Modes of Extracorporeal Therapies For ESRD Patients

Suhail Ahmad, MD
Dialysis:

“Movement of molecules across a semipermeable membrane” (Bi-directional)

Movement of Molecules:

- Solvent (water): Ultrafiltration
ULTRAFITRATION
Movement of water molecule on pressure gradient: From High to Low pressure

DIFFUSION
Movement of solute molecule on concentration gradient: From High to Low Concentration

Convection
Movement of solute molecule on pressure gradient: with water “solvent drag”

Adsorption/Sorbent-Exchange

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**MODES OF THERAPY**

**HD: DIFFUSION**

1. IHD
2. SLED

**CONVECTION**

- **Pre-Dilution**
  - Sterile
  - 1. HF: Large UF replaced by sterile replacement fluid
  - No dialysate present
  - 2. HDF: HF plus dialysis, dialysate present.

- **Post-Dilution**
  - Sterile
  - Based on site where RF is introduced the HF and HDF:
  - 1. Pre-dilution
  - 2. Post-dilution
  - 3. Mixed (both Pre- and Post-)
  - 4. Mid-dilution (special dialyzer)
Solute fluxes in different treatment modalities

(Diffusion)

HD

Convection

HF

Mol. weight

Clearance

Urea  Creatinine  Inulin  Albumin
REQUIREMENTS

1. $Q_b > 350$

2. Hemofilter: Biocompatible membrane (AN6, PS etc); Permits high $Q_b$, low resistance, small PV, high Kuf

3. Adequate Anticoagulation

4. RF = Sterile, pyrogen free
   Composition similar to plasma water

**Generic Set-up for IHF**

**Pre-Dilution**

- RF = about 100 - 120 L/Rx
- UF = RF + desired Wt loss

**Post-dilution**

- RF = about 30 - 40 L/Rx
- UF = RF + desired Wt loss

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MODES OF HEMOFILTRATION

Pre-dilution: Lower risk of fouling of membrane and clotting  
Dilution of blood solutes reduces clearance  
Larger volume of UF is needed to improve clearance (3x)  
Dilution of anticoagulant may increase risk of clotting

Mid-dilution: RF delivered in the dialyzer midway; lowers the risk  
of fouling in the lower half of filter, requires larger UF  
Special dialyzer with additional port.

Post-dilution: Achieves maximum clearance for given volume.  
Clearance = UF volume x Sieving coefficient:  
If SC = 1 (urea), & Volume = 30 L/Rx  
Urea Clearance = 30 L / Rx  
With high UFR, hemoconcentration  fouling of  
membrane, clotting, increased TMP, reduced clearance

Mixed-dilution: RF delivered pre- and post dialyzer
Hemofiltration

- Currently, HF is used as a continuous process limited to acute dialysis, not ESRD.
- In past HF has been used intermittently, 3 x wk, in ESRD.
- Complexity and cost limited its use.
- Interesting data worth reviewing.
Due to Convective Transport, HF Provides Higher MM & Lower SM (Urea) Clearance

Quellhorst et al: Compared 120 Chr. IHF Pts with HD, Data from Diaphene & EDTA Registries

HF: 3-4 Hrs Session 3 Times a Week
  • Mean Kt/Vurea 0.55 per Rx or 1.56 / Week

Patients from 20 centers (Italian Study)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hemofiltration</th>
<th>Low Flux HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 yr survival</td>
<td>78%</td>
<td>57%</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.07</td>
<td>1.42</td>
</tr>
</tbody>
</table>

P=0.05, P<0.0001

Intermittent Hemofiltration

- Improved clearance of larger molecule (MM)
- Improved outcome
- Complex → Balance UF with RF
- Expensive → Large volume of sterile and pyrogen free fluid
- Lack of safe, automated system
- Reduced removal of smaller molecules (urea, electrolytes etc.)

HD remained universally used treatment for ESRD

Reduce the HF volume (Cost) by combining it with HF → HDF

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Our Early Experience (18 months of HDF, 1982-84)

Major Findings:
1. Dialysis time reduced from 5-6 hrs to 3.5-4 hrs 3xwk
2. PO4 binder requirement reduced Al load from 9.9 to 2.7 grams
3. Better volume control
4. Anthropometry Improved

Because of complexity & Expense
It was discontinued after ~ 2 years

Ahmad et al: Trans ASAIO, 32: 370-373, 1986
ol-HF

- HD - Good Clearance of SM (urea)
  - But despite highflux Rx, MM clearance remains a problem
    - Due to reduction in time
- HF – Very good MM clearance
  - But the need for large volume of RF, major obstacle
- Use dialysate as RF
- Modify existing HD systems to provide ol-HF
Ultrafilters (Sterile Fluid)

Fluid Balancing Chamber

Ultrafiltrate

ol-Hemofiltration
HF – Challenges, ol-HDF

- Large volume of UF/RF needed, requiring:
  - High Qb to prevent clotting and membrane fouling
- Limited clearance of SM was also a concern
- Continued interest in convective dialysis:
  - Positive data, and
  - The limitation of shorter HD – poor outcome
- Emergence of ol-HDF:
  - Use dialysate as replacement fluid (reduce cost)
  - Utilize new volumetric controller to automate & simplify the procedure (reduce complexity)
On-Line HDF
Mostly in Europe & Japan
Current ESRD Modalities

1. High Flux HD
2. Ol-HDF
Definitions (EUDIAL)

- **High-flux dialysis**: Uses High-flux dialyzer
  - High hydraulic permeability ($K_{uf} > 20 \text{ ml/mmHg/hr}$).
  - With sieving coefficient of $>0.6$ for B2mcg (solute requirement recently added).

- **HDF**: Combination of diffusive & convective solute transport using high-flux dialyzer where,
  - Convective volume is more than 20% of total blood volume processed ($>18 \text{ L}$) – Post-dilution
  - Combined with infusion of appropriate volume of sterile pyrogen free solution into blood.
  - Various modes based on site of RF delivery
**Pre-dilution:** Lower risk of fouling of membrane and clotting
   Dilution of blood solutes reduces clearance →
   Larger volume of UF is needed to improve clearance (3x)
   Dilution of anticoagulant may increase risk of clotting

**Mid-dilution:** RF delivered in the dialyzer midway; lowers the risk of fouling in the lower half of filter, requires larger UF
   Special dialyzer with additional port.

**Post-dilution:** Achieves maximum clearance for given volume.
   Clearance = UF volume x Sieving coefficient:
   If SC = 1 (urea), & Volume = 20 L/Rx
   Urea Clearance = 20 L / Rx
   With high UFR, hemoconcentration → fouling of membrane, clotting, increased TMP, reduced clearance

**Mixed-dilution:** RF delivered pre- and post dialyzer
On-Line HDF (New machines with pumps & Circuits)
Mostly in Europe & Japan
Not available in US
Use of HD Machine

For ol-HDF
Modification of HD machine to deliver automated HDF
Addition of a pump and sensors with alarms
ol-HDF Vs HD

Brief discussion of results
The effect of dialysis modality on phosphate control: haemodialysis compared to haemodiafiltration. The Pan Thames Renal Audit

Andrew Davenport¹, Carrie Gardiner², Michael Delaney³
and on behalf of the Pan Thames Renal Audit Group⁴

Nephrol Dial Transpl 2010; 25: 897-901

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Short term effects of online HDF on phosphate

Convection volume 19 ± 4 L

N=242

N=251

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Retrospective analysis of intradialytic symptoms

RCT showing decrease of intradialytic hypotension with convective therapies

% of dialysis sessions with symptomatic intradialytic hypotension

<table>
<thead>
<tr>
<th>Episodes per session</th>
<th>On-line HDF</th>
<th>High-flux HD</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>intradialytic hypotension</td>
<td>0.03</td>
<td>0.05</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>saline bolus administration</td>
<td>0.02</td>
<td>0.03</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>cramping</td>
<td>0.01</td>
<td>0.01</td>
<td>ns</td>
</tr>
<tr>
<td>UF rate (ml/h)</td>
<td>700-800</td>
<td>500-600</td>
<td>0.003 - &lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>at baseline</th>
<th>at 24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD, n=70 low-flux</td>
<td>7.1</td>
<td>7.9</td>
</tr>
<tr>
<td>HDF, n=40 predilution, 40L</td>
<td>10.6</td>
<td>5.2 *</td>
</tr>
<tr>
<td>HF, n=36 predilution, 60L</td>
<td>9.8</td>
<td>8.0 *</td>
</tr>
</tbody>
</table>

* p<0.001


J Am Soc Nephrol 2010
DOPPS: risk of mortality

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Relative risk of mortality</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>1.00</td>
<td>0.83</td>
</tr>
<tr>
<td>Low-flux HD (1366)</td>
<td>1.03</td>
<td>0.68</td>
</tr>
<tr>
<td>Low-ef fic HDF (156)</td>
<td>0.93</td>
<td>0.01</td>
</tr>
<tr>
<td>High-flux HD (546)</td>
<td>1.03</td>
<td></td>
</tr>
<tr>
<td>High-ef fic HDF (97)</td>
<td>0.65</td>
<td></td>
</tr>
</tbody>
</table>

n = 2165, adjusted for age, sex, time on dialysis, comorbidity, weight, catheter, Hb, alb, nPCR, lipids, Kt/V, EPO, QoL

Survival differences between patients in whom the predominant treatment modality was HDF and high-flux HD

152 000 session of on-line HDF in 232 patients compared to 291 000 sessions on HFHD in 626 patients

## Outcomes of HDF versus HD up to 2011

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>HDF vs Comparator</th>
<th>Type of study</th>
<th>β2-M</th>
<th>Annual Mortality HD/HDF</th>
<th>Survival Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wizemann V et al, 2000</td>
<td>HDF vs LFHD</td>
<td>RCT</td>
<td>↓</td>
<td>9.5/4.3</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>12.7/8.9</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>12.7/8.9</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>14.8/8.2</td>
<td>↑ 36%</td>
</tr>
<tr>
<td>Schiffi H et al, 2007</td>
<td>HDF vs HFHD</td>
<td>RCT</td>
<td>↓</td>
<td>4.1/4.2</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>19.9/8.9</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>13.2/10</td>
<td>↑ 15%</td>
</tr>
<tr>
<td>Santoro A et al, 2008</td>
<td>HF vs HFHD</td>
<td>RCT</td>
<td>↓</td>
<td>13.3/12</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>
<td>=</td>
</tr>
<tr>
<td>Vilar E et al, 2009</td>
<td>HDF vs HFHD</td>
<td>Historical prospective cohort</td>
<td>↓</td>
<td>9/6</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>
<td>=</td>
</tr>
</tbody>
</table>
Effect of ol-HDF on mortality risk

• Uncontrolled Studies: Showing survival benefit of ol-HDF

• Controlled Studies:
  – CONTRAST, ESHOL, French & Turkish:
  – Show 39% and 46% reduction in mortality in high convective volume (>15 Liters/session)
  – ESHOL (n=906, HDF Vs HF, >18 L/session)
Ol-HDF Survival Study (ESHOL) Spain, HR (risk of mortality)

18.6% Vs 27.1% rate, HDF Vs HD
### Unadjusted Mortality Risk by HDF volume per session (pooled from 4 studies)

Peters SAE et al, NDT Advance Access published October 22, 2015

<table>
<thead>
<tr>
<th>Cause</th>
<th>BSA adjusted convection volume (L/session)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;19</td>
</tr>
<tr>
<td>All Cause</td>
<td>0.91</td>
</tr>
<tr>
<td>Cardiovasc.</td>
<td>1.00</td>
</tr>
<tr>
<td>Infections</td>
<td>1.50</td>
</tr>
<tr>
<td>Sudden Death</td>
<td>1.24</td>
</tr>
</tbody>
</table>

- CONTRAST: 714 (6-24 L/session)
- ESHOL: 906 (>18 L/session)
- French: 391 (?)
- Turkish: 782 (>15 L/session)
High Volume HDF - benefits

• Reduced mortality (all cause, CV, infection)
• Improved fluid and BP control
• Reduced intradialytic hypotension
• Better PO4 control and Hb levels (not in all studies)
• Improved B2-mcg removal
• Reduced inflammation inflammatory markers
• Improved nutritional markers
TECHNICAL SPECIFICS

01-HDF
Blood Flow

- Dose of convective dialysis is directly related to UF volume (=RF volume)
- Large UF volume increases hemoconcentration:
  - Increases risk of clotting
  - Interferes with dialytic clearance
- Above risks can be reduced by increasing Qb (Qp)
Increased risk of clotting
With increased shear force & hemoconcentration

Convective transport
Increases loss of heparin:
- UFH → over 50% loss
- LMWH → over 80% loss

Priming bolus should be
Given in venous line
Allow 3-5 mins. to mix
Systemically, before Rx starts

**UFH use:**
- start with bolus 80 IU/Kg in venous line, circulate for 3-5 mins. Without dialysis
- continuous Infusion 25 IU/Kg/hr.

If clotting occurs or TMP increases:
- Increase bolus - 100 IU & infusion - 35 IU/kg/hr

**LMWH use:**
- Bolus Lovenox 0.5 mg/Kg (50 IU/Kg) in venous line, circulate for 3-5 mins. Without dialysis
(If Rx >4 hrs, repeat 400 IU bolus at mid Rx)
Direct Feed System

Backflow Preventor

Muti-media
Softener
1 Carbon Columns
2 Carbon Columns

Filter

RO (DI)

0.1u filter

Distribution Loop
Replacement Fluid

- Dialysate is used as RF
- It is ‘sterilized’ by:
  - Using ultrapure water (<0.1 CFU, <0.03 EU).
  - Double filtering the dialysate across membrane with nominal cut-off of about 25000 D
- Routine sterilization of the circuit, between uses
- Check for membrane integrity by pressure drop, before each use
- Change ultrafilters periodically

Sterilization & Integrity testing
Specifics (contd.)

- Hemodialyzer → High-flux, with low resistance
- Access: Should be able to provide >350 ml/min Qb
- Dialysate: Ultra-pure; Flow rate 600-1000 ml/min
- RF (& UFR):
  - Pre-dilution mode ~200 ml/min
  - To reduce hemoconcentration & membrane fouling:
    - Post-dilution → UFR < 33% of Qb (Qb 400, max. UFR130 ml)
    - Pre-dilution → UFR < 50% of Qb (Qb 400, UFR 200 ml/min)
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Maximum UFR 50% of Qb
If Qb 400, UFR <200 ml/min.

Maximum UFR 33% of Qb
If Qb 400, UFR <130 ml/min.

Recommend: UFR ≤30% Qb

PRE-DILUTION

POST-DILUTION
The usual dose calculated by Kt/Vurea should still be at target minimum of 1.2.

For other solutes (MM):

- The RCT are suggesting that for Post-dilution HDF:
  - Minimum Convective Volume must be >20 L per Rx
  - Or, a four hour of HDF the UFR should be around 100 ml/min
Reported Benefits of Convective process
Highflux HD or HDF (>20 L/Rx)

- Reduction in mortality & hospitalization
- Better intra-dialytic symptoms
- Lower levels of inflammatory markers
- Better response to ESA, anemia correction
- Better PO4 control
- Improvement in nutritional indicators
- Improvement in Beta-2-microglobulin
Potential Risks

- Exposure to dialysate/water contaminants
- Increased protein loss
- Deficiency syndromes, soluble vitamins, trace elements, small peptides
- Lack of understanding of the procedure
  - Increased TMP
  - Balancing chamber alarms
  - Sterilization of HDF module
  - Membrane integrity tests etc.
Conclusion

- Addition of convection to diffusion dialysis increases uremic solute clearance
  - Without increasing dialysis time or frequency
- Use of large convective volume are associated with other reported benefits (controversial)
- Use of ultrapure dialysate, ? Higher MM clearance, and biocompatible membrane reduces inflammatory responses
- Lack of affordable equipment & disposable makes it impractical for US
- With better technical understanding, current machines can be used safely for HDF at a fractional increase in cost.
Adsorbant & Sorbent Dialysis
Adsorption

- Removal of uremic toxins by activated charcoal by adsorption
- Charcoal columns in series with dialyzer have been used with reported benefits
- Additional cost, complexity & complications made it less desirable
- However, adsorption on some new dialyzer membranes is well documented
Sorbent Dialysis

- Regeneration of dialysate has always been very attractive
- It reduces water use from >120 L/Rx to 6-8 L/Rx
  - With global water shortage, critically important
- Elimination of complex proportioning system results in a simpler easy to use machines
Regeneration of Dialysate

- Ion Exchange resins can exchange cation or anions
- Enzymes can break down uremic substance such as urea
- Activated charcoal can remove various organic and inorganic contaminants
- Columns of above materials can be stacked in a cartridge
- Spent dialysate passed through the cartridge regenerates the dialysate.
- Renewed Interest in this technology – new machines are being developed & tested
First sorbent system was used in 1970s

The REDY was a simple transportable machine that used very little water and regenerated dialysate.

Its use declined in 1980s:

- Popularity of high efficiency fast and short dialysis
- Concerns regarding aluminum load etc.
- Limitation related to acidosis & uremia correction

Recently there has been a resurgence of interest, with modified sorbent cartridges.
SORBENT DIALYSIS MACHINE

Total water use = 6 Liters
No proportioning system
No balancing chamber
Size and complexity is reduced
Concerns & Limitations

- Leaching of sorbent materials
- Limitation of enough bicarbonate generation particularly later in dialysis when urea has dropped.
- Positive Na balance at the end of dialysis
- Length of dialysis limited by the cartridge contents & exhaustion of sorbents
- Channeling through various layers impacting the efficiency of treatment
Extracorporeal Therapies

- Three times/week HD has limitations
- Sub-optimal clearance of MM & volume control
- Increasing frequency/length of Rx has logistical challenges
- Combining HF and HD makes the Rx more acceptable and may have clinical benefits
- Need well trained nephrologist to maximize benefits and reduce risks
Current HD machines are too complex, require too much water

- It limits self care such as Home Rx
- With global water shortage, limiting water use is needed

- Regeneration of dialysate has advantages of reducing water use, and simplifying the machine
- Well trained nephrologists are necessary to maximize benefits and protect patients

Thank you