Prescribing the dose of dialysis
60 years ago…

FIRST CHRONIC HEMODIALYSIS PATIENT

- March 1960:
  - First session of 76 h
  - Next sessions depending on arterial pressure and dyspnea (every 7 to 14 days for 24 to 48h)
Adequate Dialysis: What’s that??

• By the End of 1960s - 2 goals:
  – Eradication of *signs and symptoms of uremia* (blood pressure, albumin, pericarditis, neuropathy, concept of dry weight (1969))
  – Rehabilitation

• 1965 - Square meter / hour hypothesis:
  – Importance of removing *middle molecule* ++ (neuropathy): *Minimum number of hours of dialysis per week* > maintenance of specific levels of blood urea and creatinine

→ **Dialysis Index** = (3.5 x 10^{-3}) \left( T_D K_B + 168 K_K \right) / S

TD = Weekly Dialysis Time  
KB = MM clearance (Mb characteristics and UF)  
KK = Residual renal creatinine clearance  
S = body surface area
Adequate Dialysis: What’s that ??

• By the End of 1960s - 2 goals:
  – Eradication of **signs and symptoms of uremia** (blood pressure, albumin, pericarditis, neuropathy, concept of dry weight (1969))
  – Rehabilitation

• 1965 - Square meter / hour hypothesis:
  – Importance of removing **middle molecule ++** (neuropathy) : **Minimum number of hours of dialysis per week** > maintenance of specific levels of blood urea and creatinine

• 1969: Clinical improvement with **increased frequency** of sessions for a same weekly duration (De Palma, 1969) (4h x 3 ≠ 6h x 2)

• In the 1970s: Shortening sessions

*Babb et al. Trans Am Soc Artif Intern Organs 1971; 17: 81 – 91*
Kt/V$_{\text{UREA}}$ = Yardstick of HD adequacy

- In the late 1970s and early 1980s....
  - Shorter dialysis = measure of dialysis adequacy based on urea kinetics

- 1975: National Cooperative Dialysis Study (NCDS)
  - Randomized controled trial to define quantitative criteria for the adequate dose of dialysis
  - Criterion of dialysis dose: Urea kinetics coupled with monitoring of nutrition (Kt/V)
  - Is there a relationship between residual morbidity and magnitude of dialysis prescribed ??
    ⇒ Comparison of outcomes btw high (16 mmol/L) or low (8 mmol/L) urea levels and short (2.5 – 3.5 h) or long dialysis (4.5 – 5.5 h)

Lowrie EG. Et al. Kidney Int Suppl 13; 1983: S1 –S7
Adequate Dialysis - NCDS

⇒ Correlation between MORBIDITY and Kt/V

Patients with high urea and short dialysis are more hospitalized than patients with high urea and long dialysis … but … \( p = 0.056 \)

Gotch FA, Sargent JA. A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). Kidney Int. 1985;28:526-34
Acceptation of $\text{Kt} / \text{V}_{\text{UREA}}$ as a single mesure of dialysis adequacy

$\Rightarrow$ Justified short Dialysis !!!
Just need blood sampling to measure pre and post concentration of urea

Lowrie EG. et al. Kidney Int Suppl 13; 1983: S1 –S7
1985 - $Kt/V_{\text{UREA}}$ = dependent variable of PCR

$Kt/V_{\text{UREA}} = 1$: Indicator of dialysis adequacy with a thrice weekly dialysis scheme with cellulosic dialysers and adequate nutrition

Gotch FA, Sargent JA. A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). Kidney Int. 1985;28:526-34
Evolution of the $\text{Kt/V}_{\text{UREA}}$ target

USA annual mortality in percent
Weekly hemodialysis time in hours

Time of dialysis by week (h)

1970 to 1988
Mortality / year
10 to 25%!!
From Observational Studies

445 patients - 10 year actuarial survival of 75%
Mean Kt/V\textsubscript{UREA} 1.66 ± 0.44

<table>
<thead>
<tr>
<th>KT/V\textsuperscript{a}</th>
<th># pts</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.60</td>
<td>222</td>
<td>85</td>
<td>71</td>
<td>50</td>
<td>33</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>≥ 1.60</td>
<td>223</td>
<td>91</td>
<td>82</td>
<td>63</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>455</td>
<td>87</td>
<td>75</td>
<td>55</td>
<td>43</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MAP\textsuperscript{b}</th>
<th># pts</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 99 mm Hg</td>
<td>222</td>
<td>93</td>
<td>85</td>
<td>67</td>
<td>53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ 99 mm Hg</td>
<td>223</td>
<td>81</td>
<td>65</td>
<td>43</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>445</td>
<td>87</td>
<td>75</td>
<td>55</td>
<td>43</td>
<td></td>
</tr>
</tbody>
</table>

Significantly **better survival** in high group Kt/V 1.97 vs Kt/V 1.67

Concept of \( eK_t/V_{UREA} \)
Hemo Study

- NIH – Sponsored randomized controlled trial on HD outcomes – 1846 patients
  - **High dose** dialysis: \( \text{spKt/V}_{\text{UREA}} = 1.71 \) / \( \text{eKt/V}_{\text{UREA}} = 1.53 \) (t: 219 min / \( Q_b : 375 \) mL/min) *VS*
  - **Standard dose** dialysis: \( \text{spKt/V}_{\text{UREA}} = 1.32 \) / \( \text{eKt/V}_{\text{UREA}} = 1.16 \) (t = 190 min / \( Q_b : 311 \) mL/min)

- Validation of the concept of \( \text{eKt/V}_{\text{UREA}} \)
- No major benefit from a higher dialysis dose than that recommended by KDOQI

Problems with V (Urea Distribution Volume)

High Dose

<table>
<thead>
<tr>
<th>t (min)</th>
<th>( Q_b ) (mL/min)</th>
<th>Kt (L)</th>
<th>t (min)</th>
<th>( Q_b ) (mL/min)</th>
<th>Kt (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>231</td>
<td>381</td>
<td>200</td>
<td>330</td>
<td>45.5</td>
</tr>
<tr>
<td>Female</td>
<td>210</td>
<td>367</td>
<td>182</td>
<td>295</td>
<td>38.2</td>
</tr>
</tbody>
</table>

Lightest and malnourished patients: Good Kt/V but worst survival

Kopple JD. Et al. Kidney Int 1999; 56: 1136 - 1148
Kt: indicator of Survival

Retrospective Study - 17 141 patients

Kt = Valid outcome-based measure of Dialysis Dose

Dose of Dialysis: the targets

\[ \text{eqKt/V}_{\text{UREA}} > 1.2 \quad (= \text{spKt/V}_{\text{UREA}} > 1.4) \]

AND

Kt > 40 L in women and Kt > 45 L in men

In anuric patients treated by three times per week dialysis

How to achieve these goals?

- Effective clearance $k$ depends on
  - Dialyzer used
  - Blood flow rate
  - Dialysate flow rate

\[
K_0A = \frac{Q_b Q_d}{Q_b - Q_d} \ln \left[ \frac{1 - K_d/Q_b}{1 - K_d/Q_d} \right]
\]
Impact of blood flow rate

67 HD patients

Impact of Dialysate Flow rate on Clearance of Urea

20 haemodialysis patients - $Q_b$ 400 mL/min – $Q_d$ 350, 500 and 800 mL/min

Which Dialyzer?

- **Dialyzer with high KoA (> 600)**
  - Depends on physical properties of dialyzer
  - Importance of a greater area

*Wizemann V. et al. Nephrol Dial Transplant 2001; 16 (Suppl.4); 27 - 30*
Optimization of Surface functionalization

- Improved design of blood flow distributor
- Avoid Dialysate flow channeling: spacing filaments, fiber undulation

- Anticoagulation adaptation of the circuit

Ronco. C. et al. Nature Reviews Nephrology 2018
High flux Dialyzer

645 hemodialysis patients – Survival over 2 years

- Mortality 38% with High Flux Membrane ($K_{uf} > 20 \text{ mL/h/mmHg/m}^2$)

Depends on porosity = Pore Surface / Surface of the Membrane

High Flux Dialyzers and clearance of $\beta_2$m

1846 patients from Hemo Study

Impact of **Backfiltration** on large molecule clearance

- **Inner diameter**
- **Fiber Length**

Ronco. C. et al. Nature Reviews Nephrology 2018
The best is to test dialyzers commercialized by the industry !!!
Optimization of Concentration Gradient of solutes
How to achieve these goals?

- Which length of session?

**DOPPS Study – 22 000 HD in 7 countries**

![Bar chart showing Kt/V values for Japan, US, and Europe with different Tt times (180, 210, 240, 270 min). R² values are 0.14, 0.01, and 0.03 for Japan, US, and Europe respectively, with P < 0.0001.](image)

Longer Treatment Time is associated with lower Mortality

From DOPPS Study (Japan, Europe, Australia and New Zealand, Canada and US)

MORTALITY IN US: 22% Higher than Europe and 40% Higher than Japan

<table>
<thead>
<tr>
<th></th>
<th>GE</th>
<th>UK</th>
<th>SP</th>
<th>FR</th>
<th>IT</th>
<th>US</th>
<th>JP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivered Dose (Kt/V&lt;sub&gt;sp&lt;/sub&gt;)</td>
<td>1.26</td>
<td>1.36</td>
<td>1.31</td>
<td>1.49</td>
<td>1.37</td>
<td>1.43</td>
<td>1.37</td>
</tr>
<tr>
<td>% Kt/V&lt;sub&gt;sp&lt;/sub&gt; &lt; 1.2</td>
<td>45</td>
<td>30</td>
<td>36</td>
<td>17</td>
<td>28</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>Session Duration (mn)</td>
<td>243</td>
<td>226</td>
<td>214</td>
<td>247</td>
<td>218</td>
<td>213</td>
<td>246</td>
</tr>
<tr>
<td>KoA (mL/min)</td>
<td>748</td>
<td>740</td>
<td>876</td>
<td>770</td>
<td>740</td>
<td>860</td>
<td>866</td>
</tr>
<tr>
<td>Prescribed Q&lt;sub&gt;b&lt;/sub&gt; (mL/min)</td>
<td>247</td>
<td>314</td>
<td>324</td>
<td>294</td>
<td>308</td>
<td>401</td>
<td>195</td>
</tr>
</tbody>
</table>

NCDS (p = 0.056)
Longer Treatment Time is associated with lower Mortality

18% of dialysis patients 3 times a week have dialysis durations of less than 4 hours (REIN Register 2016)!!
The « V » : What ?

On-line urea clearance estimation on selected monitors (K and Kt)

3 methods suitable for routine estimation of V

1. Anthropometric Watson formula
   \[ V_{Wat} \]

2. Body composition Monitor (BCM) (FMC) based on bio-impedance
   \[ V_{BCM} \]

3. Indirect Estimation from measured of Kt / \( (Kt/V)_{sp} \) ratio
   \[ V_{Daug} \]

Koubaa A. et al. Nephrol Ther 2010; 6 (6): 532 - 536
The « V » : What ?

15 patients, 25 dialysis sessions
Comparison $V_{\text{Wat}}$, $V_{\text{BCM}}$ et $V_{\text{Daug}}$ to $V_{\text{DDQ}}$ (Gold Standard)

<table>
<thead>
<tr>
<th></th>
<th>$V_{\text{DDQ}}$</th>
<th>$V_{\text{BCM}}$</th>
<th>$V_{\text{Wat}}$</th>
<th>$V_{\text{Daug}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Médiane [extrêmes] (L)</td>
<td>29.2 [20.6-40.6]</td>
<td>28.5 [20.3-41.8]</td>
<td>34.5 [24.5-50.1]</td>
<td>28.9 [20.6-37.3]</td>
</tr>
<tr>
<td>Moyenne ± S.D. (L)</td>
<td>29.9 ± 5.2</td>
<td>29.1 ± 5.6</td>
<td>36.2 ± 7.1</td>
<td>29.5 ± 4.6</td>
</tr>
<tr>
<td>%</td>
<td>42.9 ± 8.2</td>
<td>41.8 ± 8.1</td>
<td>51.1 ± 5.6</td>
<td>42.2 ± 6.8</td>
</tr>
<tr>
<td>$p$</td>
<td>0.02</td>
<td>&lt; 0.001</td>
<td>0.24</td>
<td>0.85</td>
</tr>
<tr>
<td>$r$</td>
<td>0.94</td>
<td>0.75</td>
<td>0.85</td>
<td></td>
</tr>
</tbody>
</table>
Kt / V\textsubscript{UREA}

- Anemia
- Blood pressure
- Nutritional Status
- Phospho-Calcium balance
- Hydro-sodic status
- Hemodynamic Stability

Not alone !!!!
The convective Dose of Dialysis

- **1965 (Seattle Group):** Responsible molecules bigger than urea and creatinine but smaller than molecules in peripheral neuropathy: « *Middle Molecules* »

⇒ How to remove?
- membrane porosity and membrane surface area
- duration of dialysis
- Interest of residual renal function
- Convective therapy (HDF1977 (Leber HW))
HDF_{ol} Purification **targets**

**Diffusive dose**

\[ \text{eq} \frac{Kt}{V_{\text{UREA}}} > 1.2 \]

AND

\[ Kt > 40 \text{ to } 45 \text{ L} \]

**Convective dose**

**Convective Volume (CV)???

\[ = SV \]

(Substitution Volume)

\[ + \]

Ultrafiltration
## What Convective Dose in HDF post dilution?

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Design</th>
<th>n patients</th>
<th>Primary Outcome</th>
<th>Mean CV (Liters)</th>
<th>Results</th>
<th>Results All cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTRAST 2012</td>
<td>HDF ol post vs HD LF</td>
<td>714</td>
<td>All-cause Mortality</td>
<td>20,7</td>
<td>NS</td>
<td>≤ 39% mortality if CV &gt; 21,95 L</td>
</tr>
<tr>
<td>TURKISH 2013</td>
<td>HDF ol post vs HD HF</td>
<td>782</td>
<td>Composite Death from any cause and non fatals CV evts</td>
<td>20,7</td>
<td>NS</td>
<td>≤ 46% mortalité if SV &gt; 17,4 L</td>
</tr>
<tr>
<td>ESHOL 2013</td>
<td>HDF ol post vs HD HF</td>
<td>906</td>
<td>All-cause Mortality</td>
<td>23,7</td>
<td>30% Survey with HDF</td>
<td>40% and 45% mortality if CV &gt; 23 L and 25 L</td>
</tr>
</tbody>
</table>

What Convective Dose in HDF post dilution?

HDF post dilution and mortality (HDF vs HD)
4 large multicenter RCTs: CONTRAST, ESHOL, French Study et Turkish Study

2793 patients – Mean age 64 years – Mean Q_b 337 mL/min – mean follow-up: 2.5 years
BSA adjusted Convection Volume

RR All-cause Mortality
(Ajusted for age, sexe, albumin, créatinin, diabetes, History of CVD)

HDF versus HD
> 14% All-cause Mortality
> 22% All-cause Mortality if CV > 23 L / 1.73m^2

What **Convective Dose** in HDF post dilution?

**VC target per session**

CV > 23,1 L
AND
CV/BSA > 23 L / 1.73 m²

*Peters S. and coll. Nephrol Dial Transplant 2016; 31: 978 - 984*
Determinants of convective Volume

Albumin and protide and:

+ 10 min → CV: + 0.9 L
Determinants of convective Volume

Albumin and protide and:

+ 10 min → CV: + 0.9 L

CV + 53.4 %
What Blood Flow ($Q_b$) in HDFol Post dilution?

<table>
<thead>
<tr>
<th></th>
<th>Mean duration (min)</th>
<th>Mean $Q_b$ (mL/min)</th>
<th>Mean CV (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTRAST</td>
<td>226</td>
<td>300</td>
<td>20,7</td>
</tr>
<tr>
<td>TURKISH</td>
<td>236</td>
<td>310</td>
<td>20,7</td>
</tr>
<tr>
<td>ESHOL</td>
<td>236</td>
<td>387</td>
<td>23,7</td>
</tr>
</tbody>
</table>

CV + 53.4 %
Which Dialyzer in HDF post dilution?

Synthetic, biocompatible,
\( K_{UF} > 40 \text{ mL/h.m}^2.\text{mmHg} \)
High KoA and SC
Which Dialyzer in HDF post dilution?

**PERFORMANCE**

- RR β2m > 80%  
  (CT β2m > 0.6)
- RR Myoglobin > 65%
- CV (SV + UF)  
  >23 L and 23L/ 1.73 m²BSA

**SECURITY**

- Loss of albumin < 5g / session

---

Which Dialyzer in HDF post dilution?

- $Q_b$ 400 mL/min
- $Q_D$ 800 mL/min
- $Q_S$ 108 mL/min (mean SV: 25.9 L)

**Loss of Albumin**

- **≤ 5 gram**
  - FX 1000, Cordiax
  - Pureflux, Elisio
  - VitaPES, TS SL
  - APS 21 U/H, Renak
  - TS 2.1 UL
  - FX 100
  - EVODIAL 2.2
  - BG 2.1

- **> 5 gram**
  - APS 1050
  - REXEED 21
  - FDY 210
  - PHYLTER 22 S

Le Roy et al. Oral communication Société de Néphrologie Toulouse 2009
Which Dialyzer in HDF post dilution?

\[ Q_b \ 400 \text{ mL/min} \quad Q_D \ 800 \text{ mL/min} \quad Q_S \ 108 \text{ mL/min (mean VS: 25,9 L)} \]

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- **> 5 gram**
  - APS 1050
  - REXEED 21
  - FDY 210
  - PHYLTER 22 S

Le Roy et al. Oral communication Société de Néphrologie Toulouse 2009
Generator with **Automated Infusion**

**Ultracontrol Evosys®**

« Pressure Controlled » Mode optimized

**Autosubplus 5008 Fresenius®**
Prescribing the Dose of dialysis

\[ eq \frac{Kt}{V_{\text{UREA}}} > 1.2 \]
AND
\[ Kt > 40 \text{ to } 45 \text{ L} \]

Prescriptions
- \( Q_b \)
- \( Q_d \)
- Membrane
- ….

Evaluation
+++  

Corrective Actions

\[ CV > 23.1 \text{ L} \]
AND
\[ CV/BSA > 23 \text{ L} / 1.73 \text{ m}^2 \]