Adjusting hemodialysis dose for protein catabolic rate
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APPENDIX

Main algorithm of the optimization procedure

Qb and td are continuous variables, fr and Qd discrete ones. The frequency values are 2, 3, 3.5, 4, 5, 6 and 7 /wk. The intermediate dialysate flow (intQd) is fixed to 500 mL/min and minQb to 50 mL/min.

01 fr = minfr
02 repeat while fr < 8
03     OK = True
04     Qb = minQb
05     Qd = minQd
06     td = mintd
07     if OK
08         compute the target with current values of fr, Qb, Qd and td
09         if not OK
10             compute required Qb with current Qd and td
11             if not OK
12                 if Qd < intQd
13                     Qd = intQd
14                 compute required Qb
15                 if not OK
16                     Qb = maxQb
17                     compute required td
18             if not OK
19                 if Qd < maxQd
20                     Qd = maxQd
21                 compute required Qb
22                 if not OK
23                     Qb = maxQb
24                     compute required td
25     if not OK
26         increase fr

OK means that the target has been achieved.

Rows 07 - 24 are repeated successively for each target (stdK/V, stdEKR, PAC and TAC), if checking of the previous target has succeeded (row 07). The treatment intensity is increased in every step, if required. Qb, Qd and td are updated only if the procedure has succeeded (OK). If the prescription from the previous step has given a value better than the current target, nothing is done. As the last means, fr is increased and searching for the other treatment parameters begins at start again.
Computing the required \( Q_b \) and \( t_d \) is based mainly on numeric solutions of the double pool UKM equations.

Roughly identical target combinations can be achieved with different combinations of \( Q_b \), \( Q_d \) and \( t_d \). The algorithm returns only one (or none) prescription for each target set. It prioritizes short \( t_d \) (within the min and max limits). The resulting prescription depends slightly on the order in which the four targets are checked. It is fixed to \( \text{stdK/V} \rightarrow \text{stdEKR} \rightarrow \text{PAC} \rightarrow \text{TAC} \).

The optimization is a compromise between speed and accuracy. One minute intervals are used in the Runge-Kutta procedure. In other calculations a 0.5 \% tolerance is allowed.

It is possible that the optimization fails. If \( V \) and/or \( G \) are high and maximum time and/or \( Q_b \) and \( Q_d \) limits low, the targets cannot be achieved even in daily treatment schedule. On the other hand, if frequency and treatment time are high and \( V \) and/or \( G \) low, the minimum blood flow 50 mL/min may be too much.

The optimization procedure was tested with 10 000 sets of random values of input parameters:
\[ K_r: 0 - 8 \text{ mL/min} \]
\[ V: 15 - 70 \text{ L} \]
\[ G: 50 - 500 \mu\text{mol/min} \]
\[ \text{max} Q_b: 200 - 800 \text{ mL/min} \]
\[ \text{weekly UF: 0 - 30 L} \]
\[ \text{dialyzer } K_o A: 400 - 1500 \text{ mL/min} \]
\[ \text{mintd: 90 - 480 min} \]
\[ \text{maxtd: mintd - 600 min} \]
\[ \text{maxTAC: 10 - 30 mmol/L} \]
\[ \text{maxPAC: maxTAC - 50 mmol/L} \]
\[ \text{minstdK/V: 1.8 - 3.5 /wk} \]
\[ \text{minstdEKR: minstdK/V - 5.0} \]

The targets were not achieved in less than 10 \% of cases. In the actual material, based on real patients and treatments, the targets could be achieved in 99.7 \% of 10 000 simulated sessions with randomly assigned targets.
Applying optimization in the current material (205 dialysis sessions)

All schedules in tables 5 - 8 fulfill the stdEKR, stdK/V, TAC and PAC targets described in Table 2 of the main article.

Table 5. Frequency distribution of sessions with different treatment times

<table>
<thead>
<tr>
<th>fr (/wk)</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1</td>
<td>2</td>
<td>12</td>
<td>30</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>29</td>
<td>139</td>
<td>180</td>
<td>171</td>
<td>152</td>
</tr>
<tr>
<td>3.5</td>
<td>3</td>
<td>65</td>
<td>42</td>
<td>10</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>60</td>
<td>17</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>77</td>
<td>43</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>74</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>31</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sum</td>
<td>197</td>
<td>205</td>
<td>205</td>
<td>205</td>
<td>205</td>
<td>205</td>
</tr>
</tbody>
</table>

The resulting prescription depends on both the minimum and maximum treatment time limits. In tables 5 and 6 the treatment times are exactly as stated, the lower and upper limits being equal (in contrast to the main article, where td is between 4 and 5 hours). Eight sessions could not be converted to any two hour schedule. All could be converted to 3 - 8 h schedules.

The frequency distribution is sensitive to concentration limits. A 0.1 mmol/L change in urea concentration probably has no significant effect on treatment outcome, but may change the frequency distribution in table 5 – and changing the frequency may affect the outcome.

As the optimization procedure changes the treatment frequency, the number of optimized sessions differs from the original (205 in this material).

Different targets have different prerequisites to time, frequency, Qb and Qd. Because all requirements must be fulfilled, in some cases no one value is exactly at the limit, but is a little bit "better" (higher clearance, lower concentration).

By adjusting frequency and treatment time limits the schedule can be converted f. ex. to a short or long daily or nightly one with equal stdEKR, stdK/V and concentration targets. By keeping the "dose" constant it were possible to examine the independent effect of time and frequency, which may have effect on the "unphysiology" of the treatment. In the FHN studies stdK/V was higher in the high frequency groups than in the conventional schedules. Increasing frequency is the most efficient way to increase the dose.
Converting to a conventional schedule
141 (69 %) sessions could be converted to 3 x 4 h/wk schedule (Table 6), 190 sessions (93 %) to 3 x 4 - 5 h/wk schedule (Table 7).

Table 6. Frequency distribution with 4 h treatment time, minimum frequency 3 /wk

<table>
<thead>
<tr>
<th>fr /wk</th>
<th>Sessions N</th>
<th>Kr mL/min</th>
<th>nPCR g/kg/day</th>
<th>stdEKR /wk</th>
<th>stdK/V /wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>141</td>
<td>1.0</td>
<td>1.07</td>
<td>3.50</td>
<td>2.47</td>
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<tr>
<td>3.5</td>
<td>42</td>
<td>0.5</td>
<td>1.06</td>
<td>3.57</td>
<td>2.55</td>
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<td>4</td>
<td>17</td>
<td>0.1</td>
<td>1.20</td>
<td>3.64</td>
<td>2.67</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>1.6</td>
<td>1.51</td>
<td>4.37</td>
<td>3.28</td>
</tr>
<tr>
<td>sum</td>
<td>205</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 7. Frequency distribution with 4 - 5 h treatment time, minimum frequency 3 /wk

<table>
<thead>
<tr>
<th>fr /wk</th>
<th>Sessions N</th>
<th>Kr mL/min</th>
<th>nPCR g/kg/day</th>
<th>stdEKR /wk</th>
<th>stdK/V /wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>190</td>
<td>0.8</td>
<td>1.06</td>
<td>3.51</td>
<td>2.45</td>
</tr>
<tr>
<td>3.5</td>
<td>12</td>
<td>0.6</td>
<td>1.35</td>
<td>3.91</td>
<td>2.74</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>2.1</td>
<td>1.74</td>
<td>4.87</td>
<td>3.37</td>
</tr>
<tr>
<td>sum</td>
<td>205</td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Converting to a short daily schedule
In all 205 sessions the targets could be achieved in 7 x 2 - 3 h/wk and in 197 (96 %) in 5 - 7 x 1.5 - 2 h/wk (Table 8).

Table 8. Frequency distribution with 5 - 7 x 1.5 - 2 h /wk schedule (short daily)

<table>
<thead>
<tr>
<th>fr /wk</th>
<th>Sessions N</th>
<th>Kr mL/min</th>
<th>nPCR g/kg/day</th>
<th>stdEKR /wk</th>
<th>stdK/V /wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>104</td>
<td>1.23</td>
<td>1.12</td>
<td>3.53</td>
<td>2.80</td>
</tr>
<tr>
<td>6</td>
<td>72</td>
<td>0.39</td>
<td>0.98</td>
<td>3.47</td>
<td>2.80</td>
</tr>
<tr>
<td>7</td>
<td>21</td>
<td>0.51</td>
<td>1.18</td>
<td>3.66</td>
<td>3.01</td>
</tr>
<tr>
<td>sum</td>
<td>197</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Converting to a long daily or nightly schedule
All sessions could be converted to 5 x 8 h /wk schedule fulfilling the defined clearance and concentration targets.

Observe, that a symmetric (equally spaced) schedule has been applied in all simulations!
Examples
A simplified version of the program used in generating the optimized prescriptions can be downloaded from http://www.verkkomunuainen.net/optimize.html. It gives the optimized treatment time and frequency, blood and dialysate flow and dialyzer clearance (for comparing to OCM readings) for a single session. It is intended to be used in demonstrating and testing the optimization principle, not in actual patient care.

Example 1. Clearance (stdEK and stdK/V) is well above HEMO-equivalent targets, but predialysis concentration (PAC) and TAC are high due to high nPCR. Optimization results in increasing treatment frequency to 4/wk. TAC is the critical variable, it’s optimized value is exactly at the limit. Although treatment intensity has been increased, the Kt/V values have decreased due to increased frequency.
Example 2. The patient has encountered problems with blood access after the modeling session and the maximum blood flow is only 200 mL/min. This is compensated by increasing the frequency to 5 /wk.