Hemodiafiltration: practical points

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Effectiveness of RRT modalities

CKD Stage | % of normal renal function |
---|---|
I | 100% |
II | 75% |
III | 50% |
IV | 25% |
V | 0% |

Transplant 50%  
HNHD 40%  
SDHD 25%  
PD, IHD 15%  

Mcfarlane, Seminars in dialysis, 2009
No benefit from increased urea clearance

HEMO study, NEJM, 2002
Outline

- Mechanisms of hemodiafiltration (HDF)
- Theoretical advantages of HDF vs HD
  - Clinical benefits of HDF vs conventional HD
    - lessons from adult studies
    - focus on growth and nutrition
- Practical aspects of setting up HDF in your unit
Diffusion

Rate of diffusion $\propto$ concentration gradient
$\propto 1/\sqrt{\text{mol weight}}$

Excellent removal of small molecules
Very little effect on large solute removal
Convection

Removes small and middle mol wt solutes

Rate of convective clearance
- molecular weight
- bound fraction
- tissue distribution
- sieving coefficient (KoA & KUF)
HDF – clearance by diffusion and convection
Advantages of HDF

1. Clearance of uraemic solutes across a wide molecular weight range
2. Biocompatibility
3. Hemodynamic stability
1. Clearance on HDF vs HD

**Clearance [ml/min]**

- **HD:** $Q_b = 200 \text{ ml/min}, Q_d = 500 \text{ ml/min}$
- **HF:** $Q_b = 200 \text{ ml/min}, Q_f = 74 \text{ ml/min}$
- **HDF:** $Q_b = 200 \text{ ml/min}, Q_d = 500 \text{ ml/min}, Q_f = 67 \text{ ml/min}$

**Chromatograms:**
- **60** Urea
- **11,800** β2M
- **55,000** Amylase
- **67,000** Albumin
β₂ microglobulin clearance

- HDF achieves 70 – 78% reduction in β₂ microglobulin (vs 40 – 50% with high-flux HD)
  Thomas et al, Semin Dialy, 2009

- No signs of amyloidosis after 8 yrs on HDF (vs 100% pts on HD have amyloid by 13 yrs)
  Canaud et al, NDT, 1998

- 82% reduced incidence of carpal tunnel syndrome and 67% reduced incidence of erosive arthritis
  Dember et al, Semin Dialy, 2006
Predialysis $\beta_2$m levels correlate with mortality (HEMO Study).

For every 10 mg/l increase in predialysis $\beta_2$M there is a 11% increase in the relative risk of death.

*Cheung et al, JASN 2000*
Other middle molecules cleared by HDF

- Parathyroid hormone
- Inflammatory cytokines (IL-6, IL-8, IL-12)
- Homocysteine
- Guanidines
- Polyamines
- Appetite suppressants (leptin, cholecystokinin, tryptophan)
- Complement factor D

**Influence endothelial function:**
- Reduce nitric oxide production
- Promote AGE formation
- Affect cell cycle and cause senescence
2. Reduced inflammation and oxidative stress

1. reduces inflammation (↓ TNFα, IL-6, IL-8, IL-12)
2. suppresses oxidative stress (↓ reactive oxygen species and superoxide)
3. improves antioxidant capacity
4. reduces generation of AGEs

**Mechanisms**

1. Biocompatible membranes
2. ‘Ultrapure’ dialysate
3. Removal of cytokines
Chronic low-grade exposure to endotoxins

- Chronic inflammation

- Anorexia, poor nutrition and growth, catabolism, loss of lean body mass – cachexia

- Anaemia – poor ESA response

- Risk of atherosclerosis

Malnutrition – inflammation – atherosclerosis complex
3. Hemodynamic stability

1. Fewer intra-dialytic hypotensive episodes
2. Higher UF better tolerated by patient
3. Reduced post-dialysis fatigue
4. Overall better BP control

**Mechanisms:**
1. Cooling of dialysate
2. Removal of vasodilating mediators
3. High Na content of infusion fluid
Cooling is a part of on-line HDF
Reduced risk of intra-dialytic hypotension on HDF

- Blood returning to the patient is cooler during o-HDF than HD - enhanced energy loss within the extracorporeal system

- In the patients’ circulation the mean blood temperature is lower during o-HDF than HD

Blankestijn et al, KI, 2010
Cardiovascular and survival advantage of HDF vs HD
1. Dutch HDF Study: CONTRAST

A. Survival curve for online HDF compared to lowflux HD.

B. Cardiovascular event-free survival curve.

Patients at risk:
- HD: 356, 337, 307, 269
- HDF: 358, 346, 324, 287

Hazard Ratio:
- online HDF
- lowflux HD

P-values:
- P=0.016
2. Turkish HDF Study: High vs Low Efficiency HDF

OK E; Kircelli F; Turkish Online Haemodiafiltration Study; NDT 2013
3. Spanish HDF Study: High vs Low Efficiency HDF

switching 8 patients from HD to HDF prevents one death / year
On-line HDF provides better overall and CV survival only when high convective volumes are achieved.
# Meta-analysis: all cause mortality

<table>
<thead>
<tr>
<th>Study name</th>
<th>HDF (Events/Pat)</th>
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<th>RR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Grooteman et al.</td>
<td>131/358</td>
<td>138/356</td>
<td>0.94</td>
<td>0.78 – 1.15</td>
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<td>Ok et al.</td>
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<td>Maduell et al.</td>
<td>85/456</td>
<td>122/450</td>
<td>0.69</td>
<td>0.54 – 0.88</td>
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<tr>
<td><strong>Pooled</strong></td>
<td><strong>268/1205</strong></td>
<td><strong>326/1197</strong></td>
<td><strong>0.83</strong></td>
<td><strong>0.72 – 0.95</strong></td>
</tr>
</tbody>
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*Sem Dial 2014; 27:119-27*
Meta-analysis: cardiovascular deaths

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<td>Grooteman et al. (3)</td>
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<tr>
<td>Ok et al. (4)</td>
<td>32/391</td>
<td>44/391</td>
<td>0.73</td>
<td>0.47 – 1.12</td>
</tr>
<tr>
<td>Maduell et al. (5)</td>
<td>37/456</td>
<td>55/450</td>
<td>0.66</td>
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<td>145/1197</td>
<td>0.73</td>
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Cochrane review - 2015

- Convective dialysis had no significant effect on all-cause mortality (11 studies, 3396 participants: RR 0.87, 95% CI 0.72 to 1.05).
- Convective dialysis significantly reduced cardiovascular mortality (6 studies, 2889 participants: RR 0.75, 95% CI 0.61 to 0.92).
- Effects on nonfatal cardiovascular events & hospitalisation inconclusive.

Criticism
- Studies on HF were also included under ‘convective therapies’
- Studies with different end-points were combined
- Some studies were underpowered to examine CV or all-cause mortality.
Growth on daily HDF

NOTE:
- High convective volume
- Daily HDF

Height SDS
- start: -1.5 ± 0.3
- end: +0.2 ± 1.1
- target height relative to mid-parental height: +0.3

Height velocity
- before daily HDF: 3.8 ±1.1 cm/y
  - first year of daily HDF: 14.3 ± 3.8 cm/
  - mean : 10.4 cm/y
Growth study in children

- 15 children on daily HDF; mean age: 7.3 (2.8 – 16.7 yrs)
- 7 converted from PD & 5 from 3/week HD
- Vascular access: fistula (n=13) & catheter (n=4)
- Pre-dilution HDF; Qb & Qd adjusted to achieve a Kt/Vurea ≥1.4 per session x 18 hours per week

Fischbach et al; NDT, 2010
Dialysis efficiency & tolerance

- Mean weekly $Kt/V_{\text{urea}} = 10$
  - dialysis dose $\sim 35\%$ GFR

- Phosphate: $1.39\ (1.65 - 0.63)\ \text{mmol/l}$
  - despite high protein intake ($>2\ \text{g/kg/day}$)
  - 2/15 child on chelators

- CRP – normal in 13/15 (2 children had chronic infections)

- $\beta_2$ microglobulin $13.5 \pm 3.5\ \text{mg/L}$
Dialysis dose and growth

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).
Anabolic effect of daily HDF

- Stimulates appetite - removal of circulating satiety factors (leptin, cholecystokinin, tryptophan)

- Correction of metabolic acidosis. Acidosis can:
  - activate the ubiquitin-proteosome pathway & increase protein degradation
  - suppresses endogenous GH secretion

- Minimises inflammatory cytokine release

- ? Removal of somatomedin and gonadotropin inhibitors by HDF

- ? reverses rhGH resistance

Schaefer et al, NDT 2010
Paediatric HDF in Europe

144 cases of HDF in children in 2013
(~12% of all HD cases)

ESPN/ERA-EDTA registry
The effects of HDF vs conventional HD on growth and cardiovascular markers in children

3H (HDF, Hearts and Height) study
Hypothesis

Children on HDF compared with HD have improved:

- Cardiovascular risk profile
- Growth and nutritional status
- Quality of life
Primary outcome measures:
- Change in carotid artery intima-media thickness (cIMT) standard deviation score (SDS)
- Change in height SDS

Secondary outcome measures:
- For nutritional status
  - Body mass index SDS
  - Markers of appetite regulation and nutritional status
- For cardiovascular status
  - 24-hour mean arterial BP SDS
  - Left ventricular mass index
  - Pulse wave velocity SDS
  - Biomarkers of cardiovascular disease
- Quality of life (QoL) questionnaires
Recruitment

185 children screened (from 28 centres in 10 countries)

- No baseline scans (n = 6)
- Transplanted on day of study (n = 2)
- Did not fulfil inclusion criteria (n = 1)
- No data entry (n = 11)

165 included
Conclusion

- HDF is a superior dialysis modality in adults PROVIDED high convective clearance is achieved

- Mechanisms:
  - Improved clearance across a wide mol wt range
  - Reduced inflammation
  - Hemodynamic stability

- A study in children is under way
Practical aspects of HDF
Potential limitations for setting up HDF in your centres

1. **HDF machine**
   - X newer machines can all do HDF

2. **Water quality**
   - one time installation cost, then 1-3 monthly monitoring
   - must use ultrapure water with all high flux membranes

3. **Staff training**
   - X provided by company

4. **Costs**
   - £38/patient/month >HD

5. **Lack of paediatric data**
   - ✓ We need a study!
Requirements for HDF

1. High-flux membrane

2. Large quantities of IV quality fluid (‘ultrapure’ dialysate) as replacement fluid

3. Machines with accurate UF control systems
1. Dialysis Membranes

[Graph showing sieving coefficients for low-flux and high-flux membranes, comparing different molecules like urea, β2-microglobulin, and albumin across different molecular weight ranges.]
### Solute Clearance Depends on Its Mol Wt

<table>
<thead>
<tr>
<th>Mol wt (Daltons)</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;100,000</td>
<td>Albumin (55,000 - 60,000)</td>
</tr>
<tr>
<td>50,000</td>
<td>Beta2 Microglobulin (11,800)</td>
</tr>
<tr>
<td>10,000</td>
<td>Inulin (5,200)</td>
</tr>
<tr>
<td>5,000</td>
<td>Vitamin B12 (1,355)</td>
</tr>
<tr>
<td>1,000</td>
<td>Aluminum/Desferoxamine Complex (700)</td>
</tr>
<tr>
<td>500</td>
<td>Glucose (180)</td>
</tr>
<tr>
<td>100</td>
<td>Uric Acid (168)</td>
</tr>
<tr>
<td>50</td>
<td>Creatinine (113)</td>
</tr>
<tr>
<td>10</td>
<td>Phosphate (80)</td>
</tr>
<tr>
<td>5</td>
<td>Urea (60)</td>
</tr>
<tr>
<td>1</td>
<td>Potassium (35)</td>
</tr>
<tr>
<td>0</td>
<td>Phosphorus (31)</td>
</tr>
<tr>
<td></td>
<td>Sodium (23)</td>
</tr>
</tbody>
</table>

- **Large** molecules need convective clearance.
- **Middle** molecules are easily removed by diffusion.
- **Small** molecules are easily removed by diffusion.
High-flux membranes
Characteristics of high-flux membranes

1. **Flux** - Measure of ultrafiltration capacity
   - Low flux: $K_{uf} < 10 \text{ mL/hr/mm Hg}$
   - High flux: $K_{uf} > 20 \text{ mL/hr/mm Hg}$

2. **Permeability** - Measure of the clearance of $\beta_2$-microglobulin
   (= middle mol wt solutes)
   - Low permeability: $\beta_2$-microglobulin clearance $< 10 \text{ mL/min}$
   - High permeability: $\beta_2$-microglobulin clearance $> 20 \text{ mL/min}$

3. **Efficiency** - Measure of urea (= low mol wt solute) clearance
   - Low efficiency: $K_{OA} < 500 \text{ mL/min}$
   - High efficiency: $K_{OA} > 600 \text{ mL/min}$
Polyflux™ H
For high-flux and convective dialysis treatment

### Clearances in vitro (mL/min) +/- 10%:

**Hemodialysis**
- UF=0 mL/min, Qp=500 mL/min

<table>
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<th>Polyflux 170H</th>
<th>Polyflux 210H</th>
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<tr>
<td>Urea</td>
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</tr>
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<td>300</td>
<td>300</td>
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<tr>
<td></td>
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</tr>
<tr>
<td></td>
<td>500</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>Creatinine</td>
<td>181</td>
<td>186</td>
<td>218</td>
</tr>
<tr>
<td>Phosphate</td>
<td>174</td>
<td>186</td>
<td>249</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>128</td>
<td>137</td>
<td>183</td>
</tr>
<tr>
<td>Insulin</td>
<td>91</td>
<td>100</td>
<td>131</td>
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**Hemodiafiltration**
- UF=60 mL/min, Qp=500 mL/min

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<td>161</td>
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### KoA for Urea:

<table>
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<tr>
<th></th>
<th>993</th>
<th>1145</th>
<th>1450</th>
</tr>
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<tbody>
<tr>
<td>UF-coefficient* (mL/h mmHg) +/- 20%</td>
<td>60</td>
<td>70</td>
<td>85</td>
</tr>
</tbody>
</table>

### Specifications:

- **Membrane**
  - Effective surface area (m²): 1.4, 1.7, 2.1

- **Fiber dimensions**
  - Wall thickness (µm): 50, 50, 50
  - Inner diameter (µm): 215, 215, 215

*UF-coefficient* and KoA for Urea calculations vary with blood flow rate and other factors, please consult the manufacturer's guidelines for precise application.
2. Substitution fluid to drive UF

Pharmaceutical preparation

1. Large volumes of bagged fluid
2. Cannot use bicarbonate

or

on-line preparation

1. Requires a high dialysate flow rate
2. Ensure fluid is of ‘IV’ quality
‘Ultrapure’ water for HDF

Microbiological quality:
- CFU/ml
  - 100 - 200
  - 0.25 – 2.0
- EU/ml

Application in dialysis:
- pretreatment + RO
  - mix with concentrates
- ultrafiltration
  - ultrafiltration

Ultrafilters:
- size selective barrier – filter particles >30-40KD
- Hydrophobic adsorption of bacteria
Type and frequency of \( \text{H}_2\text{O} \) testing

<table>
<thead>
<tr>
<th>Contaminant</th>
<th>Frequency of testing</th>
</tr>
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<tbody>
<tr>
<td>Total chlorine</td>
<td>At least weekly</td>
</tr>
<tr>
<td>Total viable counts</td>
<td>At least monthly</td>
</tr>
<tr>
<td>Endotoxin</td>
<td>At least monthly</td>
</tr>
<tr>
<td>Chemical contaminants other than chlorine</td>
<td>At least every 3 months</td>
</tr>
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</table>

- Daily and seasonal variations in chlorine and chloramine levels
- Water supplier must know that \( \text{H}_2\text{O} \) is used for dialysis and inform of changes in additives
- If the chlorine level in the source \( \text{H}_2\text{O} \) is consistently low (<0.5mg/L) and chloramines are not used then weekly monitoring of dialysis \( \text{H}_2\text{O} \) is sufficient
Replacement of substitution fluid - pre-dilution vs post-dilution HDF
Post-dilution HDF is superior

1. Requires ½ vol of replacement fluid compared to pre-dilution
2. More efficient removal of low mol wt solutes
3. Risk of high hematocrit and filter clotting
4. Pre-dilution is only useful if low blood flows or hemodynamically unstable patient
3. High UF rate for convective transport

1. membrane properties
   - flux
   - surface area

2. UF rate - depends on bl flow rate
   - optimise access
   - AVF preferred to CVL

Aim for a target convection volume of 12-15L/m² body surface area
If $Q_{UF}$ too high

Start of dialysis

hct 32%

End of dialysis

if blood volume reduction is 10%

hct 35%

Increasing hemoconcentration $\rightarrow$ rise in TMP
Backfiltration in high-flux HD

- Small and unquantified amounts

High flux HD is the poor man’s HDF!

With any high flux dialyser the water must be ‘ultrapure’
Writing an HDF prescription

- **Gambro programme:**
  - Pressure control – ‘ULTRA<sub>CONTROL</sub>’
  - Volume control – calculated at 25 - 30% of Qb

- **Fresenius programme:**
  - Auto-sub – set TMP
  Auto-sub plus – automatically calculates substitution vol based on max allowed TMP
Typical HDF prescription

15 year old boy
Wt = 42.0kg  SA = 1.4m²
Dialyser Polyflux 140
Q_b = 300ml/min
Q_d = 500 ml/min
Desired wt loss = 1.6L

Calculation if in volume control = %blood flow x number of hours x 60minutes (or consult chart)

25% x 300 x 4 x 60 = 18 litres
Subtract UF loss (1.6L) = 16.4L substitution volume