Hemodiafiltration in children, a history

1) July 1981 HDF with bags, reverse osmosis at bedside, diffusion and convection, tolerance

2) November 1989 HDF on line production of substitution fluid, purity of the dialysis fluids (endotoxins)

3) September 2002 daily OL-HDF (autosub+) : catch up growth

high efficiency hemodiafiltration
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...
High technology, and life
OL-HDF in infants > 7/10 kg:
FX3 (30mL), baby lines postdilution (54mL),
children lines (75mL) predilution
Intensified dialysis? What is new?

Hemodiafiltration with high convective volume « daily »

a rescue therapy or for « all »?

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Children Dialysis Unit - Strasbourg - France
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, patients/children treated by this conventional dialysis regime still have an increased risk of cardiovascular morbidity, impaired growth, malnutrition due to protein wasting and bad volume control.

As a result, there is a growing interest in the delivery of more intensive hemodialysis, that is hemodiafiltration, high efficiency HDF, daily “optimized” dialysis.
Increased cardiovascular risk for children on ESRF: predialysis, dialysis, transplantation

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

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

Foley RN, Parfrey PS, Sarnak MJ 1998
Major progress of final adult height have been made during the past decades for dialysed children, nevertheless ongoing improvement is necessary.

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

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


- At the time of Tx children with CRF are significantly shorter than their peers

- The final adult height correlated with the height deficit at the time of kidney Tx: need to optimize growth during dialysis time

- Spontaneous catch-up growth remains often insufficient after pediatric kidney transplantation despite satisfactory GFR function

- As long as corticosteroids are believed to be essential after renal Tx, rhGH should be considered to optimize longitudinal growth in children
Nutritional status in dialyzed children

- Malnutrition due to poor appetite and restrictive diet, could be cured by dietary replacement, supplementation: nasogastric and gastrostomy feeds (PD) and intradialytic feeding (HD).

- Cachexia is due to loss of protein stores despite no inadequate diet: no optimal dialysis (acidosis, inflammation, purification).

- All together impacting on final outcome:
  - statural growth retardation: rhGH « resistance », morbidity
  - uremic cardiomyopathy and vasculopathy: mortality
Muscle wasting in chronic kidney disease: the role of the ubiquitine proteasome system and its clinical impact

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

Cachexia in uremic patients: loss of protein stores, muscle wasting, growth impairment: ATP-dependent, ubiquitin-proteasome system
From adequate to intensified dialysis

• « adequacy » assessment: outcomes
  (morbidity/mortality/cachexia/growth) and surrogates like urea kinetics (diffusion process) and more (β2 microglobuline or convective volume for convection mass transport?),

• How to improve conventional HD:
  ✓ high flux membrane for « all »
  ✓ biocompatibility/purity of the dialysis fluids (endotoxin’s level),
  ✓ volume control (dry weight/BP/LVH): interest of an objective assessment (bioimpedancemetry, BCM), reduction in UF demands per dialysis session
  ✓ should HDF become the standard for in center dialysis?

• More dialysis, more frequent/longer sessions: « daily » dialysis, daily in center high efficiency hemodiafiltration
Dialysis dose and growth
(Surface area normalized standard Kt/V: SAN)

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

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

Do we need indicators of dialysis adequacy based on middle molecule removal?


• From urea to MMW toxins purification: major importance of the convective flow/volume (HDF)
• At present, the most valid candidate is β₂ microglobulin, a threshold of 25 mg/l (predialysis) might be proposed
• Phosphate should be considered as a MMW uremic toxin in terms of dialysis purification: water molecular environment
• The need for high flux membranes and the importance of a high convective volume (HDF)

Predialysis β₂m level significantly correlated with all-cause mortality (p= 0.001) Cheung et al, JASN 2000
Adequacy of dialysis in children: does small solute clearance really matter?
Goldstein SL. Pediatr Nephrol 19: 1-5, 2004
Dialysis and outcome: dialysis dose, dialysis time, specific impact of convection

- A minimum Kt/V urea (equilibrated) level of 1.2-1.4 (URR 65 to 75 %) is thought to be desirable
- Only « small solute urea clearance » prescription? Dialysis prescription should be not only a « urea dialysis dose »: phosphate and β2 microglobuline clearances +++ (convective flow)
- Dialysis and residual renal small-solute clearance are not equivalent

Optimal Hemodialysis Prescription: Do children need more than a urea dialysis dose?


Kt/Vurea (diffusion) and a “high” convective volume (HDF)
From adequate to optimal dialysis

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

• How to improve conventional HD:
  ✓ high flux membrane for « all »
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  ✓ should HDF become the standard for in center dialysis ?

• More dialysis, more frequent/longer sessions: « daily » dialysis, daily in center high efficiency hemodiafiltration
High-flux or low-flux dialysis? High-flux membranes recommended for all patients


Guideline 2.1 (EBPG, 2002): synthetic, high-flux membranes should be considered to delay long-term complications of HD therapy.

Specific indications include: to reduce dialysis-related amyloidosis (III); to improve control of hyperphosphataemia (II); to reduce the increased cardiovascular risk (II); to improve control of anaemia (III).

Guideline 2.1 (ERBP Advisory Board, 2010): synthetic, high-flux membranes should be used to delay long-term complications of HD therapy in patients at high risk (alb<40 g/L) (level 1A: strong recommendation based on high-quality evidence).

In view of underlying practical considerations, and the observation of a reduction of an intermediate marker (β2-microglobulin), synthetic, high-flux membranes should be recommended even in low-risk patients (level 2B: weak recommendation, low quality evidence).
The clinical benefits of high-performance (HPM) dialyzers have often been reported since the advent of the synthetic polyacrylonitrile dialysis membrane.

HPMs, which have high water permeability, eliminate a wide spectrum of uremic toxins and offer excellent biocompatibility, are now essential for hemodialysis, hemofiltration, and hemodiafiltration.

For HPMs whose mean pore size is enlarged to secure better dialysis membrane performance, however, the dialyzing fluid must be highly purified to prevent contamination.
Masakane Ikuto ASN 2008: 
mortality risk and dialysis fluids purity

1) Endotoxines in the dialysat < 0,05 UI/ml 
in 93,6 % dialysis center from Japan 

2) Mortality risk correlate to the endotoxin level in the dialysate: 
RR 1 if < 0.001 ET/ml versus RR 1.48 if 0.1 à 0.25 ET/ml
### Recommandations for a « standard » dialysate

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

### Recommandations for an « ultrapur » dialysate

<table>
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<tr>
<th></th>
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<tbody>
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<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 for the substitution fluid (convective volume)

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High-flux dialysis: limitations?

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

Not determined and internal convective flow, that is « internal » hemodiafiltration compenstate by backfiltration, from dialysate (purity, endotoxines free?)

High-flux dialysis: limitations?

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

High-flux HD
- Not determined and internal convective flow, compensate by backfiltration
- UF = (weight loss) +/- backfiltration
- Uncontrolled and unknown convective removal

On-line HDF
- Determined and high convective flow = « no » backfiltration
- UF = (weight loss) + convective flow
- No backfiltration
- Filtered / pure dialysate
- Controllable and measurable convective removal

1) **If economically feasible,** high-flux membranes should be used in combination with ultrapure disposable dialysate, but small convective volume, low efficiency HDF…for the same price!

2) **High efficiency Hemodiafiltration** (high convective volume), is a safe routine replacement therapy: a “complete” use of a high flux membrane, with a large determined convective volume (no more cost, but more efficiency)
From adequate to optimal dialysis

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

• How to improve conventional HD:
  ✓ high flux membrane for « all »
  ✓ biocompatibility/purity of the dialysis fluids (endotoxin’s level),
  ✓ volume control (dry weight/BP/LVH): interest of an objective assessment (bioimpedancemetry, BCM), reduction in UF demands per dialysis session
  ✓ should HDF become the standard for in center dialysis ?

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

1) Highly permeable membranes for « all »

2) One should consider, as a new standard in HD, that the minimal treatment time of \textit{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)

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 12mL/H/kgBW
- Importance of dialysis time
- Reduction in UF demands per session
From adequate to optimal dialysis

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Hémodiafiltration modalities

If the convective flow exceeds the desired weight loss, the fluid balance is maintained by an infusion of replacement fluid (bags, dialysate, on-line substitution), as applied in HF or HDF

- **Conventional, classical, historical HDF**: substitution fluid (bags) with « balanced » compensation

- **High flux hemodialysis i.e. internal HDF**: highly permeable membranes with retrofiltration due to the high hydraulic permeability coefficient (dialysate backfiltration risks)

- **On line HDF**: substitution fluid produced from the « ultrafiltered ultrapur dialysate »
Different forms of HDF: internal HDF, classical HDF (with bags), on-line HDF
On line HDF: substitution fluid produce on line from the dialysate

On-line HDF

blood

ultrapure dialysis fluids

controllable and measurable convective removal
Hemodiafiltration: pre/post dilution, or mixed

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

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

- **Membrane adsorption (+++ ?)**
HDF combines HD and HF

Solute removal profiles
diffusion vs convection

From: Ledebo, ARRT 1999
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**

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

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

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

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

**If** \( K_{HD} \) **is equal to** \( K_{max} \) **then** \( Q_{HDF} = K_{HD} \)
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
### Hemodiafiltration with high permeable membranes in children


<table>
<thead>
<tr>
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<th>HD 15 h/week</th>
<th>HDF 9 h/week</th>
<th>HDF 9 h/week</th>
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<tr>
<td></td>
<td>cuprophane</td>
<td>PAN</td>
<td>polysulfone</td>
</tr>
<tr>
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<td>12 months</td>
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</tr>
<tr>
<td>TAc urea</td>
<td>28±4</td>
<td>18±3</td>
<td>20±2</td>
</tr>
<tr>
<td>mmol/L</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PCRn g/kg/j</td>
<td>0.7±0.2</td>
<td>1±0.1</td>
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<td>Phosphate</td>
<td>1.65±0.28</td>
<td>1.34±0.15</td>
<td>1.15±0.18</td>
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<tr>
<td>mmol/L</td>
<td></td>
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<td>Aluminium</td>
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<tr>
<td>prescription g/day</td>
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<td></td>
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<tr>
<td>Hemoglobin g/dl</td>
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<td>8.3</td>
<td>8.9</td>
</tr>
<tr>
<td>Need of</td>
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<td>2</td>
<td>1</td>
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<tr>
<td>transfusion per year</td>
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<tr>
<td>Date</td>
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## Hemodiafiltration with high permeable membranes in children


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The effect of dialysis modality on phosphate control: HD compared to HDF.
The Pan Thames Renal Audit
A. Davenport et al. Nephrol Dial Transplant 2010; 25:897-901

- HDF offers improved phosphate control compared to standard intermittent HD

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

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

- 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).

- 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.
HF and HDF predilution, reduce intradialytic hypotension in ESRD

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)
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 (β2 microglobulin
  - regulation of calcification inhibitors, like: fetuin-A, matrixGLA protein, osteoprotegrin
High-efficiency postdilution OL-HDF reduces all-cause mortality in hemodialysis patients

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.
# 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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<tbody>
<tr>
<td>DOPPS (Canaud) 2006</td>
<td>&gt; 15 L</td>
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<tr>
<td>Riscarid (Panichi) 2008</td>
<td>&gt; 23 L</td>
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<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>
</tbody>
</table>

**Minimal convective volume**, post dilution or predilution (easier to achieve?)

- ? 3 L/m²/h or 12-15 L/m²/session
- ? 18-27 L/m²/session
Convective therapies *versus* low-flux hemodialysis for chronic renal failure: a meta-analysis of randomized controlled trials


While clinical practice guideline for adequacy of hemodialysis have traditionally focused on the removal of small molecular-weight solutes, *annual mortality rates of patients with chronic kidney failure treated by conventional hemodialysis have remained alarmingly high.*

**Convective therapies resulted in a decrease:**

- in all-cause mortality,
- cardiovascular mortality,
- all-cause hospitalization,
- and therapy-related hypotension.
HDF and $\text{Na}_D$ (sodium in dialysate)

- The substitution fluid (convective volume/dose) has the same sodium concentration as the dialysate ($\text{Na}_D$): « on-line »
- Napl : the « on line » diffusible sodium
- $\text{Na}_D$ versus Napl, BCM®, BVM®
- In predilution $\text{Na}_D$ 134 – 138 mmol/L
- In postdilution $\text{Na}_D$ 138 – 142 mmol/L
Adequate HDF prescription: *importance of the membrane*

- Hydraulic permeability: high convective volume
  (> 25 L in postdilution; > 60L in predilution)
- Molecular permeability: extraction coefficient
  (phosphate and $\beta_2$ m 80 %)
- Loss of albumine (< 5 gr)
- Purity of the dialysis fluids
On-line HDF: *a combination of solute removal, « purification » and dialysis fluids purity*


**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
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\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’Analyses, Institut de Chimie biologique (Pr. J. Vincendon), Strasbourg, France

Fig. 1. $\beta_2$M serum level variations in HDF with different membranes (mean $\pm$ SEM, n = 30 sessions).

Fig. 2. $\beta_2$M Serum level variations with a polysulfone membrane versus condition of dialysis management: HF, HD or HDF (mean $\pm$ SEM; n = 30 sessions).
Beta-2-Microglobulin in Hemodiafiltered Children: Long-Term Efficiency Follow-Up

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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)

<table>
<thead>
<tr>
<th>Pooled dialysate and/or filtrate</th>
<th>Serum, mg/l</th>
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</thead>
<tbody>
<tr>
<td>volume</td>
<td>$\beta_2$M</td>
<td>mg/l</td>
</tr>
<tr>
<td>HF</td>
<td>9 ± 0.6</td>
<td>3.4 ± 0.5</td>
</tr>
<tr>
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<td>0.8 ± 0.2</td>
</tr>
</tbody>
</table>

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 × 3 h/week</td>
<td>1.5 years</td>
<td>3 × 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.

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>
### Uremic toxins

*Vanholder R et al. KI 2003; 1934-43*

The small water soluble compounds (prototype urea): < 500D
The protein-bound compounds (prototype p-cresol)
The larger “middle molecules” (prototype β₂-microglobulin): > 500D

<table>
<thead>
<tr>
<th>Low MW</th>
<th>Middle large MW</th>
<th>Protein bound compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 500 D²</td>
<td>&gt;500 &lt;60 000</td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>β₂ m</td>
<td>Paracresol</td>
</tr>
<tr>
<td>Guamidine</td>
<td>Leptine</td>
<td>Indoxyl sulfate</td>
</tr>
<tr>
<td>Phosphate</td>
<td>AGE</td>
<td></td>
</tr>
<tr>
<td>Acide urique</td>
<td>Interleukines, TNFα</td>
<td></td>
</tr>
<tr>
<td>Oxalate</td>
<td>Ig light chain</td>
<td>Homocysteine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTH</td>
</tr>
</tbody>
</table>
The gut-kidney axis: indoxyl sulfate, \( p \)-cresyl sulfate and CKD progression

Björn KI Meijers and Pieter Evenepoel.
Nephrol Dial Transplant 2011; 26:759-761
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
P-cresol, a protein-bound uremic toxin impact on survival


Total solute removal (mg)

- HD high-flux
- HDF post 20L
- HDF pre 60L

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

Improved survival

N= 175 HD patients, pros. obs. study
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>Q_{b 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).
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 (fistulla quality, session time, membrane)
From adequate to optimal dialysis

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

• How to improve conventional HD:
  ✓ high flux membrane for « all »
  ✓ biocompatibility/purity of the dialysis fluids (endotoxin’s level),
  ✓ volume control (dry weight/BP/LVH): interest of an objective assessment (bioimpedancemetry, BCM), reduction in UF demands per dialysis session
  ✓ should HDF become the standard for in center dialysis ?

• More dialysis, more frequent/longer sessions: « daily » dialysis, daily in center high efficiency hemodiafiltration.
dialysis dose and outcome in children: more intensive, more frequent, a « complete » dialysis dose

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


high KT/V: weekly KT/V of ~ 10?
Complete dialysis dose
Longer or more frequent sessions?
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
Dialysis regimen: in center daily on-line HDF

- In center daily **on line/high efficiency HDF** (since September 2002)
- **6 times per week** (18h/week; 3 hour session)
- "floating" dry weight
- **ultrapure dialysate**, highly permeable membrane (polysulphone),
- **Kt/Vurea** of at least 1.4 per session; Kt/Vurea assessed at each session by the on line clearance monitoring, quality tool
- Convective volume 27 L/m²/session, predilution reinfusion (equivalency of 9 to 12 L/m²/session in postdilution)
Dialysis tolerance:

- During the sessions: **no symptoms of intolerance**, no dyscomort, optimal UF tolerance and dry weight easily reached over the weekly dialysis procedure, adhesion to school working during the sessions (no « fatigue »)

- Post dialysis: **no recovery time**, less sleep disturbances, normal feeling out of the dialysis center, « natural » compliance to whole therapy (dialysis, diet and medications in attempt to be kidney transplanted)
Dialysis purification capacities: DIH

- Weekly $\text{Kt/V}_{\text{urea}}$ around 10 (SAN $\text{Kt/V}$ over 2.45): high dialysis dose, equivalency of 35% GFR (from CKD5 to CKD3)

- Predialytic phosphate values: median 1.39 mmol/l (range 1.65 to 0.63), despite high protein intake (more than 2 g/kg/day) and only 2/15 child on chelators (normal $\text{Ca x P}$)

![Graph showing calcification score vs age](image1)

normal $\{\text{Ca x P}\}$ product

Less vascular risk ???
### In center daily on line hemodiafiltration: a five years children experience.


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

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

Posterior Wall thickness

Interventricular Septum

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


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

FISCHBACH M, TERZIC J, MENOUER S, DHEU C, SEUGE L, ZALOSCZIC A.
Nephrol Dial Transplant 2010; 25: 867-73
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/\(\text{y}\)
  - first year of daily: 14.3+/-3.8 cm/\(\text{y}\)
  - mean over daily: 8.9+/-2.2 cm/\(\text{y}\)
- **Height (SDS)**
  - start: -1.5+/-0.3
  - end: +0.2+/-1.1
  - target parental height: -0.3
  - end- target: +0.5
Patient 1 on daily OL-HDF

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

1 growth in SD  2 growth velocity  3 BMI
Patient 2 on daily OL-HDF

PDI (g/kg/d) : 2.9 ± 0.3
nPNA (g/kg/d) : 1.31 ± 0.11
Mean growth velocity (cm/year) : 8.1
Achieved height versus familial expected height (SDS) : -1.3

1 growth in SD  2 growth velocity  3 BMI
Results

- **BMI kg/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 (β₂ microglobuline)
– improved physical activity, less sleep disturbances
Daily hemodiafiltration in children in center, from CKD5 to CKD3

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

High flux membranes (for « all »)
Purity of dialysis fluids (endotoxins< 0.001 UI / ml)
Volume control (BP, LVH…) UF rate < 10mL/kg/h
Determined convective volume (urea and more) : HDF
Phosphate control « without » phosphate binder
Inflammation control (beta2 micro)
Anabolisme, growth, preservation of life chance

More dialysis time (daily and intensive)
Hemodialysis prescription: passed, present and near future

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

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

« first class » therapy: in center daily high efficiency hemodiafiltration
Cost is of importance, but the highest standard should be offered to children waiting for TX.
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
Intensified hemodialysis regimens: 

neglected treatment options for children and adolescents


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

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

Recent advances in pediatric dialysis, a review of selected articles

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

Intensified HD may improve growth and LVH in children

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
How to improve conventional hemodialysis

- *Prescribe high flux membrane for all at risk patients*, « children », but: 1) high flux = risk of backfiltration; 2) high flux = non determined (low) convective flow/volume; 3) high flux = need for ultrapure dialysate (same cost)+++  
- Dialysis time: *not too short and from intermittent (and some « rescue sessions ») to daily dialysis* («physiologically/no peak-valley» dialysis without stress)  
- Consider not only a urea dialysis dose (diffusive process) but also a convective dialysis dose (middle molecular weight compounds/Ph-β₂micro):  
  
  *HDF is superior to HD, HDF adds a convective flow to HD, OL-HDF allows the prescription of a determined/high convective volume per session*  
- Tools for hemodialysis, on line monitoring during the session:  on line Kt/Vurea, BVM, dialysate modelling (sodium, dialysate temperature), UF modelling  
- BCM (multiimpedancemetry): Vurea, nutrition, hydration assessment, BP management (volodependent or not)
How to improve conventional hemodialysis

- **Prescribe high flux membrane for all at risk patients**, « children », but: 1) high flux = risk of backfiltration; 2) high flux = non determined (low) convective flow/volume; 3) high flux = need for ultrapure dialysate (same cost)+++  

- **Dialysis time**: *not too short and from intermittent (and some « rescue sessions ») to daily dialysis («physiologically/no peak-valley» dialysis without stress)*

- Consider not only a urea dialysis dose (diffusive process) but also a convective dialysis dose (middle molecular weight compounds/Ph-β₂micro):  
  
  *HDF is superior to HD, HDF adds a convective flow to HD, OL-HDF allows the prescription of a determined/high convective volume per session*

- **Tools for hemodialysis**, on line monitoring during the session: on line Kt/Vurea, BVM, dialysate modelling (sodium, dialysate temperature), UF modelling

- **BCM (multiimpedancemetry)**: Vurea, nutrition, hydration assessment: BP management
Differences in prescribed $Kt/V$ and delivered haemodialysis dose
why obesity makes a difference to survival for haemodialysis patients when using a « one size fits all » $Kt/V$ target

If « $V$ » is calculated from body weight (anthropometrically), « $V$ » is surestimated in obese patients (needing a higher Kt to achieve the target Kt/V)

As such obesity with increased body fat content, by containing less water than muscle, paradoxically has become a survival advantage