Hemodialysis Prescription & Adequacy Monitoring

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Objectives

• To review the distribution of urea during and after a dialysis treatment

• To discuss various methods of quantifying urea clearance during hemodialysis

• To provide equations to establish and refine the initial hemodialysis prescription

• To provide examples of maintenance hemodialysis adequacy assessments including nutritional monitoring
Why Is HD Adequacy Measurement Important?

• We are responsible for the dose of dialysis prescribed

• Less than adequate dialysis associated with poor outcomes
  – National Cooperative Dialysis Study (NCDS)
    • Lowrie EG et al, NEJM (1981)

• Your program may be expected to assess adequacy regularly (QI) and reimbursement may be based on your performance
Urea as a marker of small solute clearance

• Most abundant of organic solutes accumulating in renal failure
• Easily measured at a low cost
• Easily removed by the dialyzer
  – 60Da (small), water soluble, & uncharged
• Urea distribution volume = total body water
  – Estimated at 55-60% of body weight
  – Anthropometric equations (Mellits-Cheek)
BUN Levels & HD Adequacy

- **Monday**
- **Wednesday**

- **Pre HD**
- **Post HD**
- **Dialysis**
- **Urea Generation (G)**
Hemodialysis Adequacy: Urea Clearance Measurements

- Urea Reduction Ratio (URR)
- Single pool Kt/V (spKt/V)
  - Formal Urea Kinetic Modeling (UKM)
  - Estimated from Daugirdas II equation
- Equilibrated or double-pool Kt/V (eKt/V)
- Standard Kt/V (stdKt/V)
Hemodialysis Adequacy: Urea Reduction Ratio (URR)

\[(C_0 - C_1)/C_0 \times 100\%
\]

- \(C_0\) = pre-dialysis urea (mg/dL or mmol/L)
- \(C_1\) = post-dialysis urea (mg/dL or mmol/L)

- Extremely simple to use

- Imprecise as URR does not take 2 factors into account:
  - urea clearance corrected for ultrafiltration & volume contraction
  - urea generated during dialysis

- KDOQI guidelines: Target URR of 70% (minimum 65%)
What is Kt/V?
What is Kt/V?

• Fractional urea clearance for single HD session
  \[ K \text{ (dialyzer urea clearance) } \times t \text{ (time)} \]
  \[ V \text{ (urea volume of distribution)} \]

• Kt/V has no units
  \[ K \times t = \text{L/hr x hr} = \text{L} \]
  \[ V = \text{L} \]
  \[ \frac{(K \times t)}{V} = \text{L/L} = \text{dimensionless ratio} \]

• What does a Kt/V of 1.0 mean?
  – Implies K \times t, or the total volume of blood cleared of urea during the HD session, is equal to V
$Kt/V \sim -\ln \left( 1 - URR \right)$

$Kt/V \sim -\ln \left( \frac{C_1}{C_0} \right)$

$C_1 =$ post HD urea

$C_0 =$ pre HD urea
Urea Distribution: What does single pool mean?

- Assumes urea is distributed evenly across patient total body water.
- Urea removed at equivalent rates from all compartments of patient total body water:
  - Intracellular fluid
  - Extracellular fluid
    - Interstitial space
    - Intravascular space

Figure 1
Urea Kinetic Modelling (UKM) Fundamentals

- UKM uses advanced computational software to solve for two factors using equation with pre and post urea, dialysis time, interdialytic interval, dialyzer clearance ($K_d$), & residual function ($K_r$)
  - $V =$ end-dialysis urea distribution volume
  - $G =$ interdialytic urea generation rate

- spKt/V is calculated from $K_d$ (dialyzer urea clearance), $t$ (time of dialysis in minutes) and “modeled” $V$
UKM Fundamentals

• A computational algorithm solves for V and G by “reiteration” over several HD sessions using pre & post BUN
  — Both values are initially unknown

• V initially estimated with a formula based on height and post-dialysis weight
  — G is then calculated with the UKM equation
  — V is then calculated using the new G value

• Practically not used by most centers for monthly adequacy
Natural Logarithmic spKt/V Estimation
Daugirdas II formula

• The natural logarithm formula of Daugirdas:
  – has been validated\(^1\) in children
  – has gained acceptance\(^1,2,3\) as an accurate estimation of single-pool Kt/V in adults and children
  – is accurate by accounting for intradialytic urea generation and ultrafiltration
  – gives no information regarding nPCR

3. CMS-TEP, NQF
spKt/V: Daugirdas’ Approximation Formula

\[ Kt/V = -\ln \left( \frac{C1}{C0} - 0.008t \right) + (4 - 3.5 \times \frac{C1}{C0}) \times \frac{UF}{W} \]

- **C0** = pre dialysis BUN (mmol/L or mg/dL)
- **C1** = post dialysis BUN (mmol/L or mg/dL)
- **t** = time on dialysis (hours)
- **UF** = ultrafiltration volume (liters)
- **W** = post dialysis weight (kg)

**KDOQI Target:** spKt/V 1.4 per HD session for pts treated thrice weekly, with a minimum delivered spKt/V of 1.2

Natural Logarithmic Estimates of Kt/V in the Pediatric Hemodialysis Population

Stuart L. Goldstein, MD, Jonathan M. Sorof, MD, and Eileen D. Brewer, MD

American Journal of Kidney Diseases, Vol 33, No 3 (March), 1999: pp 518-522
Double Pool Kinetics & eKt/V

eKt/V generally 0.2 units less than spKt/V

Figure 4: Diagram of fluid compartments (ICF and ECF).

Figure 3: Graph showing Urea Rebound over time.

Hemo Int Depner 2005: spKt/V predicted urea concentration (-) and measured urea concentration (.) during and after dialysis.
Urea rebound mostly related to the efficiency or rate of dialysis (K/V ratio)

% urea rebound (pediatrics)
Mammen\(^1\) et al 2011 (22.5 +/- 10.7%, n=30)
Goldstein\(^2\) et al 2000 (25 +/- 7.5%, n=16)
Marsenic\(^3\) et al 1999 (18 +/- 8%, n=15)

1. NDT 2010 2010;25:3044-3050
Equilibrated Kt/V Estimation Methods

- Rate equation (Daugirdas)\(^1\)
  - \(eqKt/V = spKt/V(1-0.6/t_{\text{hours}}) + 0.03\) (arterial access)
  - \(eqKt/V = spKt/V(1-0.4/t_{\text{hours}}) + 0.02\) (venous access)
- Mid-Dialysis Method (Smye)\(^2\)
- *Log Extrapolation of 15 min post-HD BUN (Goldstein)\(^3\)*
- Linear regression model (Marsenic)\(^4\)
  - \(Ceq \text{ (mmol/L)} = 1.085 Ct + 0.729\)

---

Utilizing 30 sec & 15 min BUN (Goldstein)

\[ \text{eqBUN} = \text{BUN}_{30\text{sec}} + \frac{\left(\text{BUN}_{15\text{min}} - \text{BUN}_{30\text{sec}}\right)}{0.69} \]
# Equilibrated Kt/V Estimation Methods: Pediatric Study

<table>
<thead>
<tr>
<th>Method</th>
<th>Total % error</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daugirdas</strong> <em>(Rate equation)</em></td>
<td>11.3% to 25.6%¹,²</td>
</tr>
<tr>
<td><strong>Smye</strong> <em>(Mid-Dialysis)</em></td>
<td>46%¹</td>
</tr>
<tr>
<td><strong>Goldstein</strong> <em>(Log extrapolation)</em></td>
<td>8%²</td>
</tr>
<tr>
<td><strong>Marsenic</strong> <em>(Linear Regression)</em></td>
<td>26.5%³</td>
</tr>
</tbody>
</table>

Frequent HD Dose Calculation

• How do we compare HD adequacy from 3x weekly hemodialysis to more frequent hemodialysis (eg: 4x/week)?

• Simple algebra is not accurate
  – More frequent HD = more efficient dialysis
  – To compare, you need to convert to a continuous equivalent of dialyzer clearance

• **Standard Kt/V (stdKt/V) is the answer!**
Standard Kt/V

• **Rationale**: Therapies that achieve the same mean pre-treatment BUN concentrations are equivalent in delivered dose and should produce similar patient outcomes
• Defined as a **weekly** urea clearance
• Can be used to compare any dialysis modality, frequency, and duration
• **KDOQI 2015 update (adults)**: Target stdKt/V of 2.3 with a minimum of 2.1
stdKt/V calculation

\[
\text{stdKt/V} = 168 \times \frac{(1 - \exp[-Kt/V])}{t}/\left[\frac{(1 - \exp[-Kt/V])}{(Kt/V) + 168/(N \times t) - 1}\right],
\]

\(t\) = treatment time in hours

Kt/V in stdKt/V calculation is eKt/V

N = number of treatments/week

• 398 HD sessions representing 30 patients (age 9.2-25 yrs)
  – ROC Curve Analysis using paired spKt/V and stdKt/V values

• **stdKt/V > 2.0** was best (93.5% sensitivity & 96.7 % specificity) to predict spKt/V ≥ 1.2

• **stdKt/V ≥ 2.2** was best (73.4% sensitivity & 96.1 % specificity) to predict spKt/V ≥ 1.4
Urea as a marker of nutrition

• Your chronic HD patient has a low pre-HD “BUN”
  • Patient could be adequately nourished with good clearance or
  Patient could be inadequately nourished

• Urea generation (G) correlates with protein catabolism, which reflects protein intake

• nPCR is the “normalized protein catabolic rate” used to estimate interdialytic protein intake in g/kg/day
  • Calculated by UKM or algebraic methods

Borah MF Kidney Int 1978
Cottini EP J Nutr 1973
Variables needed for nPCR calculation

\[ \text{BUN} \]

\[ \text{Dialysis} \]

\[ (C1, V1) \]

\[ (C2, V2) \]

\[ \text{Wednesday} \]

\[ \text{Friday} \]

\[ C1 = \text{post HD urea} \]

\[ C2 = \text{pre HD urea} \]

\[ V1 = \text{post HD V} \]

\[ V2 = \text{pre HD V} \]

\[ t = \text{time between HD in min} \]
nPCR Estimation for Children

• Urea generation rate (estG, mg/min) calculated from the BUN rise between HD treatments

\[
estG = \frac{[(C2 \times V2) - (C1\times V1)]}{t}
\]

• \(nPCR_{est}\) (grams/kg/day) calculated using the modified Borah equation:

\[
nPCR_{est} = 5.42 \times \frac{estG}{V1} + 0.17
\]

Concerns of nPCR estimation in children

• Varying sizes, growth rates, and metabolic needs
  – No known nPCR targets in pediatrics
  – Trending is more IMPT than absolute values
• An absolute steady state is needed
  – Cannot be in anabolic (underestimates nPCR) or catabolic (overestimates nPCR) state
• Effect of other sources of nitrogen loss
  – Residual urine output
Table 1. Nutrition and hemodialysis adequacy parameters before and during intradialytic parenteral nutrition (IDPN) (BMI body mass index, nPCR normalized protein catabolic rate)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre IDPN</th>
<th>IDPN</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Weight change</td>
<td>-0.6±2.70</td>
<td>1.8±2.1</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>% BMI change</td>
<td>-1.3±2.7</td>
<td>1.3±2.1</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>nPCR (g/kg per day)</td>
<td>1.05±0.36</td>
<td>1.35±0.37</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>3.7±0.8</td>
<td>3.8±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>spKt/V</td>
<td>1.49±0.29</td>
<td>1.43±0.18</td>
<td>NS</td>
</tr>
</tbody>
</table>

\textsuperscript{a} All values mean monthly±SD
Weight loss: 2% monthly weight loss for 3 consecutive months
Clinical Case:
Initial Hemodialysis Prescription:

• Aim to prescribe a dose of dialysis for desired quantity of urea removal.

• Urea removal occurs by 1st order (logarithmic) kinetics.

• Initial patient $V_d$ of urea (total body water) is unknown.
Initial Hemodialysis Prescription & Refinement: Iterative Process

\[ \text{Kt/V} \sim -\ln \left( \frac{C_1}{C_0} \right) \]

1. Determine desired urea removal (e.g. 50%)
2. Choose appropriate dialyzer and enter K
3. Estimate V (600 ml/kg) using initial pre-weight
4. Obtain pre dialysis [BUN] \( C_0 \), perform dialysis for prescribed t, obtain post dialysis [BUN] \( C_1 \)
5. Calculate V using K, t, and measured \( C_0 \) & \( C_1 \)
6. Repeat steps 1-5 using calculated V
13 year-old female with FSGS to initiate hemodialysis. Desired urea reduction ratio is 50%. Pre BUN 94 mg/dL. A dialyzer with surface area 1.3m² is chosen. ($K_{\text{urea}} = 210 \text{ ml/min} @ Q_b \text{ of } 250 \text{ ml/min}$)

Patient pre-dialysis weight is 42 kg.

Using equation: $Kt/V \sim -\ln (C_1/C_0)$

$210 \text{ ml/min} \times \frac{t}{(42 \text{ kg} \times 600 \text{ ml/kg})} = -\ln(0.5)$

leading to $t = 83$ minutes
Initial Hemodialysis Prescription & Refinement: Example

Hemodialysis performed.
Pre-HD [BUN] C0 = 94 mg/dL
Post -HD [BUN] C1 = 65 mg/dL
Time delivered = 83 minutes, URR 30%

Using equation: $\frac{Kt}{V} = -\ln \left( \frac{C1}{C0} \right)$

$210\text{ml/min} \times 83\text{min/V} = -\ln \left( \frac{65}{94} \right)$

leading to $V = 47.2$ liters
(Previous $V = 25.2$ litres)

Plug in new $V$ and start process again
Clinical Cases: Moving from Initiation to Maintenance

- Initiation equation does not account for ultrafiltration—more precise equations like spKt/V or stdKt/V needed
- Target weight usually determined within one month after hemodialysis initiation
- Vascular access often changes
- Hemodialysis adequacy should be measured monthly including nPCR
Maintenance HD Scenario #1: Real Weight Gain

- Patient with increasing weight, adequate nutrition (nPCR) and decreasing spKt/V
- Recommend increase of dialyzer size or time of treatment

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>SpKt/V</th>
<th>nPCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>34.3</td>
<td>1.40</td>
<td>1.20</td>
</tr>
<tr>
<td>35.2</td>
<td>1.32</td>
<td>1.15</td>
</tr>
<tr>
<td>36.1</td>
<td>1.21</td>
<td>1.18</td>
</tr>
</tbody>
</table>
Maintenance HD Scenario #2
Fluid Weight Gain

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>SpKt/V</th>
<th>nPCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>34.3</td>
<td>1.40</td>
<td>1.20</td>
</tr>
<tr>
<td>35.2</td>
<td>1.32</td>
<td>0.89</td>
</tr>
<tr>
<td>36.1</td>
<td>1.21</td>
<td>0.65</td>
</tr>
</tbody>
</table>

- Patient with increasing weight, decreasing spKt/V and worsening nPCR
- Check for edema, hypertension, albumin level
- Recommend decreasing target weight, addressing nutrition
Maintenance HD Scenario #3
Catabolic State

- Patient with decreasing weight, stable Kt/V and rising nPCR
- Severe malnutrition
- Recommend aggressive nutrition management

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>SpKt/V</th>
<th>nPCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>34.3</td>
<td>1.40</td>
<td>1.20</td>
</tr>
<tr>
<td>32.5</td>
<td>1.32</td>
<td>1.65</td>
</tr>
<tr>
<td>31.6</td>
<td>1.35</td>
<td>1.7</td>
</tr>
</tbody>
</table>
Conclusions

• HD adequacy measurements are an essential component of hemodialysis care delivery
• Understanding hemodialysis & nutrition adequacy can improve patient care
• HD adequacy calculations are not that complex
• Adequacy of dialysis is **not** equivalent to adequacy of patient care
  – Anemia, phosphate, blood pressure, fluid/Na intake, quality of life, growth, sleep, school attendance, etc...........
Thank You

• Email me for Excel spreadsheet calculators

• mammenchenry@gmail.com
Urea Clearance During Hemodialysis: 
Single-Pool Model

G → V → K*C

Urea Generation  Patient Compartment  Urea Removal
Urea kinetics (single pool)

- Constant fractional removal leads to curvilinear decline (solid line).
- When urea is expressed as a logarithm, decline becomes linear (dotted line) with a slope that is equal to \(-\frac{K}{V}\) (efficiency).

*Figure 2: Urea concentration decline during dialysis expressed in standard units (C) and as a logarithm (\(\ln(C)\)).
Urea Mass Transfer During Hemodialysis

Harmon W, Jabs K: Hemodialysis (chap 77) in Pediatric Nephrology, 4th ed
Barratt, Avner, Harmon (ed) Lippincott, 1999
Initial Hemodialysis Prescription: Equation

\[ Kt/V \sim -\ln \left( \frac{C_1}{C_0} \right) \]

- **K** = dialyzer urea clearance (ml/min)
- **t** = treatment time (minutes)
- **V** = estimated total body water (600 ml/kg)
- **C_0** = pre dialysis BUN (mmol/L or mg/dL)
- **C_1** = post dialysis BUN (mmol/L or mg/dL)
Two-point normalized protein catabolic rate overestimates nPCR in pediatric hemodialysis patients

Poyyapakkam R. Srivaths • Scott Sutherland • Steven Alexander • Stuart L. Goldstein

### Table 2 Comparison of BUN and nPCR in pediatric hemodialysis patients

<table>
<thead>
<tr>
<th>BUN normalized</th>
<th>Total patient sample cohort (n=76)</th>
<th>Percent of samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>nPCR &lt; 1</td>
<td>68</td>
<td>89.5%</td>
</tr>
<tr>
<td>nPCR ≥ 1</td>
<td>7</td>
<td>9.2%</td>
</tr>
</tbody>
</table>

### Table 3 Difference between two-point and three-point nPCR results

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Total patient sample cohort (n=76)</th>
<th>Percent of samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two-point model incorrectly categorizes nPCR as &gt;1</td>
<td>7</td>
<td>9.2%</td>
</tr>
<tr>
<td>Two-point model incorrectly categorizes nPCR as ≤1</td>
<td>1</td>
<td>1.3%</td>
</tr>
<tr>
<td>Two-point and three-point nPCR calculations agree</td>
<td>68</td>
<td>89.5%</td>
</tr>
</tbody>
</table>
Normalized Protein Catabolic Rate Versus Serum Albumin as a Nutrition Status Marker in Pediatric Patients Receiving Hemodialysis

Marisa Juarez-Congelosi, RD, LD,* Pamela Orellana, RD, LD,* and Stuart L. Goldstein, MD†

Table 1. Adequacy, Normalized Protein Catabolic Rate, and Serum Albumin by Age Group

<table>
<thead>
<tr>
<th></th>
<th>INF</th>
<th>CH</th>
<th>AD</th>
<th>All</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>nPCR</td>
<td>1.63 ± 0.73</td>
<td>1.29 ± 0.33</td>
<td>1.13 ± 0.28</td>
<td>1.20 ± 0.34</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>sAlb</td>
<td>4.4 ± 0.4</td>
<td>4.1 ± 0.5</td>
<td>4.2 ± 0.4</td>
<td>4.2 ± 0.5</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>spKt/V</td>
<td>1.94 ± 0.42</td>
<td>1.53 ± 0.22</td>
<td>1.43 ± 0.15</td>
<td>1.48 ± 0.21</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>eqKt/V</td>
<td>1.74 ± 0.38</td>
<td>1.33 ± 0.33</td>
<td>1.24 ± 0.17</td>
<td>1.27 ± 0.19</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

nPCR, normalized protein catabolic rate; sAlb, serum albumin; spKt/V, single-pool Kt/V; eqKt/V, estimated equilibrated Kt/V; INF, infant; CH, child; AD, adolescent.

*Analysis of variance comparing mean values (± standard deviation) across age strata.
National Cooperative Dialysis Study (NCDS)

- NIH-sponsored multicenter study (1981) of outcomes related to randomized HD doses
- 4 different 3x/week prescriptions in 151 pts based on time averaged BUN & time
  - $TAC_{\text{urea}}$ 31.5 mmol & 17.5 mmol/L in both groups
  - Duration 4.5 hrs & 3.25 hrs
- Protein intake not randomized but meant to be 0.8-1.4 g/kg/day
- High BUN groups were hospitalized and withdrawn from study at much higher rates

BUN Levels & Nutrition Adequacy

- Dialysis
- Protein intake (nPCR)

Pre HD
Post HD
NCDS (1985)

- Reanalysis by Gotch & Sargent (1985) separated out variables according to spKt/V
- Poor outcomes more often seen in those with spKt/V <1.0
HEMO Study (2002)

- 1846 adult pts randomized to high or low flux HD and standard or high dose 3x/week HD
- Dose targets: eKt/V calculated from spKt/V
  - Standard dose: 1.05
  - High dose: 1.45
- Achieved mean eKt/V in both groups:
  - 1.16 (standard) & 1.53 (high dose)
  - No difference in morbidity & mortality from any cause
HEMO Study (2002)

• Provides strong evidence that the minimum 3x/week HD dose suggested by KDOQI is also the optimal dose
• No benefit in increasing dose further
• Providers have reached a limit with 3x/week HD
  – Higher std Kt/V achieved with more frequent HD
• No randomized studies in children!!!!

Eknoyan G N Eng J Med 2002
Relationship of spKt/V & eKt/V

Figure 6

Sem Dia Depner 2001: Relationship of eKt/V to fixed spKt/V varying time.