Online Hemodiafiltration: Renal Replacement Therapy of the Future Available Today

Prof. Bernard Canaud
Néphrologie, Dialyse et Soins Intensifs
Hôpital Lapeyronie – CHRU Montpellier
Outline of the presentation

• Concerns related to renal replacement therapy
• Technical aspects of online HDF
• Safety of online HDF
• Efficacy of online HDF
  – Biological effects
  – Clinical effects
    • Clinical tolerance
    • Morbidity and Mortality
• Take home message
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How to Reduce Mortality in Hemodialysis Patients Still a Puzzle

Mike Mitka

CHICAGO—A recently concluded study has failed to show differences in treatment options that would reduce US mortality rates for patients who receive hemodialysis.

The results from the Hemodialysis (HEMO) Study showed that mortality rates were basically the same for patients regardless of combinations of standard or high doses of hemodialysis and low and high dialysis membrane flux. The study results were presented at the National Kidney Foundation’s (NKF) Clinical Nephrology Meetings by lead investigator Garabed Eknoyan, MD, a professor of medicine at Baylor College of Medicine in Houston.

Eknoyan said the results were surprising because evidence from observational studies suggested that a higher dose of dialysis resulted in improved patient health.

“The trend had been to give more and more dialysis, with the notion that more and that the high-flux filter appeared to reduce mortality in those who had been receiving hemodialysis longer than 3.5 years when they joined the study.”

Mitka M. JAMA, 2002; 287(20): 2643-2644
Dialysis and CKD-related pathology

β2-Amyloidosis

Tissular calcinosis

Annual crude mortality, %

Japan: 6.6%
Europe: 15.6%
USA: 21.7%
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Hemodiafiltration mimics the “native nephron”

1. Filtration
2. Reabsorption
3. Secretion
4. Excretion

1. Ultrafiltration
2. Diffusion
3. Adsorption
Factors affecting HDF efficacy

- Hemodiafilter characteristics
- Blood flow – Dialysate flow
- Site of infusion for substitution
- Flow and/or volume of substitution
- Weight loss - Ultrafiltration
- Dialysate composition
- Duration of HDF session
- Weekly frequency of sessions
- Patient’s characteristic
Standard prescription for high-efficiency on-line HDF

- **Treatment schedule**
  - 3 sessions of 4 hours weekly (minimum)

- **Highly permeable synthetic membrane**

- **Large surface area > 1.8 m²**

- **Ultrapure bicarbonate dialysis fluid**

- **High blood flow** (effective QB: 350 - 400 ml/min)

- **High dialysate flow** → **diffusive dose**
  - Optimize 500-700 ml/min

- **Large volume of substitution** → **convective dose**
  - Post-dilution ($Q_{sub}$ : 100 ml/min, 24 l / session)
  - Pre-dilution ($Q_{sub}$ : 200 ml/min, 48 l / session)
On-line HDF, post-dilution mode

Ultrafiltrate (Fluid balance)

Ultrafiltrate (Weight loss)

Blood Flow

Ultrafilter

Substitution fluid

Ultrapure dialysis fluid
On-line HDF, pre-dilution mode

Blood Flow

UF
Substitution fluid

Ultrafilter

Ultrapure dialysis fluid
On-line HDF, mixed-dilution mode

Ultrafilters

Blood Flow

UF Substitution fluid

Ultrafilters

UF dialysis fluid

Ultrafilters
On-line HDF, mid-dilution mode

Mid-Reverse

Blood Flow

Ultrafilters

Ultrafilters

Substitution fluid

Mid-Double Reverse

Blood Flow

Ultrafilters

Ultrafilters

Substitution fluid
Convective dose is a linear function of substitution volume in post-dilution HDF.

PR β2-Microglobulin, %

Reduction Rate (%) vs. HDF (ml/min)

Mean ± SEM

P = 0.01

P = 0.001

P = 0.000

Post-dilution HDF increases removal of middle molecules

Matching dialysis dose in pre vs post HDF

RCT Cross-Over Study
8 HD patients 4h x 3 wk
Qb 400 Qd 800 Qinf 100/200

Matching efficacy pre vs post-dilution HDF requires double substitution flow

RCT Cross-Over Study
8 HD patients 4h x 3 wk
Qb 400 Qd 800 Qin 100/200

Optimal flow substitution in mid-dilution HDF

Percent reduction per session, %

PR β2-M

PR-Myog

Percent reduction per session, %

69,9

72,9

72,3

82,7

82,7

82,4

84,9

84

84,8

84

80,7

77,4

77

78,2

79,6

50

55

60

65

70

75

80

85

90

95

100

Mid 0

Mid 50

Mid 100

Mid 150

Mid 200

Mid 250

Mid 300

20pts – Mid-dilution HDF OI-PUR190
t_{HDF} 275mn - Q_b 450ml/mn - Q_d 800ml/mn

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Factors affecting safety of online HDF

- Hemodiafiltration machine
- Ultrapurity of water feeding HDF machines
- Cold sterilization of dialysis fluid by ultrafilter
- Hygienic handling of water and HDF machines
- Microbiological monitoring of dialysis fluid
- Periodical change of ultrafilters
Certified online hemodiafiltration machines
Microbiological quality of purified water and ultrapure dialysis fluids for online HDF in clinical routine practice

- Subgroup analysis after enrolment
- 10 centers - One year follow-up
- 97 patients - 11258 HDF sessions
- 3961 samples

Clinical safety is confirmed on a routine basis and large scale

- One year follow-up
- 97 patients
- 11258 HDF sessions
- No febrile reactions
- No clinical adverse events

Water treatment system mainly used

Ultrapurity of dialysis fluid is confirmed in 85 to 98% of samples

10 centers
One year follow-up
11258 HDF sessions
97 patients – 3961 samples

Ultrapurity of infusate is confirmed in 99 to 100 % of samples

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Biological and clinical effects of HDF

**Short term studies**

**Biological effects**
- Enhance solute transfer
  - Enhances low and middle molecule removal
  - Enhances solute and electrolyte mass transfer
- Reduce blood/dialysis interaction
  - Reduces protein and cells activation
  - Reduces micro-inflammation

**Clinical effects**
- Morbidity
  - Reduces intradialytic hypotension
  - Prevents $\beta_2$M-amylloidosis
  - Improves nutritional state
  - Facilitates anemia correction
- Mortality
  - Reduces overall mortality
  - Reduces cardiovascular events

**Long term studies**
Biological and clinical impact of HDF

**Biological impact**

- Enhance solute transfer
  - Enhances low and middle molecule removal
  - Enhances solute and electrolyte mass transfer
- Reduce blood/dialysis interaction
  - Reduces protein and cells activation
  - Reduces micro-inflammation

**Clinical impact**

- Morbidity
  - Reduces intradialytic hypotension
  - Prevents $\beta_2$M-amyloidosis
  - Improves nutritional state
  - Facilitates anemia correction
- Mortality
  - Reduces overall mortality
  - Reduces cardiovascular events
HDF vs LF-HD, Impact on circulating β2-M concentrations

β2-M concentrations is reduced after switching from HFHD to ol-HDF

Tiranathanagul K et al. *Ther Apher Dial* 2009; 13: 56-62
Comparison of percent reduction of solutes mid-dilution vs post-dilution


10 HD pats
Randomized cross-over study
1 week Mid-dil ol-Pur190 vs Post-dil HF80

β2-Microglobulin concentrations tend to be lower with Mid-HDF

10 HD pats
Randomized cross-over study
1 week Mid-dil ol-Pur190 vs Post-dil HF80

High efficiency HDF increases the phosphate mass removal

Lornoy W et al, J Ren Nut 2006; 16: 47-53

4hrs x 3wk
HF80 - QD800
Direct dialysate quantification

22 HD pats

HD → HD

HDF → HDF

on-line haemodiafiltration
haemodialysis

p < 0.001

p < 0.05
High efficiency HDF increases the erythropoietic response to ESA

Effects of oL-HDF and HFR on inflammatory and nutritional markers

Effects of oL-HDF and HFR on inflammatory and nutritional markers

Cross-over, randomized multicentre trial

Effect of HD and HDF on CD14^+CD16^+ monocytes, TNFα, IL6 and inflammatory markers

Cross-over, randomized study (31 HD patients)

- Polysulfone membrane
- Ultrapure dialysate
- Same dialysis conditions

OL-HDF reduces proinflammatory CD14+CD16+ monocyte-derived dendritic cells

Comparison of different RRT modalities on inflammation and survival of HD patients

- Prospective observational study
- Prevalent HD patients (Tuscany, Italy) (70±76 months)
- 757 HD patients (age 66±14)
- Stratified at start in 3 RRT groups: BHD, bag-HDF, ol-HDF
- Prospective follow-up for 30 months

RISCAVID Study

### Demographic data at start of study period

<table>
<thead>
<tr>
<th></th>
<th>BHD</th>
<th>HDF with bags</th>
<th>HDF online</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>424</td>
<td>204</td>
<td>129</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68.1 ± 13.2</td>
<td>63.4 ± 14.4</td>
<td>61.7 ± 15.9</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>247/177</td>
<td>128/75</td>
<td>85/44</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.9 ± 4.3</td>
<td>24.1 ± 4.1</td>
<td>24.3 ± 4</td>
</tr>
<tr>
<td>BW (kg)</td>
<td>65.8 ± 13.6</td>
<td>67.5 ± 12.8</td>
<td>68.1 ± 13.7</td>
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<tr>
<td>Diabetes</td>
<td>92/424</td>
<td>29/204</td>
<td>21/129</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV disease</td>
<td>117/424</td>
<td>43/204</td>
<td>21/129</td>
</tr>
<tr>
<td>Hypertension</td>
<td>101/424</td>
<td>68/204</td>
<td>48/129</td>
</tr>
<tr>
<td>Malignancy</td>
<td>28/424</td>
<td>10/204</td>
<td>10/129</td>
</tr>
<tr>
<td>Others</td>
<td>9/424</td>
<td>5/204</td>
<td>2/129</td>
</tr>
<tr>
<td>None</td>
<td>75/424</td>
<td>46/204</td>
<td>45/129</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.39</td>
<td>1.41</td>
<td>1.43</td>
</tr>
<tr>
<td>Type of membrane</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified cellulose</td>
<td>0%</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>Synthetic</td>
<td>100%</td>
<td>100%</td>
<td>97%</td>
</tr>
<tr>
<td>Infusion volume (L/session)</td>
<td>14 ± 3</td>
<td>23 ± 3*</td>
<td></td>
</tr>
</tbody>
</table>

Effects on chronic inflammation

Biological and clinical impact of HDF

**Biological impact**

- **Enhance solute transfer**
  - Enhances low and middle molecule removal
  - Enhances solute and electrolyte mass transfer
- **Reduce blood/dialysis interaction**
  - Reduces protein and cells activation
  - Reduces micro-inflammation

**Clinical impact**

- **Morbidity**
  - Reduces intradialytic hypotension
  - Prevents $\beta_2$M-amyloidosis
  - Improves nutritional state
  - Facilitates anemia correction
- **Mortality**
  - Reduces overall mortality
  - Reduces cardiovascular events
## Hemodynamic tolerance is improved in HDF

<table>
<thead>
<tr>
<th>Condition</th>
<th>HFHD (Baseline)</th>
<th>On-line HDF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>6 months</td>
</tr>
<tr>
<td>Hypotension</td>
<td>20.2 ± 17.1</td>
<td>10.4 ± 17.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.9 ± 4.7</td>
<td>2.2 ± 7.7</td>
</tr>
<tr>
<td>Muscle cramp</td>
<td>7.8 ± 9.5</td>
<td>5.3 ± 7.7</td>
</tr>
<tr>
<td>Headache</td>
<td>1.7 ± 2.6</td>
<td>1.3 ± 3.2</td>
</tr>
</tbody>
</table>

Tiranathanagul K et al. *Ther Apher Dial* 2009; 13: 56-62

ol-HDF in Southeast Asia: 3 years experience
22 HD patients HFHD → ol-HDF
Convective therapies (HF, HDF) reduce intradialytic symptomatic hypotension (ISH)

Total incidence of ISH 7.5% 28950 sessions

Italian Multicentric Study RCT LFHD, HF, HDF Ratio 2/1/1

## Outcomes of HDF versus HD

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>HDF vs Comparator</th>
<th>Type of study</th>
<th>Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wizemann V et al, 2000</td>
<td>HDF vs LFHD</td>
<td>RCT</td>
<td>Ia</td>
</tr>
<tr>
<td>Bosch JP et al, 2006</td>
<td>HDF vs LFHD vs HFHD</td>
<td>Historical prospective cohort</td>
<td>IIb</td>
</tr>
<tr>
<td>Canaud B et al, 2006</td>
<td>HDF± vs LFHD vs HFHD</td>
<td>Historical prospective cohort</td>
<td>IIa</td>
</tr>
<tr>
<td>Jirka et al, 2006</td>
<td>HDF vs LFHD vs HFHD</td>
<td>Historical prospective cohort</td>
<td>IIa</td>
</tr>
<tr>
<td>Schiffl H et al, 2007</td>
<td>HDF vs HFHD + UPD</td>
<td>RCT</td>
<td>Ia</td>
</tr>
<tr>
<td>Vinhas J et al, 2007</td>
<td>HDF vs HFHD</td>
<td>Prospective controlled study</td>
<td>IIb</td>
</tr>
<tr>
<td>Panichi V et al, 2008</td>
<td>HDF+/− vs LFHD</td>
<td>Prospective controlled study</td>
<td>IIa</td>
</tr>
<tr>
<td>Santoro A et al, 2008</td>
<td>HF vs HFHD</td>
<td>RCT</td>
<td>Ia</td>
</tr>
<tr>
<td>Tiranathanagul K 2009</td>
<td>HDF vs HFHD</td>
<td>Prospective controlled study</td>
<td>IIa</td>
</tr>
<tr>
<td>Vilar E et al, 2009</td>
<td>HDF vs HFHD</td>
<td>Historical prospective cohort</td>
<td>IIb</td>
</tr>
<tr>
<td>Locatelli F et al, 2010</td>
<td>HDF vs HD vs LFHD</td>
<td>RCT</td>
<td>Ia</td>
</tr>
</tbody>
</table>
On-line HDF versus low flux HD, prospective randomized study

On-line HDF versus low flux HD, Mortality

Prospective randomized cross-over long-term comparison of on-line HDF vs HFHD

Prospective randomized cross-over long-term comparison of on-line HDF vs HFHD

### Distribution of dialysis modality for prevalent patients

<table>
<thead>
<tr>
<th>Country</th>
<th>n</th>
<th>Low-efficiency HDF&lt;sup&gt;a&lt;/sup&gt; (%)</th>
<th>High-efficiency HDF&lt;sup&gt;a&lt;/sup&gt; (%)</th>
<th>Low-flux HD (%)</th>
<th>High-flux HD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>460</td>
<td>5.4</td>
<td>8.9</td>
<td>45.9</td>
<td>39.8</td>
</tr>
<tr>
<td>Germany</td>
<td>440</td>
<td>11.1</td>
<td>4.8</td>
<td>50.5</td>
<td>33.6</td>
</tr>
<tr>
<td>Italy</td>
<td>443</td>
<td>14.7</td>
<td>5.4</td>
<td>74.9</td>
<td>5.0</td>
</tr>
<tr>
<td>Spain</td>
<td>383</td>
<td>1.8</td>
<td>0.0</td>
<td>61.4</td>
<td>36.8</td>
</tr>
<tr>
<td>UK</td>
<td>439</td>
<td>2.3</td>
<td>2.5</td>
<td>83.4</td>
<td>11.8</td>
</tr>
<tr>
<td>All</td>
<td>2165</td>
<td>7.2</td>
<td>4.5</td>
<td>63.1</td>
<td>25.2</td>
</tr>
</tbody>
</table>

<sup>a</sup>Low-efficiency HDF includes replacements of 5–14.9 L, while high-efficiency HDF includes replacement of 15–24.9 L.

HD, hemodialysis; HDF, hemodiafiltration.
Mortality risk for patients receiving high efficiency HDF vs. HD is reduced

European Results from DOPPS

Crude mortality of CKD patients according to their treatment modality HD vs HDF

Euclid, FMC

Jirka et al, Kidney Int 2006; 70:1524

Euclid
56 clinics
2564 pats
HD2170, HDF394
4 countries
Relative risk of mortality in CKD patients
HDF versus HD

- OL-HDF: 0.636
- Treat time >240: 1.642
- Time on RRT: 1.036
- Arteriopathy: 1.653
- Heart Fail: 1.36
- Neoplasia: 1.458
- Diabetes: 1.578
- Age: 1.05

↓ 36.4%

Jirka et al, Kidney Int 2006; 70:1524
Retrospective analysis of cohort, HF-HD versus HDF

Sep 2003
HFHD
161 pats

Oct 2006
115 pats

Dec 2006
HDF
168 pats

Demographic
Comorbidity
Dialysis efficacy indicators
Crude mortality
RR mortality (all-causes)
RR morbidity (hospitalization)

Crude mortality, death/100 patient-years

Cause of death in CKD, repartition by modality

% of total death

Cardiac: 36.4%
Infection: 10.9%
Neoplasia: 7.3%
Malnutrition: 3.6%
Others: 0%

Cardiovascular mortality is reduced in ol-HDF

Categorical and continuous variables distribution according to ERI values categorized into four quartiles

<table>
<thead>
<tr>
<th>ERI quartiles</th>
<th>I QI &lt;5.6 Mean ± SD</th>
<th>II QI 5.7-9.6 Mean ± SD</th>
<th>III QIII 9.4-15.4 Mean ± SD</th>
<th>IV QIV &gt;15.4 Mean ± SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/L)</td>
<td>7.8 ± 5.2</td>
<td>10.1 ± 10.8</td>
<td>10.0 ± 10.6</td>
<td>12.1 ± 21.1</td>
<td>NS</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>7.1 ± 6.5</td>
<td>9.3 ± 15.8</td>
<td>7.5 ± 7.8</td>
<td>11.1 ± 21.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.8 ± 0.3</td>
<td>3.71 ± 0.4</td>
<td>3.7 ± 0.4</td>
<td>3.6 ± 0.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>12.1 ± 1.2</td>
<td>11.7 ± 1.2</td>
<td>11.4 ± 1.4</td>
<td>10.6 ± 1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>633.1 ± 572.0</td>
<td>535.7 ± 571.6</td>
<td>580.9 ± 519.2</td>
<td>494.0 ± 480.8</td>
<td>NS</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>34.6 ± 16.2</td>
<td>28.4 ± 14.1</td>
<td>32.0 ± 20.1</td>
<td>27.1 ± 19.0</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
Survival (all causes mortality) of dialysis patients stratified by ERI

Q I   <5.6
Q II  5.7-9.6
Q III 9.4-15.4
Q IV  >15.4

RISCAVID Study

Panichi V et al, Nephrol Dial Transplant 2011 ePub
Effect of on-line high-flux hemofiltration versus low flux hemodialysis in CKD

130 screened for eligibility

64 randomized

64 Excluded:
- 45 did not meet the inclusion criteria
- 10 refused the informed consent
- 11 logistical reasons

32 Hemodialysis

• 9 drop outs
• 12 deaths

Assessed for primary outcome and overall morbidity

32 Hemofiltration

• 14 drop outs
• 7 deaths

11 completed the trial

Survival is improved in high efficiency HF

Convective dialysis dose and β-2 Microglobulin levels seem to play a major role in this positive effect

---

**Table**

<table>
<thead>
<tr>
<th></th>
<th>Hemodialysis</th>
<th>On-Line Hemofiltration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 Months</td>
</tr>
<tr>
<td><strong>Hemoglobin (g/dL)</strong></td>
<td>11.1 ± 0.34</td>
<td>11.3 ± 0.38</td>
</tr>
<tr>
<td><strong>Hematocrit (%)</strong></td>
<td>33.3 ± 1.04</td>
<td>33.6 ± 1.03</td>
</tr>
<tr>
<td><strong>Urea (mg/dL)</strong></td>
<td>160.5 ± 45.20</td>
<td>162.7 ± 46.16</td>
</tr>
<tr>
<td><strong>Calcium (mg/dL)</strong></td>
<td>9.2 ± 0.53</td>
<td>10.4 ± 0.86</td>
</tr>
<tr>
<td><strong>Phosphate (mg/dL)</strong></td>
<td>5.1 ± 0.41</td>
<td>5.2 ± 0.36</td>
</tr>
<tr>
<td><strong>Calcium × phosphorus (mg²/dL²)</strong></td>
<td>50.3 ± 4.8</td>
<td>54.8 ± 4.3</td>
</tr>
<tr>
<td><strong>Potassium (mEq/L)</strong></td>
<td>5.7 ± 0.19</td>
<td>5.8 ± 0.23</td>
</tr>
<tr>
<td><strong>Bicarbonate (mEq/L)</strong></td>
<td>20.6 ± 0.53</td>
<td>22.2 ± 0.92</td>
</tr>
<tr>
<td><strong>Kt/V (Daugirdas)</strong></td>
<td>1.44 ± 0.07</td>
<td>1.30 ± 0.09</td>
</tr>
<tr>
<td><strong>Albumin (g/dL)</strong></td>
<td>3.8 ± 0.09</td>
<td>3.8 ± 0.39</td>
</tr>
<tr>
<td><strong>β₂-Microglobulin (mg/L)</strong></td>
<td>33.9 ± 2.04</td>
<td>35.1 ± 2.07</td>
</tr>
<tr>
<td><strong>Parathyroid hormone (pg/mL)</strong></td>
<td>177.5 ± 66</td>
<td>178.7 ± 66</td>
</tr>
</tbody>
</table>

**β₂-Microglobulin (mg/L)**

|                  | 30.2 ± 3.54 | 23.9 ± 2.47 | 22.2 ± 2.75 | 23.9 ± 1.77 |

**Infusate flow (L/session)**

|                  | 69.8 ± 7    | 77 ± 10    | 75.5 ± 3    | 76.1 ± 2    |

Long-term outcomes in ol-HDF vs HFHD, a comparative analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Patients</th>
<th>Predominantly High-Flux HD Group</th>
<th>Predominantly HDF Group</th>
<th>HD versus HDF Group (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>858</td>
<td>626</td>
<td>232</td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>22.1</td>
<td>23.8</td>
<td>17.7</td>
<td>0.055&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>17.2</td>
<td>19.6</td>
<td>10.8</td>
<td>0.002&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Malignancy</td>
<td>13.1</td>
<td>15.2</td>
<td>7.3</td>
<td>0.002&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Underlying renal disease (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>16.8</td>
<td>17.1</td>
<td>15.9</td>
<td>0.69&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>17.9</td>
<td>16.3</td>
<td>22.4</td>
<td>0.04&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Obstructive uropathy</td>
<td>8.6</td>
<td>8.6</td>
<td>8.6</td>
<td>1.00&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Congenital cystic renal disease</td>
<td>5.9</td>
<td>4.6</td>
<td>9.5</td>
<td>0.008&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Renovascular disease</td>
<td>7.7</td>
<td>8.9</td>
<td>4.3</td>
<td>0.02&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chronic renal failure of uncertain cause</td>
<td>31.2</td>
<td>32.9</td>
<td>26.7</td>
<td>0.08&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Other causes</td>
<td>11.8</td>
<td>11.5</td>
<td>12.5</td>
<td>0.16&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Repartition according to time spent on HD vs HDF

Survival is improved in patients who predominantly received HDF


RR 0.66 vs 1.0 for HDF

Life gain +34%
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>HDF vs Comparator</th>
<th>Type of study</th>
<th>β2-M</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wizemann V et al, 2000</td>
<td>HDF vs LFHD</td>
<td>RCT</td>
<td>↓</td>
<td>=</td>
</tr>
<tr>
<td>Bosch JP et al, 2006</td>
<td>HDF vs LFHD vs HFHD</td>
<td>Historical prospective cohort</td>
<td>?</td>
<td>↑ 45%</td>
</tr>
<tr>
<td>Canaud B et al, 2006</td>
<td>HDF+/- vs LFHD vs HFHD</td>
<td>Historical prospective cohort</td>
<td>?</td>
<td>↑ 35%</td>
</tr>
<tr>
<td>Jirka et al, 2006</td>
<td>HDF vs LFHD vs HFHD</td>
<td>Historical prospective cohort</td>
<td>?</td>
<td>↑ 36%</td>
</tr>
<tr>
<td>Schiffl H et al, 2007</td>
<td>HDF vs HFHD + UPD</td>
<td>RCT</td>
<td>↓</td>
<td>=</td>
</tr>
<tr>
<td>Vinhas J et al, 2007</td>
<td>HDF vs HFHD</td>
<td>Prospective controlled study</td>
<td>?</td>
<td>↑ 50%</td>
</tr>
<tr>
<td>Panichi V et al. 2008</td>
<td>HDF+/- vs LFHD</td>
<td>Prospective controlled study</td>
<td>↓</td>
<td>↑ 15%</td>
</tr>
<tr>
<td>Santoro A et al, 2008</td>
<td>HF vs HFHD</td>
<td>RCT</td>
<td>↓</td>
<td>↑ 18%</td>
</tr>
<tr>
<td>Tiranathanagul K 2009</td>
<td>HDF vs HFHD</td>
<td>Prospective controlled study</td>
<td>↓</td>
<td>=</td>
</tr>
<tr>
<td>Vilar E et al, 2009</td>
<td>HDF vs HFHD</td>
<td>Historical prospective cohort</td>
<td>↓</td>
<td>↑ 34%</td>
</tr>
<tr>
<td>Locatelli F et al, 2010</td>
<td>HDF vs HD vs LFHD</td>
<td>Prospective randomized controlled study</td>
<td>?</td>
<td>=</td>
</tr>
</tbody>
</table>
**Daily online HDF promotes catch-up growth in CKD children**

<table>
<thead>
<tr>
<th>Patient ((n = 15))</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Height (SDS)</strong></td>
<td></td>
</tr>
<tr>
<td>Start of D-OL-HDF</td>
<td>−1.5 ± 0.3</td>
</tr>
<tr>
<td>End of D-OL-HDF (1)</td>
<td>+0.2 ± 1.1*</td>
</tr>
<tr>
<td>Mid-parental target height (2) (1) − (2) (SDS)</td>
<td>−0.3 ± 0.7</td>
</tr>
<tr>
<td><strong>Growth velocity (centimetres per year)</strong></td>
<td></td>
</tr>
<tr>
<td>The year before daily</td>
<td>3.8 ± 1.1</td>
</tr>
<tr>
<td>First year of daily</td>
<td>14.3 ± 3.8°</td>
</tr>
<tr>
<td>Mean over daily</td>
<td>8.9 ± 2.2°</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
</tr>
<tr>
<td>At start of daily</td>
<td>16.5 ± 2.0°</td>
</tr>
<tr>
<td>End of daily</td>
<td>18.0 ± 2.4°</td>
</tr>
</tbody>
</table>

---

Patient 1, a boy on daily online hemodiafiltration.
Protein diet intake (g/kg/d) : 2.7±0.2 ; protein nitrogen appearance (g/kg/d) : 1.44 ±0.15
Mean growth velocity (cm/year) : 10.4
Achieved height versus mid parental target height (SDS) : +0.2
Outline of the presentation

- Concerns related to renal replacement therapy
- Technical aspects of online HDF
- Safety of online HDF
- Efficacy of online HDF
  - Biological effects
  - Clinical effects
    - Clinical tolerance
    - Morbidity and Mortality
- Take home message
Randomized clinical trials in Europe evaluating HDF vs HD

**Dutch Trial**
CONTRAST
LFHD vs HDF 350/350
CV events Mortality 36 months

**French Trial**
HFHD vs HDF
> 65yo
300/300
Tolerance CV events Mortality 24 months

**Catalonian Trial**
HFHD vs HDF 300/300
CV events Mortality 24 months

**Turkish Trial**
HFHD vs HDF 300/300
CV events Mortality 24 months

**Italian Trial**
LFHD vs HF/HDF 150/75/75
Tolerance Morbidity Mortality 24 months

Enrolment period of all these studies is closed.
Take home message

- Online hemodiafiltration is
  - Safe,
  - Very effective,
  - Economically affordable,
  - Improving session tolerance,
  - Not inferior to high flux hemodialysis
  - Superior to high flux hemodialysis (? RCT)
Analysis and comment

Controversy

Parachute approach to evidence based medicine

Malcolm Potts, Ndola Prata, Julia Walsh, Amy Grossman

Waiting for the results of randomised trials of public health interventions can cost hundreds of lives, especially in poor countries with great need and potential to benefit. If the science is good, we should act before the trials are done.
Sometimes it’s best just to jump in!
Why not using online hemodiafiltration?

Potts M et al, *BMJ* 2006; 333:701-703