mL),
children lines (75mL) predilution
Baby arterial line and children veinous line
OL-HDF in infants / children feasibility and material availability

• « baby lines » 56mL, no arterial chamber, postdilution, « children lines » 78mL, arterial chamber, predilution, possibility to mix the lines babyArt +childrenVe=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)
HDF versus HD : advantages

• Hemodynamic stability over the session : increased tolerance to weight loss and blood pression control improvement (*hemofiltration effect*) : osmotic stability, compartment preservation, peripheral vascular resistances, myocardial contractility

• Optimal blood purification capacities both for urea and middle molecular weight compounds : high level dialysis dose easily achieved. A high dialysis dose usually induce a good nutrition status, especially with an increased caloric intake (*apetite*)
OL-HDF in infants:
FX3, baby lines
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)


Acidosis prevents growth hormone-induced growth in experimental uremia

• The presence of severe metabolic acidosis blunts the response to GH in uremic and non-uremic rats: protein wasting
• Plasma IGF₁ was unrelated to pH or HCO₃-
• 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 IGF₁ 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

- Besides uremia per se, the effectiveness of GH might be attenuated by factors often found in CKD patients, 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 tissue potassium uptake.
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
Survival in pediatric dialysis and transplant patients

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.

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).
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
Endotoxin level: not detectable
CHU Strasbourg 2012

<table>
<thead>
<tr>
<th>Dialysat</th>
<th>Résultats</th>
<th>Niveau cible</th>
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<tbody>
<tr>
<td>Flore aérobie revivifiable à 22°C</td>
<td>E 3921</td>
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<td>Endotoxines bactériennes</td>
<td>E 3923</td>
<td>&lt; 0,005 UI/ml</td>
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<th>Résultats</th>
<th>Niveau cible</th>
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Endotoxin level: not detectable
CHU Strasbourg 2014

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<tr>
<th>Dialysat :</th>
<th>N° analyse</th>
<th>Résultats</th>
<th>Niveau d’alerte*</th>
<th>Niveau d’action*</th>
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<td>E 6813</td>
<td>&lt; 1 UFC/100ml</td>
<td>&lt; 5 UFC/100ml</td>
<td>&lt; 10 UFC/100ml</td>
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<td>Endotoxines bactériennes</td>
<td>E 6815</td>
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<th>Résultats</th>
<th>Niveau d’alerte*</th>
<th>Niveau d’action*</th>
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<td>Endotoxines bactériennes</td>
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<td>&lt; 0,005 UI/ml</td>
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* d’après la norme internationale ISO 23500:2011
ISO 23500:2011/2014
Guidance for the preparation and quality management of fluids for haemodialysis and related therapies

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<tr>
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<th>Résultats</th>
<th>Niveau d’alerte*</th>
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</tbody>
</table>

* d’après la norme internationale ISO 23500:2011
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)
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 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

- Charcoal filtration (0.2 µ)
- Reverse osmosis
- Dialysate filtration
- Filtered ultrapure dialysate: on line production of hemofiltration substitution fluid
HDF allows an optimal blood purification not only for urea, but also for the middlemolecular weight compounds (Babb theory).

*From M Fischbach et al. *Contr Nephrol* 1985
### 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

<table>
<thead>
<tr>
<th>Small water soluble solutes</th>
<th>Protein-bound solutes</th>
<th>Middle molecules</th>
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<tbody>
<tr>
<td>Asymmetric dimethylarginine</td>
<td>3-Deoxyglucosone</td>
<td>Adrenomedullin</td>
</tr>
<tr>
<td>Benzylalcohol</td>
<td>CMPF</td>
<td>Atrial natriuretic peptide</td>
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<tr>
<td>β-Guanidinopropionic acid</td>
<td>Fructoselysine</td>
<td>β2-Microglobulin</td>
</tr>
<tr>
<td>β-Lipotropin</td>
<td>Glyoxal</td>
<td>B-Endorphin</td>
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<tr>
<td>Creatinine</td>
<td>Hippuric acid</td>
<td>Cholecystokinin</td>
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<td>Cystidine</td>
<td>Homocysteine</td>
<td>Clara cell protein</td>
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<td>Guanidine</td>
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<td>Guanidinocinnamic acid</td>
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<td>Uric acid</td>
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<td>Xanthine</td>
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Dialysis dose and growth
(Surface area normalized standard Kt/V: SAN)

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).

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

Over 2.45
Hemodiafiltration: The addition of convective flow to hemodialysis: “a complete dialysis dose”.


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.
Impact of convective flow on phosphorus removal in maintenance haemodialysis patients


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.

Phosphate should be considered as a MMW uremic toxin in terms of dialysis purification: water molecular environment; importance of the convection (HDF)
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).
Serum $\beta_2m$ levels and mortality in the HEMO study: less than 27.5 is "better"

Predialysis $\beta_2m$ level significantly correlated with all-cause mortality ($p = 0.001$)

Cheung et al, JASN 2000

<table>
<thead>
<tr>
<th>Cumulative mean predialysis serum $\beta_2m$ (mg/L)</th>
<th>Relative Risk</th>
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</thead>
<tbody>
<tr>
<td>&lt; 27.5</td>
<td>1.0</td>
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<tr>
<td>27.5–35</td>
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<td>42.5–50</td>
<td>1.6</td>
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<tr>
<td>&gt; 50</td>
<td>1.8</td>
</tr>
</tbody>
</table>

$n = 1,813$
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): $\beta_2$ microglobulin, phosphate
4) A complete dialysis dose : Kt/V urea (>1.4) and the convective volume (?, >14L postdilution /adult; impact on $\beta_2$ microglobulin, phosphate)
Impact of treatment time:

Longer treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality in the DOPPS.

1) UF rate /session time/ ECV control : a UF over 10mL/h/kg BW is a mortality risk factor

2) Phosphate, the “silent 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)
Phosphate end dialysis value: a misleading parameter of hemodialysis efficiency


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

- 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

Postdialytic phosphate rebound
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 inflammation /cachexia),
  - global purification capacity: « a complete dialysis dose », a determined diffusive dose (Kt/Vurea) and a determined convective dose (convective volume/phosphate/ \( \beta_2 \)-microglobulin) , and
  - optimal hemodynamic tolerance (HF)
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 chosen 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: beta2microglobulin story (amyloidosis, marker of purification/outcome)
High convective volume: need for a change of the dialysis composition (Na$_D$) ?

- We learned the need for 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 sufficient to restore normal blood pressure.
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 ?
Hemodiafiltration versus hemodialysis in children

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TABLE I - PARAMETERS USED FOR THE STUDY

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HD (12 months)</th>
<th>HDF (12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>dialyzer</td>
<td>plate (0.92 m²) cuprophane</td>
<td>capillary (1 m²) PAN</td>
</tr>
<tr>
<td>Qb</td>
<td>120-160 ml/min</td>
<td>120-160 ml/min</td>
</tr>
<tr>
<td>Qp</td>
<td>500 ml/min</td>
<td>500 ml/min</td>
</tr>
<tr>
<td>dialysis time</td>
<td>3 X 5 h/week</td>
<td>3 X 3 h/week</td>
</tr>
<tr>
<td>substitution fluid</td>
<td>7.9 (lactate)</td>
<td>TMP less than 300 mmHg</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>HD (15 h/week)</th>
<th>HDF (7.5 - 9 h/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>start</td>
<td>end</td>
</tr>
<tr>
<td>urea mmol/l</td>
<td>40 ± 6</td>
<td>16 ± 3</td>
</tr>
<tr>
<td>creatinine μmol/l</td>
<td>1,080 ± 256</td>
<td>410 ± 167</td>
</tr>
<tr>
<td>phosphate mmol/l</td>
<td>1.65 ± 0.28</td>
<td>0.9 ± 0.19</td>
</tr>
</tbody>
</table>

TAC urea:
HD : 28 mmol/l
HDF : 18 mmol/l
Hemodiafiltration advantages

- Optimized hemobiocompatibility: bicarbonate dialysate, synthetic membrane, retrofiltration control
- Better anemia control
## Hemoglobine values and need for transfusions

<table>
<thead>
<tr>
<th></th>
<th>HD (12 months)</th>
<th>HDF (12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb g/dl</td>
<td>7.4</td>
<td>8.3</td>
</tr>
<tr>
<td>Number of transfusions for the whole group</td>
<td>32 (mean 5)</td>
<td>12 (mean 2)</td>
</tr>
<tr>
<td>Membrane</td>
<td>Cuprophane</td>
<td>Polyacrylonitrile</td>
</tr>
<tr>
<td>Duration (sessions)</td>
<td>3x5 h</td>
<td>3x3 h</td>
</tr>
</tbody>
</table>

M Fischbach, Y Attal, J Geisert, J of Pediatr Nephrol 1984; 5:151-4
Hemodiafiltration with high permeable membranes in children


<table>
<thead>
<tr>
<th></th>
<th>HDF PAN</th>
<th>HDF Polysulfone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb g/dl</td>
<td>8.3±0.3</td>
<td>8.9±0.2</td>
</tr>
<tr>
<td>Need of transfusion (ml/kg)</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Duration</td>
<td>3x3 h</td>
<td>3x3 h</td>
</tr>
</tbody>
</table>
Hémofiltration, volume échangé (litre/séance), clairance (extraction moléculaire)

\[
\text{Cl}_{HF} = Q_{HF} \times Ct
\]

\[
Q_{HF} \leq \frac{1}{3} Q_{sg} \text{ (post dilution)}
\]

\[
Q_{HF} > \frac{1}{3} (>1/1) Q_{sg} \text{ (predilution)}
\]
Hemodiafiltration (1)

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


- 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.
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.
High efficiency OL-HDF : (re)consider the Na\textsubscript{D}

Ali, 3 years old, congenital nephrotic syndrom, anuric, 14 kg BW, 0.75 m\textsuperscript{2} BSA, central catheter:

**On pre dilution HDF, 4008**
- Blood flow 80 ml/min,  
- Substitution flow 80 ml/min  
- Na\textsubscript{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 phosphate removal

**Converted on HDF 5008 Autosub +**
- Blood flow 80 ml/min,  
- Pre dilution flow 280-300 mL/min  
- Na\textsubscript{D} 140 mmol/L  
- CorDiax 60  
- After 4 weeks, volume overloaded with high blood pressure 145/95 mmHg, after decreasing Na\textsubscript{D} to 134 mmol/L : normalization of BP (95/45)