Choosing dialysate and replacement solutions for convective therapies

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We know that the primary factor in HDF is convection... in addition to diffusion...

---

**A**

Concentration gradient based transfer.
Small molecular weight substances (<500 Daltons) are transferred more rapidly.

**B**

Movement of water across the membrane carries solute across the membrane.
Middle molecules are removed more efficiently.

Slides from Dr. Tamaddondar’s presentation (from Hormozgan University of Medical Science)
We know that HDF is good post-dilution is better...

Fig. 1. Clearance as a function of substitution fluid flow $Q_S$ (Fresenius FX60, blood flow 400 ml/min, dialysate flow 800 ml/min). Clearance increase by convection is more pronounced for $\beta_2$-microglobulin.
We know that the higher the convective volume, the better is the outcome...

<table>
<thead>
<tr>
<th>Study name</th>
<th>Patients (HDF/HD)</th>
<th>Event nr (HDF/HD)</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grooteman et al. (3)</td>
<td>358/356</td>
<td>37/46</td>
<td>0.80</td>
<td>0.53 – 1.20</td>
</tr>
<tr>
<td>Ok et al. (4)</td>
<td>391/391</td>
<td>32/44</td>
<td>0.73</td>
<td>0.47 – 1.12</td>
</tr>
<tr>
<td>Maduell et al. (5)</td>
<td>456/450</td>
<td>37/55</td>
<td>0.66</td>
<td>0.57 – 0.92</td>
</tr>
<tr>
<td>Pooled</td>
<td>1205/1197</td>
<td>106/145</td>
<td>0.73</td>
<td>0.57 – 0.92</td>
</tr>
</tbody>
</table>

21 liters/session is advised...
We know that to reach a higher convective volume, higher $Q_d$ and $Q_b$ is necessary...and...
Exposure to water in dialysis modes

• In 4 hours HD, the patient is exposed to 300-800 ml/min (72-192 liters) of dialysate!

• In 4 hour HDF, an extra of upto 30 liter of replacement fluid (made of dialysate) is infused!

• Total exposed in 4 hours in HDF: upto 200 liters of dialysate!

• We infuse replacement fluid directly into blood!
Shall we modify our dialysate composition in HDF?
The Dialysate
Water System in HD and HDF

Hemodialysis
- Tap water
- Pretreatment + RO
- Water for dialysis*
- Mix with concentrates
- Standard dialysis fluid*
- Ultrafiltration
- Ultrapure dialysis fluid*
- Ultrafiltration

Hemodiafiltration
- Sterile, non-pyrogenic* substitution fluid

Microbiological quality:
- CFU/ml: <10²
- EU/ml: <0.25
- <10²
- <0.50
- <10⁻¹
- <0.03
- SAL ≥ 6
- <0.03

Application in dialysis:
- Basis for all fluid preparation
- Dialysis fluid in low-flux HD with synthetic membranes
- Dialysis fluid in all forms of HD & HDF
- Infusion solution in HDF & HF
Some of the dialysate go as substitution and most go as dialysis fluid.

- Reverse Osmosis (RO)
- Ready-made concentrate fluid
- Sterile, non-pyrogenic substitution fluid
- Dialysis fluid

Directly into the Blood

Diffusion + Convection
Issue 1: The Blood Flow and Infusion Rate
Online haemodiafiltration: definition, dose quantification and safety revisited

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Richard A. Ward² on behalf of the EUDIAL group*

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*The details of the EUDIAL group are given in Appendix 2.

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Keywords: haemodiafiltration, review, definition, safety

HDF is a blood purification therapy combining diffusive and convective solute transport using a high-flux membrane characterized by an ultrafiltration coefficient greater than 20 mL/h/mm Hg/m² and a sieving coefficient (S) for β₂-microglobulin of greater than 0.6. Convective transport is achieved by an effective convection volume of at least 20% of the total blood volume processed. Appropriate fluid balance is maintained by external infusion of a sterile, non-pyrogenic solution into the patient’s blood.
2 fluids: Replacement and Dialysis

BFR = 200 ml/min

- Dialysis fluid: 300-800 ml/min (Diffusion and Convection)
- Sterile, non-pyrogenic substitution fluid: 50 ml/min (Directly into the blood)
2 fluids: Replacement and Dialysis

BFR = 300 ml/min

Dialysis fluid
300-800 ml/min
Diffusion and Convection

Sterile, non-pyrogenic substitution fluid
75 ml/min
Directly into the blood
2 fluids: Replacement and Dialysis

BFR=400 ml/min

- Dialysis fluid
  - 300-800 ml/min
  - Diffusion and Convection

- Sterile, non-pyrogenic substitution fluid
  - 100 ml/min
  - Directly into the blood
2 fluids: Replacement and Dialysis

BFR 300 → 400 ml/min

- Stays the same
- 25 ml/min (6 L/4 hours) directly into the blood

Sterile, non-pyrogenic substitution fluid
Issue 2: Solute Clearance Rate by Time
Blood Flow Rate and Solute Removal

BFR 300 → 400 ml/min

We process 24 Liters of more blood
The issue of clearance and time

**Fig. 2.** Relationship between solute clearance \( (K_{HF}) \), mass removal rate and cumulative removal during a 4-hour HD treatment. Even with constant dialyzer clearance, the mass removal rate falls during the treatment due to a reduced concentration gradient. Reprinted with permission from Clark and Henderson [19].

Clearance decreases by time! In HDF?
Issue 3: How much of the work is done by diffusion? How much by convection?
Why do we need the dialysate?

Concentrations of dialysate components used in hemodialysis:

<table>
<thead>
<tr>
<th>Component</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq/L)</td>
<td>135 to 155</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>0 to 4</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>1.25 to 1.75 (2.5 to 3.5 mEq/L)</td>
</tr>
<tr>
<td>Magnesium (mmol/L)</td>
<td>0 to 0.75 (0 to 1.5 mEq/L)</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>87 to 120</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>25 to 40</td>
</tr>
<tr>
<td>Glucose (g/dL)</td>
<td>0 to 0.20</td>
</tr>
</tbody>
</table>


Restore: Ca++, NaHCO3

Remove: Na+, Mg++, K+, Glucose

Glucose
Abbreviations

dNa⁺ = dialysate sodium conc.
pNa⁺ = plasma sodium conc.
cNa⁺ = convective sodium conc.
sNa⁺ = serum sodium conc.
    Bic = bicarbonate
    UF = ultrafiltration
    RF = replacement fluid
Commonly used dNa\(^+\) concentration is 135-145 mmol/L

Major contributor of Posm

dNa\(^+\) determines Na\(^+\) and water exchange

UF is the major remover of Na\(^+\) and water rather than diffusion; every 1 liter of ultrafiltrate will remove around pNa\(^+\) level (i.e 135 mmol)

Some of the pNa\(^+\) is bound to anions, so not all available for diffusion. A gradient >4 mmol/L between dialysate and plasma is necessary for diffusive losses.

Albumin forces pNa\(^+\) to remain in the plasma (Gibbs–Donnan effect)

In conventional HD, >80% is convective and only 20% is diffusive (Santos SFF)
Sodium and Comparison of HD vs. HDF

**HD**
- sNa → Convection → cNa X UF → Diffusion → dNa

**HDF**
- sNa → Diffusion → dNa
- dNa X RF → Convection → cNa X UF
The effect of replacement fluid?

HDF

Replacement fluid 21 liters
Dialysate sodium 135-138-145

sNa

Convection

135

cNa X 24

135 x 21

sNa

Convection

138

cNa X 24

138 x 21

sNa

Convection

145

cNa X 24

145 x 21
The effect of replacement fluid?

HDF

RF 21 liters
UF 3 liters
dNa 135-138-145

Convection
Diffusion

135

? 135

-135 X 24 (3240)

-135 X 21 (2835)

135

+3 138

-135 X 24 (3240)

-138 X 21 (2898)

135

+10 145

-135 X 24 (3240)

-145 X 21 (3045)

mEq/L
The effect of replacement fluid?

HDF

RF 21 liters
UF 3 liters
dNa 135-138-145

mEq/L

Convection
Diffusion

140 -2 135

140 X 24 (3360)

140 -2 138

140 X 24 (3360)

140 +5 145

140 X 24 (3360)

135 X 21 (2835)

138 X 21 (2898)

145 X 21 (3045)
The effect of replacement fluid?

**HDF**

RF 21 liters
UF 3 liters
dNa 135-138-145

Convection
Diffusion

140
135
140 X 24 (3360)
135 X 18 (2430)

140
138
140 X 24 (3360)
138 X 18 (2484)

140
145
140 X 24 (3360)
145 X 18 (2610)

\(dNa\) 135-138-145

\(mEq/L\)
Factors to be taken into consideration

- Plasma/serum sodium level
- Dialysate sodium level
- Dialysate-plasma/serum gradient
- Convective Volume
- Replacement Fluid Volume
- Sodium and Water intake
- Gibbs-Donnan effect?
- Solute clearance dynamics by time?
- Dialysis session duration
- Measurement technique and standard deviation
What are we afraid of: High Dialysate Sodium!

Implications of current trends toward prescribing high dialysate sodium in HD

- Hypernatric dialysate
  - ↓ sodium removal
  - ↑ serum sodium

  - Volume overload
  - Hypertension
    - Left ventricular hypertrophy
    - Congestive heart failure
    - Stroke
    - Death
  - ↑ thirst

More and more data on osmotically inactive sodium? Deleterious?
Maybe we do not see a change in levels but what if....?
### What do the RCT’s say?

<table>
<thead>
<tr>
<th></th>
<th>dNa level (mEq/L/L)</th>
<th>Baseline sNa level (mEq/L)</th>
<th>Final sNa Level (mEq/L)</th>
<th>Baseline BP (mmHg)</th>
<th>FinalBP (mmHg)</th>
<th>IDWG (%)</th>
<th>Convection Volume (liters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTRAST</td>
<td></td>
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<td>HD</td>
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<tr>
<td>HDF</td>
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<td>ESHOL</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>138-140</td>
<td>138.7</td>
<td>138.3</td>
<td>136/71</td>
<td>136/71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDF</td>
<td>138-140</td>
<td>138.8</td>
<td>138.3</td>
<td>136/73</td>
<td>133/70</td>
<td></td>
<td>22.9-23.9</td>
</tr>
<tr>
<td>Turkish HDF</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>138</td>
<td>136</td>
<td>136*</td>
<td>127/78</td>
<td>126/77</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>HDF</td>
<td>138</td>
<td>136</td>
<td>135*</td>
<td>128/78</td>
<td>130/78</td>
<td>3.5</td>
<td>19.6</td>
</tr>
</tbody>
</table>
What about osmolar set point?

What about IDWG and Blood Pressure?
• sK⁺ level is affected by dietary K⁺ intake, dK⁺ level, KoA, the duration and frequency of dialysis as well as fecal excretion.
• sK⁺ level is not a reliable index of total body K⁺ content.
• K⁺ removal rate is largely a function of the predialysis concentration.
• dK⁺ of 2 mmol is sufficient to keep sK<6 (in dietary compliant patients)
Potassium and Comparison of HD vs. HDF

HD
- sK → Diffusion → dK
- sK → Convection → cK X UF

HDF
- sK → Diffusion → dK
- sK → Convection → cK X UF
- dK X RF
The effect of dK?

HDF

\[ \text{mEq/L} \]
The effect of replacement fluid?

HDF

Replacement fluid 21 liters
UF = 3 liters
Dialysate potassium 1-2-3

mEq/L
### What do the RCT’s say?

<table>
<thead>
<tr>
<th></th>
<th>dK level (mEq/l)</th>
<th>Baseline sK level (mEq/dl)</th>
<th>Final sK Level (mg/dl)</th>
<th>Delta</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTRAST</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD</td>
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<td>HDF</td>
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<tr>
<td>ESHOL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>1.5-2.0</td>
<td>5.3</td>
<td>5.1</td>
<td>0.1</td>
</tr>
<tr>
<td>HDF</td>
<td>1.5-2.0</td>
<td>5.2</td>
<td>5.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Turkish HDF</td>
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<td></td>
</tr>
<tr>
<td>HD</td>
<td>2</td>
<td>5.08</td>
<td>5.2*</td>
<td>0.12</td>
</tr>
<tr>
<td>HDF</td>
<td>2</td>
<td>5.11</td>
<td>5.2*</td>
<td>0.09</td>
</tr>
</tbody>
</table>

* Only data for time-averaged values are given
The effect of alkalosis?

- Alkalosis causes a shift of $K^+$ into cells and acidosis results in $K^+$ efflux from cells.
- Buffer base transfer into blood during dialysis induces cellular $K^+$ uptake and thereby attenuates the dialytic $K^+$ removal (more pronounced in acidosis).
- Other factors: dGlu level, hypertonic solutions, beta-adrenergics/blockers, surgery.
The commonly used proportioning ratios of concentrates and water include: 1:1.225:32.775, 1:1.83:34, and 1:1.72:42.28 (i.e. acid: base: water).
• Acetate content needs to be taken into consideration when calculating total Bic given.
• Certain dialysis machines use a batch system instead of a proportioning system to generate a Bic-based dialysate.
• The Bic flux from the dialysate to the patient is determined by the transmembrane concentration gradient and by the ability of the dialyzer to transfer Bic.
• Recently, there is growing evidence that alkalosis may be more harmful than expected.
Bicarbonate and Comparison of HD vs. HDF
The effect of replacement fluid?

HDF

RF 21 liters
UF 3 liters
dBic 28-32-36

mEq/L
The effect of replacement fluid?

HDF

Convection
Diffusion

RF 21 liters
UF 3 liters
dBic 28-32-36

mEq/L

16

+12

28

16 X 24 (384)

28 X 21 (588)

32

+16

16 X 24 (384)

32 X 21 (672)

36

+22

16 X 24 (384)

36 X 21 (756)
### What do the RCT’s say?

<table>
<thead>
<tr>
<th></th>
<th>Dialysate Bic content (mmol/l)</th>
<th>Baseline Blood Bic level (mEq/L)</th>
<th>End of Study Blood Bic Level (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTRAST</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HD</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HDF</td>
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<td>ESHOL</td>
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<tr>
<td>HD</td>
<td></td>
<td>34-37</td>
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<td>34-37</td>
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<td>Turkish HDF</td>
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</tr>
<tr>
<td>HD</td>
<td>32</td>
<td>22.7</td>
<td>21.9*</td>
</tr>
<tr>
<td>HDF</td>
<td>32</td>
<td>22.6</td>
<td>22.5*</td>
</tr>
</tbody>
</table>

* Only data for time-averaged values are given
What happens to bicarbonate?
Even though Ca\(^{++}\) is one of the most abundant substances in the body, the plasma ionized Ca\(^{++}\) is only about 1.1 to 1.5 mmol/L.

- 40% is bound to proteins (80–90% of that to albumin), 14% is complexed, and 46% is ionized.
- Complexed and ionized forms are dialyzable.
- The most common concentrations used: 1.25, 1.5, and 1.75 mmol/L (i.e., 2.5, 3.0, and 3.5 mEq/L; or 5.0, 6.0, and 7.0 mg/dL).
- Lower concentrations are chosen to permit vitamin D and calcium based phosphate binder user.
- However, it may be logical to base this decision according to PTH levels.
• Dietary Ca^{++} intake, pH, Vit D levels and usage, calcitonin, UF rate and P-binding drug choice affects serum Ca^{++} levels.
• dCa^{++} level affects serum PTH levels and also blood pressure.
• Patients on more frequent dialysis regimes need to be on higher dCa^{++}.
Calcium and Comparison of HD vs. HDF
The effect of dCa?

HDF

mmol/L

Convection

Diffusion

\( sCa \times U F \)

1.25

1.5

1.75

\( cCa \times U F \)

1.25 \times RF

1.5 \times RF

1.75 \times RF
The effect of replacement fluid?

HDF

- Diffusion
  - +.25
  - 1.25

- Convection
  - 1 X 24
  - (24)

- Diffusion
  - +.5
  - 1.5

- Convection
  - 1 X 24
  - (24)

- Diffusion
  - +.75
  - 1.75

- Convection
  - 1 X 24
  - (24)

RF 21 liters
UF 3 liters
dCa 1.25-1.5-1.75

mmol/L
What about.....?

- Calcimimetics
- Vitamin D
- Calcium-based phosphate binders
- Vascular Calcification
What do the RCT’s say?

<table>
<thead>
<tr>
<th></th>
<th>dCa Level (mmol/l)</th>
<th>Baseline sCa level (mg/dl)</th>
<th>Final sCa Level (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTRAST</td>
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<tr>
<td>HD</td>
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<td>1.25</td>
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<td>HDF</td>
<td>1.25</td>
<td>9.1</td>
<td>9.1</td>
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<tr>
<td>Turkish HDF</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>1.5</td>
<td>8.69</td>
<td>8.92*</td>
</tr>
<tr>
<td>HDF</td>
<td>1.5</td>
<td>8.66</td>
<td>8.94*</td>
</tr>
</tbody>
</table>

* Only data for time-averaged values are given
And finally what about.....?
What about dilution type?

More replacement fluid, more convection, and so...?
What about dilution modes?

Table 2. Typical ultrafiltration rates required to achieve effective convection rates of 20%, 30%, and 37.7% of blood flow

<table>
<thead>
<tr>
<th>Blood flow (mL/min)</th>
<th>UF rate (%)</th>
<th>UF rate (%)</th>
<th>UF rate (%)</th>
<th>UF rate (%)</th>
<th>UF rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>50</td>
<td>75</td>
<td>75</td>
<td>150</td>
<td>250</td>
</tr>
<tr>
<td>300</td>
<td>60</td>
<td>90</td>
<td>90</td>
<td>180</td>
<td>300</td>
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<tr>
<td>350</td>
<td>70</td>
<td>105</td>
<td>105</td>
<td>210</td>
<td>350</td>
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<td>400</td>
<td>80</td>
<td>120</td>
<td>120</td>
<td>240</td>
<td>400</td>
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<tr>
<td>450</td>
<td>90</td>
<td>135</td>
<td>135</td>
<td>270</td>
<td>450</td>
</tr>
</tbody>
</table>

Rates assume a haematocrit of 35%.
*A filtration fraction of 30% in post-dilution is only possible using methods designed to optimize filtration.

That needs another talk!
What about the effect of such a high convection on mass transfer rates?
#1 Major source of removal in the dialyser is convection, but replacement fluid goes directly infused into the blood.

#2 Convective volumes are huge and so are their impacts!

#3 The maximal electrolyte level in the blood can not be more than the dialysate/infusate concentration.

#4 Dialyser is important. Specially designed filters for HDF permits more solute removal.

#5 Those solutes that we want to replenish seems to be affected the most from high convection rates (calcium and bicarbonate)
We do not have sufficient data; the 3 RCT’s either did not report or reported controversial data.
We need to investigate the dialysate more especially at high blood flow and infusion rates.

We need to also look at pre-dilution HDF.

In order to perform an optimal HDF.
Final Comments

Online dynamic dialysis?
Gezi Park!

Thank you....
The effect of dNa?

HDF

Convection

Diffusion

sNa

135

cNa X UF

135 X RF

sNa

138

cNa X UF

138 X RF

sNa

145

cNa X UF

145 X RF

mEq/L
The effect of dBic?

HDF

mEq/L
The effect of replacement fluid?

HDF

RF 21 liters
UF 3 liters
dCa 1.25-1.5-1.75

mmol/L

1.25
1.5
1.75

1.25 X 21
1.5 X 21
1.75 X 21
Infusate directly goes to the patient, dialysate ‘acts’ through a filter.

What happens in 4 hours?