HEMODIAFILTRATION
IS IT IN OUR FUTURE?

Myriam Farah, MD, FRCPC
Fellow in Hemodialysis
Division of Nephrology
University of British Columbia
DISCLAIMER

I have no affiliation to or personal interests in the following companies and/or products:

BellCo
BBraun
Handidart
Starbucks
"Dialysis is a life boat"
WHY DO OUR PATIENTS DIE IF WE ARE REPLACING THE ORGAN THAT FAILED?

Indeed, the true miracle is that these very primitive devices are able to provide several decades of survival times for patients.”

Claude Jacobs

Improving the outcome of dialysis – opinion vs scientific evidence. NDT 2000
OUR MOST UNHEALTHY OBSESSION

\[ V_t = Qf \times t \left[ \left( 1 - \frac{G - C_t(K + kr - Qf)}{G - C_0(K + kr - Qf)} \right)^{\frac{Qf}{k + kr - qf}} - 1 \right] \]  

(1)

\[ G = \frac{(Kr + \alpha)(C0 - Ct(\frac{Vf + \alpha\theta}{Vf})^{-\frac{kr + \alpha}{\alpha}})}{1 - (\frac{Vf + \alpha\theta}{Vf})^{-\frac{kr + \alpha}{\alpha}}} \]  

(2)

spKt/V = -ln (R - 0.03) + [(4 - 3.5R) \times (UF + W)]

KDOQI Targets:

- spKt/V > 1.2
- URR > 65%

URR = 100 \times (1 - \text{postdialysis urea/predialysis urea})
WHAT NEEDS TO BE CLEARED?

• **Small Solutes**
  - Examples:
    - Urea
    - Creatinine
    - Electrolytes
    - Phosphate (*)

• **Middle and Larger Molecules**
  - Examples
    - Beta-2-microglobulin
    - Inflammatory markers

• **Protein-bound Solutes**
  - Examples
    - P-cresol
SMALL SOLUTE CLEARANCE

- **HEMO Study**
  - No difference in mortality between targeting spKt/V 1.45 (URR 75%) vs standard dose Kt/V 1.25 (URR 65%)
  - But trend towards lower CV mortality in high flux group

- **MPO Study**
  - Comparison of low vs high flux HD in incident pts
  - No overall difference in mortality
  - But significantly lower mortality in diabetics and hypoalbuminemic patients
SOME OF THE OBSERVED BENEFITS OF HEMODIAFILTRATION

- Decreased mortality
- Better hemodynamic stability during dialysis
- Better phosphate clearance
- Better beta-2-microglobulin clearance
- Decreased inflammatory markers
- Increased EPO responsiveness
- Clearance of light chains
THE CURRENT THINKING

• A minimum amount of small solute clearance is necessary to sustain survival on dialysis

• Above this threshold, however, no study to date has shown that increasing small solute clearance correlates with better survival

• Is it possible that the larger (?undefined) middle molecules play a bigger role than we can appreciate or measure?

• If so, should we shift our focus on getting rid of them?
RECALL: WHAT IS HEMODIALYSIS?

Hemodialysis
Movement of small solutes by diffusion through the addition of dialysate to the fluid side of the filter.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>DEPENDS ON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration gradient</td>
<td>[X]<em>{serum} and [X]</em>{dialysate}</td>
</tr>
<tr>
<td>Blood Flow Rate</td>
<td>Vascular access, hemodynamics</td>
</tr>
<tr>
<td>Dialysate Flow Rate</td>
<td>Availability of dialysate</td>
</tr>
<tr>
<td>Dialysis Time</td>
<td>Handidart</td>
</tr>
<tr>
<td>Efficiency (small solute)</td>
<td>Dialyzer surface area</td>
</tr>
<tr>
<td>Flux (middle molecule)</td>
<td>Dialyzer pore size, UF rate</td>
</tr>
</tbody>
</table>
WHAT IS HEMODIAFILTRATION?

Hemofiltration

Removal of relatively large volumes of fluid by ultrafiltration, resulting in removal of solutes through convection.

Hemodiafiltration

Dialysate Solution

Repl. Solution

LOW PRESS ← HIGH PRESS

to waste
COMPONENTS OF CONVECTIVE CLEARANCE

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>AFFECTS</th>
<th>DEPENDS ON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrafiltration</td>
<td>Water and solvent removal</td>
<td>TMP, hydraulic permeability</td>
</tr>
<tr>
<td>Sieving Coefficient</td>
<td>Degree of solvent drag with water</td>
<td>Size of molecule and size of pores</td>
</tr>
<tr>
<td>Replacement Fluid</td>
<td>Clearance</td>
<td>Amount</td>
</tr>
<tr>
<td></td>
<td>Hemodynamic preservation</td>
<td>Pre or post-dilution</td>
</tr>
</tbody>
</table>

Total ultrafiltrate + spent dialysate

Replacement (shown in post-dilution)

Dialysate
THE CRUX OF HDF – MEMBRANE EVOLUTION

- Early cellulose membranes were thin & hydrophilic, with small pore sizes
- Good small solute clearance
- Insufficient flux for water and sieving coefficients

- Modified cellulose membranes were thick & hydrophobic
- Good flux for water & sieving coefficients
- Too thick for efficient small solute clearance

- New generation of synthetic fibers with combined hydrophilic/hydrophobic structure and reduced thickness
- Allows for filtration and dialysis
HISTORY OF HDF

1947
first ultrafilter in dogs

1960’s
first hemofiltration in humans

1970’s
first hemodiafiltration in humans

1980-1990’s
Different regulatory climates lead Europe to “freely” apply techniques clinically, while the rest of world lags behind
PREVALENCE OF HDF

Australia: DOPPS II 6.6, DOPPS III 4.8
Belgium: DOPPS II 5.6, DOPPS III 4.8
Canada: DOPPS II 13.1, DOPPS III 5.6
France: DOPPS II 12.9, DOPPS III 0.2
Germany: DOPPS II 10.0, DOPPS III 5.9
Italy: DOPPS II 19.1, DOPPS III 16.0
Japan: DOPPS II 0.0, DOPPS III 4.7
Spain: DOPPS II 2.8, DOPPS III 6.0
UK: DOPPS II 5.0, DOPPS III 6.0
USA: DOPPS II 0.50, DOPPS III 0.1
CLASSIC HDF – AKA “BAG” HDF

- First used in 1970s

- Reinfusate supplied in big bags (like in CRRT) and reinfused post-dilution

- Typically ~9L / session
  - If lower volumes (3-6L / session) – “soft” HDF or “biofiltration” (likely similar to high flux HD)
  - If higher volumes (15-21L / session) – “hard” HDF

- Limited by
  - Number of available bags (cost)
  - Nursing labour!
ONLINE HDF

- Introduced in 1980s

- High volumes of replacement fluid made “ONLINE”
  - dialysate from dialysate inlet processed through a number of filtration steps to make it safe enough for infusion into patient (ie. ultrapure dialysate)

- Eliminates cost and labour

- Limiting factors
  - Water Quality
  - Equipment approval
  - Safety Data and Analysis
WATER REQUIREMENTS

What every office needs
REQUIRED WATER STANDARDS

• Criteria for Dialysate
  • European standards: <100 CFU/ml and <0.25 EU/ml

• For use as replacement fluid, must meet criteria for Ultrapure Dialysate (ie safe for infusion into patient)
  • European standards: <0.1 CFU/ml and <0.03 EU/ml

• How can we achieve this?
1. MUNICIPAL WATER TREATMENT
2. REVERSE OSMOSIS
3. ULTRAPURE DIALYSATE CREATION

Dialysate

Blood in

Spent dialysate & total UF

Replacement fluid

Blood out

Ultrapure Dialysate

2 filters installed in back of machine

Point of Testing
Or give it to your mother.
She knows how to do it.
DOSE OF HDF – MORE IS MORE

- Degree of solvent drag depends on how much fluid is being removed by filtration and subsequently replaced

- Dose of HDF therefore correlates with UF rate

- Total UF rate = prescribed replacement fluid + desired fluid loss

- What limits UF rate
  - The filter
  - The patient
  - Effect on concentration gradients
### POST-DILUTION REPLACEMENT

![Diagram of dialysis process](image)

**Total ultrafiltrate + spent dialysate**

**Dialysate**

**Replacement (post-dilution)**

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**Recommendation**: > 20L

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<table>
<thead>
<tr>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does not dilute concentration gradients, so does not decrease clearance efficiency</td>
<td>Leads to hemoconcentration within filter (high risk of filter clotting)</td>
</tr>
<tr>
<td>Should limit UF rate to &lt;25-30% of Qb (eg. at 400ml/min = 100ml/min = 24L of UF)</td>
<td>May change heparin requirements</td>
</tr>
</tbody>
</table>
PRE-DILUTION REPLACEMENT

**ADVANTAGES**
- Lower risk of filter clotting

**DISADVANTAGES**
- Dilution of blood pre-filter reduces concentrations and thus gradients for clearance
- To compensate, need to use 2x amount of replacement fluid used in post-dilution mode
- Increases filter TMP
- Increased total exposure to replacement fluid

Recommendation: > 40L
PAIRED HEMODIAFILTRATION

- Dual chamber dialyzer with two dialyzers connected in series

- Top dialyzer acts as an additional filter for reinfusate as it is delivered to patient via backfiltration

- Extra safety measure to “guarantee” ultrapure dialysate
PAIRED HEMODIAFILTRATION
Pre-Dilution Mode

Dialysate

Blood in

Replacement fluid (pre-dilution)

Spent dialysate & total UF

Ultra-ultrapure Dialysate

Blood out

Point of Testing

2 filters installed in back of machine

3rd additional filter
PAIRED HEMODIAFILTRATION
(BellCo)
Post-Dilution Mode

2 filters installed in back of machine

Ultra-ultrapure Dialysate

Dialysate

Blood in

Spent dialysate & total UF

Blood out

Replacement fluid (post-dilution)

Point of Testing

3rd additional filter
PAIRED HDF IN ACTION

Foreclean and Multipure

Pre-dilution Mode

Post-dilution Mode
WHAT DO WE KNOW

AND

WHERE DO WE GO FROM HERE?
OBSERVATIONAL TRIALS

- Decreased mortality
- Better phosphate clearance
- Better beta-2-microglobulin clearance
- Decreased inflammatory markers
- Increased EPO responsiveness
- Better hemodynamic stability during dialysis
- Use in clearance of light chains
- Use in treatment of acute hepatic failure
<table>
<thead>
<tr>
<th>STUDY</th>
<th>PATIENTS</th>
<th>STUDY DESIGN</th>
<th>HDF MODE</th>
<th>HD MODE</th>
<th>F/U</th>
<th>MAJOR OUTCOMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOPPS (2006)</td>
<td>2165 prevalent HD</td>
<td>Retrospective</td>
<td>High (15-25L)</td>
<td>High flux</td>
<td>3 Yr</td>
<td>35% reduction in all cause mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Observational</td>
<td>vs low (5-15L)</td>
<td>vs Low flux</td>
<td></td>
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</tr>
<tr>
<td>EuCLID (2006)</td>
<td>2564 prevalent HD</td>
<td>Retrospective</td>
<td>Online-HDF</td>
<td>HD</td>
<td>3Yr</td>
<td>35% reduction in mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Observational</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RISCAVID (2008)</td>
<td>757 prevalent HD</td>
<td>Prospective</td>
<td>Bag-HDF (~14L)</td>
<td>HD</td>
<td>3Yr</td>
<td>Mortality RR 0.78 for HDF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>observational</td>
<td>vs Online-HDF</td>
<td>(~23L)</td>
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<tr>
<td>UK STUDY (2009)</td>
<td>858 incident HD</td>
<td>Retrospective</td>
<td>HDF (~15L)</td>
<td>High flux</td>
<td>18Yr</td>
<td>Mortality HR 0.45 for HDF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Observational</td>
<td></td>
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</table>
THEORIES ON BENEFITS OF HDF

• Enhanced middle molecule clearance

• Improved intradialytic hemodynamic stability

• Enhanced biocompatibility of ultrapure fluid
LIMITATIONS TO CURRENT HDF DATA

• Mostly observational studies, therefore no proven cause and effect, only associations

• Relatively few people on HDF at any time, on various regimens and doses

• Comparisons mostly to low flux HD (rather than high flux HD mostly in Canada)

• No North American data
<table>
<thead>
<tr>
<th>ONGOING STUDY (COUNTRY)</th>
<th>PATIENTS</th>
<th>STUDY DESIGN</th>
<th>HDF MODE</th>
<th>HD MODE</th>
<th>F/U</th>
<th>PRIMARY OUTCOME</th>
<th>SECONDARY OUTCOMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTRAST Netherlands Norway Canada (1)</td>
<td>Prevalent HD (~700)</td>
<td>Randomized prospective</td>
<td>Post (6L/hr)</td>
<td>Low flux</td>
<td>2 Yr</td>
<td>All cause mortality CV m&amp;m</td>
<td>Phosphate, LVMI, carotid intima, PWV, inflammatory markers, uremic toxins, QoL, nutrition</td>
</tr>
<tr>
<td>ESHOL Spain</td>
<td>Prevalent HD (~750)</td>
<td>Randomized Prospective</td>
<td>?</td>
<td>?</td>
<td>3 Yr</td>
<td>All cause mortality</td>
<td></td>
</tr>
<tr>
<td>TURKISH study</td>
<td>Prevalent HD (~780)</td>
<td>Randomized prospective</td>
<td>Post (15L/run)</td>
<td>High flux</td>
<td>2 Yr</td>
<td>All cause mortality &amp; new CV events</td>
<td>CV mort, hosp rate, intradialytic cxs, QoL, med chnages, EPO req, middle molec,</td>
</tr>
<tr>
<td>ITALIAN study</td>
<td>Prevalent HD (146)</td>
<td>Randomized Prospective</td>
<td>Pre</td>
<td>Low flux</td>
<td>2 Yr</td>
<td>HD stability BP control</td>
<td>Total mortality CV m&amp;m</td>
</tr>
<tr>
<td>FRENCH study</td>
<td>Prevalent HD &gt; 60y (~600)</td>
<td>Randomized Prospective</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McGill study</td>
<td>Prevalent HD with sleep apnea</td>
<td>Randomized crossover</td>
<td>?</td>
<td>?</td>
<td>3mos</td>
<td>Reduction in AHI</td>
<td>QoL, RLS symptoms, BP, etc</td>
</tr>
<tr>
<td>KOREAN study</td>
<td>Prevalent HD</td>
<td>Cross-over non-rand.</td>
<td>?</td>
<td>Low flux</td>
<td>2mos</td>
<td>Flow mediated vasodilation</td>
<td></td>
</tr>
</tbody>
</table>
REQUIREMENTS FOR HDF

- Water that meets standards for ultrapure dialysate

- HD machines that can do HDF and have Health Canada approval to operate in HDF mode

- Extra supplies for HDF (tubing, filters, etc)

- Nursing and technician training and in-service

- Money
DIRECT COST COMPARISON

SOMEONE’S MOM

$at 5 PER RUN

2000 DIALYSIS PTS IN BC

$1.5 million PER YEAR
UNANSWERED QUESTIONS…

• Is HDF truly better than optimum high flux HD in Canada?
  • How do we define “better”?

• Are there certain patients who are most likely to derive a benefit from this modality?
  • Who are they and how do we identify them?

• Stay tuned for answers…
QUESTIONS / COMMENTS?