Dialysis Dose Prescription and Delivery

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Dose in RRT: Key concepts

- Dose definition
- Quantifying dose
- Prescribed *versus* delivered
- Factors influencing clearance
- Practical Considerations
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  - Quantifying dose
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What defines dose?

A measure of the quantity of blood purification achieved by means of extracorporeal techniques.

A **measure** of the **quantity** of a **representative marker solute** which is removed from a patient.
What defines dose?

• Major flaws in the previous concept:
  – The marker solute cannot and does not represent all the solutes that accumulate in AKI.
  – Its kinetics and volume of distribution are also different from those of the solutes of interest.
  – Its removal during RRT is not representative of the removal of other solutes.
### What Defines Dose?

“The representative marker”

<table>
<thead>
<tr>
<th>Biochemical parameters</th>
<th>Clinical Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Small-solute (Urea)</td>
<td>• Fluid balance</td>
</tr>
<tr>
<td>• Correction of electrolyte disturbances</td>
<td>• Cardiovascular stability (↓ vasopressor, MAP, etc.)</td>
</tr>
<tr>
<td>• Adequate clearance of larger middle-molecules (β2-microglobulin)</td>
<td>• Improvement in respiratory function</td>
</tr>
<tr>
<td>• nPCR</td>
<td>• Nutritional needs</td>
</tr>
<tr>
<td>• pH, HCO3, AG, SIG</td>
<td></td>
</tr>
</tbody>
</table>
Dialysis dose in acute kidney injury and chronic dialysis

*Andrew Davenport, Ken Farrington
Centre for Nephrology, University College London Medical School, Royal Free Campus, London NW3 2PF, UK (AD); and Renal Unit, Lister Hospital, Stevenage, Hertfordshire, UK (KF)

Davenport and Farrington Lancet; 2010
618 patients enrolled in a prospective multicenter observational study (PICARD).

Fluid overload was defined as more than a 10% increase in body weight relative to baseline.

\[
(\sum_{\text{daily}} (\text{fluid intake (L)} - \text{total output (L)})/\text{body weight (in kilograms)}) \times 100.
\]

Dialyzed patients, survivors had significantly lower fluid accumulation when dialysis was initiated compared to non-survivors after adjustments for dialysis modality and severity score.

Non-dialyzed patients, survivors had significantly less fluid accumulation after the peak of their serum creatinine.

Bouchard et al. Kidney Int; 2009
Prospective observational study. 297 children from 13 centers across the United States.

Fluid overload from ICU admission to CRRT initiation, defined as a % equal to (fluid in [L] – fluid out [L])/(ICU admit weight [kg]) x 100%.

Patients who developed 20% fluid overload at CRRT initiation had significantly higher mortality. Adjusted mortality OR was 1.03 (95% CI, 1.01-1.05)

Sutherland et al. AJKD; 2010
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Quantifying delivered dose: Efficiency, Intensity, Efficacy

- **Efficiency**: clearance (K); volume of blood cleared of a given solute over a given time.

- **Intensity**: clearance × time (Kt); Kt × frequency (Kt × treatment days per week)

- **Efficacy**: represents effective solute removal
  - Fractional clearance of a given solute
  - Kt/V
Clinical trials evaluating dialysis dose in AKI during the last decade

<table>
<thead>
<tr>
<th>Reference</th>
<th>Dialysis Modality</th>
<th>Assessment of Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ronco et al 2000</td>
<td>Post-dilution CVVH</td>
<td>Ultrafiltration volume (mL/kg/h)</td>
</tr>
<tr>
<td>Schiff et al 2002</td>
<td>IHD</td>
<td>Frequency (3 per wk v.s. daily)</td>
</tr>
<tr>
<td>Bouman et al 2002</td>
<td>CVVH</td>
<td>Ultrafiltration volume (mL/kg/h)</td>
</tr>
<tr>
<td>Saudan et al 2006</td>
<td>CVVH vs. pre-dilution CVVHDF</td>
<td>Ultrafiltration volume (mL/kg/h)</td>
</tr>
<tr>
<td>Tolwani et al 2008</td>
<td>Pre-dilution CVVDHF</td>
<td>Ultrafiltration volume (mL/kg/h)</td>
</tr>
<tr>
<td>Palevsky et al 2008</td>
<td>IHD, SLED &amp; CRRT</td>
<td>Ultrafiltration volume (mL/kg/h) for CRRT and frequency of session &amp; Kt/V for IHD and SLED</td>
</tr>
<tr>
<td>Faulhaber-Walter et al 2009</td>
<td>Extended dialysis</td>
<td>BUN levels</td>
</tr>
<tr>
<td>Vesconet al 2009</td>
<td>IHD, CVVH, CVVHD, CVVHDF, HVHF &amp; couple plasma filtration and adsorption</td>
<td>Frequency of sessions per week for IHD and Ultrafiltration volume (mL/kg/h) for CRRT</td>
</tr>
<tr>
<td>Bellomo et al 2009</td>
<td>Post-dilution CVVHDF</td>
<td>Ultrafiltration volume (mL/kg/h)</td>
</tr>
</tbody>
</table>

Modified from Bouchard et al. AJKD; 2009.
Dose expression characteristics

• Any dose measurement must have the ability to be associated to:
  – Process of solute removal
  – Patient outcomes

• Measurement should also be simple to calculate without sacrificing accuracy

• Ideal measurement for RRT dose should be numerically comparable across all modalities and treatment schedules
Toward the Optimal Dose Metric in Continuous Renal Replacement Therapy.

Rolando Claure-Del Granado, MD; Etienne Macedo MD, PhD; Glenn M. Chertow, MD, MPH; Sharon Soroko; Jonathan Himmelfarb, MD; T. Alp Ikizler, MD; Emil P. Paganini, MD; and Ravindra L. Mehta, MD.

University of California San Diego; University of Sao Paulo, Brazil; Stanford University School of Medicine; Kidney Research Institute, University of Washington; Vanderbilt University Medical Center; Cleveland Clinic Foundation.

Data from 52 critically-ill patients with AKI requiring dialysis.

All patients were treated with pre-dilution CVVHDF and regional citrate anticoagulation. Delivered dose was calculated using blood-side and dialysis-side kinetics.

Filter function was assessed during the entire course of therapy by calculating BUN to dialysis fluid urea nitrogen (FUN) ratios q/12 hours.

EKR and $K_D$ presented a decline in their values that was related to the decrease in filter function assessed by the FUN/BUN ratio.

Claure-Del Granado Int J Artif Organs; In press.
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## Prescribed vs. Delivered

<table>
<thead>
<tr>
<th>Reference</th>
<th>Dialysis Modality</th>
<th>Prescribed</th>
<th>Delivered</th>
<th>% of Delivered Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evanson et al. 1998</td>
<td>IHD</td>
<td>Kt/V 1.25±0.47</td>
<td>Kt/V 1.04±0.49</td>
<td>83.5%</td>
</tr>
<tr>
<td>Evanson et al. 1999</td>
<td>IHD</td>
<td>Kt/V 1.11±0.32</td>
<td>spKt/V 0.9±60.33</td>
<td>86.4 – 75.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>eKt/V 0.8±40.28</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dpKt/V 0.84±0.30</td>
<td></td>
</tr>
<tr>
<td>Venkataraman et al. 2002</td>
<td>CRRT</td>
<td>24.5±6.7 mL/Kg/h</td>
<td>16.6±5.4 mL/Kg/h</td>
<td>68%</td>
</tr>
<tr>
<td>Tolwani et al. 2008</td>
<td>CRRT</td>
<td>Standard 20 mL/Kg/h</td>
<td>17 mL/Kg/h</td>
<td>85% 82%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High 35 mL/Kg/h</td>
<td>29 mL/Kg/h</td>
<td></td>
</tr>
<tr>
<td>Vesconi 2009 et al.</td>
<td>CRRT</td>
<td>34.3 mL/Kg/h</td>
<td>27.1 mL/Kg/h</td>
<td>79%</td>
</tr>
</tbody>
</table>
Survey of 26 questions

7 questions for IHD and SLED that included:
- target dosage of therapy
- whether and how frequently delivered dose was assessed

9 questions for CRRT
- characterized dose mL/h vs. mL/kg/h
- no target dosage or assessment of delivered dose was evaluated

Only 21% of practitioners assessed delivered dialysis dose (IHD).
< 20% of practitioners reported using weight-based dosing of CRRT.

Absence of a consistent standard for prescription and monitoring of RRT during AKI.
Data from 52 critically ill patients, AKI requiring dialysis (Pre-dilution CVVHDF)

Regional citrate anticoagulation.

Filter efficacy was assessed by calculating FUN/BUN ratios q12 hr.

Prescribed urea clearance (K, ml/min)
- Effluent volume rate = Qd (ml/min) + Qr (ml/min) + Qnet (ml/min)

K Estimated = Effluent volume adjusted for effective time of treatment.

K delivered = FUN (mg/dl)/BUN (mg/dl)] x effluent volume rate (ml/min)
## Reasons for Discontinuing CRRT and Filter efficacy

<table>
<thead>
<tr>
<th>Reasons</th>
<th>Number of Filters</th>
<th>Percentage (%)</th>
<th>FUN/BUN Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors affecting treatment time without affecting filter function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D/C for surgical procedures</td>
<td>10</td>
<td>6.3</td>
<td>0.93 (0.92 to 0.99)</td>
</tr>
<tr>
<td>D/C for medical procedures</td>
<td>9</td>
<td>5.7</td>
<td>1.0 (0.95 to 1)</td>
</tr>
<tr>
<td>routine filter changes</td>
<td>16</td>
<td>10.1</td>
<td>0.95 (0.84 to 1.0)</td>
</tr>
<tr>
<td>machine problems</td>
<td>8</td>
<td>5.0</td>
<td>0.97 (0.85 to 1.0)</td>
</tr>
<tr>
<td>transition to IHD</td>
<td>17</td>
<td>10.7</td>
<td>0.96 (0.82 to 0.97)</td>
</tr>
<tr>
<td>venous access clot</td>
<td>6</td>
<td>3.8</td>
<td>0.97 (0.96 to 0.98)</td>
</tr>
<tr>
<td>physician decision</td>
<td>10</td>
<td>6.3</td>
<td>0.98 (0.94 to 1)</td>
</tr>
<tr>
<td>patient or family decision</td>
<td>11</td>
<td>6.9</td>
<td>0.96 (0.94 to 1)</td>
</tr>
<tr>
<td>patient recovery</td>
<td>6</td>
<td>3.8</td>
<td>0.95 (0.92 to 0.99)</td>
</tr>
<tr>
<td>death</td>
<td>3</td>
<td>1.9</td>
<td>0.98 (0.87 to 1.0)</td>
</tr>
<tr>
<td>access change</td>
<td>9</td>
<td>5.7</td>
<td>0.9 (0.87 to 0.95)</td>
</tr>
<tr>
<td>Factors affecting filter function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>filter clotted</td>
<td>41</td>
<td>25.8</td>
<td>0.89 (0.83 to 0.94)</td>
</tr>
<tr>
<td>filter leak</td>
<td>1</td>
<td>0.63</td>
<td>0.745</td>
</tr>
<tr>
<td>low-sieving concentration polarization</td>
<td>12</td>
<td>7.5</td>
<td>0.86 (0.79 to 1.0)</td>
</tr>
</tbody>
</table>

Claure-Del Granado et al. CJASN, 2011
Solute clearance in CRRT: prescribed dose versus actual delivered dose

William D. Lyndon¹, Keith M. Wille² and Ashita J. Tolwani¹
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Factors Influencing RRT Clearances in the ICU

- Patient factors
- Treatment factors
Patient Related Factors

- Generation of uremic toxins ($G$)
- Pool of uremic toxins ($V$)
Patient Related Factors

• Generation of uremic toxins ($G$)
  – Higher in general than for ESRD (nPCR often $> 1.5$ g/kg/day)
  – Variable

• Pool of uremic toxins ($V$)
Patient Related Factors

- Generation of uremic toxins \( (G) \)
- Pool of uremic toxins \( (V) \)
  - \( V \) is higher in AKI compared to ESRD patients, often >0.65L/kg
  - \( V \) does not equate to TBW in AKI as assessed BIA
  - \( V \) is greater than anthropometrically calculated values

Himmelfarb et al. Kidney Int; 2002
Patient Related Factors

- Generation of uremic toxins ($G$)

- Pool of uremic toxins ($V$)
  - Increased from $Na^+/H_2O$ overload combined with loss of lean body mass during ARF and critical illness
  - Increased by a 20% $H_2O$ redistribution from intracellular to extracellular space in critical illness – *cellular dehydration*
  - $V$ is a *virtual* rather than literal anatomical parameter in critical illness

Treatment Related Factors

- Catheter
- Filter
- Time out of therapy
Treatment Related Factors

- Catheter
- Filter
- Time out of therapy
Pre-dilution CVVHDF
Filter 0.9 m\(^2\) AN69
Anticoagulation LMW Heparin
Filter change each 72 hrs. or if clotted

Randomized
-15 patients (46 treatments) PNT catheter
-15 patients (46 treatments) ST catheter

Prescribed and delivered clearance was assessed

No difference in Qb

No difference in recirculation rate

ST catheters less catheter related

Klouche K et al. Am J Kidney Dis, 2007
Treatment Related Factors

- Catheter
- Filter
- Time out of therapy
Assessing and Delivering Dialysis Dose in Acute Kidney Injury

Rolando Claure-Del Granado and Ravindra L. Mehta
Division of Nephrology and Hypertension, Department of Medicine, University of California San Diego, San Diego, California

\[ K = Q_{eff} \times S \]

Small solutes (Urea)
Plasma protein
Clotting

Claure-Del Granado R and Mehta RL. Sem Dialysis; 2011
Effect of type of anticoagulation on filter life and delivered dose

<table>
<thead>
<tr>
<th>Type of anticoagulant</th>
<th>Median (IQR) Filter Life in Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citrate</td>
<td>48 (20.3-75.0)</td>
</tr>
<tr>
<td>Heparin</td>
<td>15.9 (8.5 - 27.0)</td>
</tr>
<tr>
<td>No anticoagulant</td>
<td>17.5 (9.5 to 32)</td>
</tr>
<tr>
<td>( p ) value</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>
Treatment Related Factors

- Catheter
- Filter
- Time out of therapy
The Impact of Down-Time and Filter Efficacy on Delivered Dose of Continuous Renal Replacement Therapy
Dose in CRRT: Practical considerations

- Clearances should be measured as part of routine care delivery as estimated clearances do not equate delivered.

- Optimizing RRT clearances requires constant assessment and adjustment for operational characteristics and treatment factors.

- Delivered Dose is less than Prescribed and consequently prescribed dose should compensate for the anticipated reduction (approximately 15-25%).

- Solute Clearances are not the sole measure of dialysis adequacy. Fluid removal and fluid balance are equally if not more important parameters to be monitored.
## Proposed parameters for Dose Assessment

**TABLE 2. Proposed parameters for delivered dose assessment**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Measurement</th>
<th>Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Solute</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very small waste</td>
<td>K⁺, Na⁺, Phosphate H⁻</td>
<td>Blood levels of K, Na, PO₄</td>
</tr>
<tr>
<td>products</td>
<td></td>
<td>Phosphate clearance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pH, HCO₃ AG, SIDeff,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SIDapp, SIG, Delta gap,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delta ratio.</td>
</tr>
<tr>
<td>Small waste products</td>
<td>Urea</td>
<td>Clearance (ml/minutes)</td>
</tr>
<tr>
<td>Middle-sized</td>
<td>Serum β₂ Microglobulin</td>
<td>β₂ Microglobulin clearance</td>
</tr>
<tr>
<td>molecules</td>
<td>Weight (kg)</td>
<td></td>
</tr>
<tr>
<td>Fluid</td>
<td>Inputs–Outputs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BIA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BNP</td>
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</table>