THE HEMODIALYSIS PRESCRIPTION: TREATMENT ADEQUACY

GERALD SCHULMAN MD
VANDERBILT UNIVERSITY MEDICAL SCHOOL
NASHVILLE, TENNESSEE
THE DIALYSIS CYCLE


### TABLE 7  CONTROL ACHIEVED ACCORDING TO STUDY GROUP

<table>
<thead>
<tr>
<th>Group and Factor Analyzed</th>
<th>Duration of Dialysis (Hr:Min)</th>
<th>Midweek Predialysis BUN (mg/dl) Mean ± S.E.M.</th>
<th>Time-Averaged BUN (mg/dl) Mean ± S.E.M.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>4:29 ± 0:03</td>
<td>71.2 ± 1.4</td>
<td>51.3 ± 1.1</td>
</tr>
<tr>
<td>II</td>
<td>4:31 ± 0:03</td>
<td>104.9 ± 1.7</td>
<td>87.7 ± 1.4</td>
</tr>
<tr>
<td>III</td>
<td>3:19 ± 0:03</td>
<td>73.1 ± 1.4</td>
<td>54.1 ± 1.1</td>
</tr>
<tr>
<td>IV</td>
<td>3:14 ± 0:03</td>
<td>109.1 ± 1.5</td>
<td>89.6 ± 1.2</td>
</tr>
<tr>
<td>TIME*</td>
<td></td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>BUN*</td>
<td></td>
<td>P &gt; 0.1</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Interaction*</td>
<td></td>
<td>P &gt; 0.1</td>
<td>P &gt; 0.1</td>
</tr>
</tbody>
</table>

REVISED NCDS RESULTS EXPRESSED AS Kt/V

MORBIDITY, NOT MORTALITY
COMPARATIVE MORTALITY RATES

Five year RRT survival for U.S. vs. Japan (by age)
IMPLICATION OF US DIALYSIS MORTALITY RATE
Expected Remaining Lifetime: ESRD, Cancer (3 types) & General Population
Age 40 and 59, 1988

- General Pop.
- Prostate Cancer Pop.
- ESRD Pop.
- Colon Cancer Pop.
- Lung Cancer Pop.

Exp. Remaining Lifetime (Years)

- Age 40: N.A. 9.3 4.5 1.3
- Age 59: 20.4 18.0 4.9 4.3 1.1
TASSIN EXPERIENCE

Table 6. Survival in a Dialysis Unit With Kt/V of 1.67

<table>
<thead>
<tr>
<th>Initial Age (yr)</th>
<th>No. of Patients</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5-Year</td>
</tr>
<tr>
<td>&lt;35</td>
<td>112</td>
<td>93%</td>
</tr>
<tr>
<td>35-44</td>
<td>84</td>
<td>92%</td>
</tr>
<tr>
<td>45-54</td>
<td>111</td>
<td>88%</td>
</tr>
<tr>
<td>55-64</td>
<td>98</td>
<td>83%</td>
</tr>
<tr>
<td>&gt;64</td>
<td>40</td>
<td>69%</td>
</tr>
<tr>
<td>All patients</td>
<td>445</td>
<td>87%</td>
</tr>
</tbody>
</table>

Data from Laurent et al. 71
Kt/V AND MORTALITY

<table>
<thead>
<tr>
<th>YEAR</th>
<th>Kt/V + SD</th>
<th>MR</th>
<th>SMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.82 + 0.32</td>
<td>22.8%</td>
<td>1.03</td>
</tr>
<tr>
<td>2</td>
<td>1.96 + 0.28</td>
<td>17.8%</td>
<td>0.70</td>
</tr>
<tr>
<td>3</td>
<td>1.01 + 0.40</td>
<td>15.7%</td>
<td>0.79</td>
</tr>
<tr>
<td>4</td>
<td>1.18 + 0.41</td>
<td>9.1%</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Hakim et al, JASN, May 1994
# Kt/V & Risk of Mortality

<table>
<thead>
<tr>
<th>KT/V</th>
<th>RR no DM</th>
<th>RR DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 &lt; 1.2</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1.2 &lt; 1.4</td>
<td>0.64</td>
<td>0.70</td>
</tr>
<tr>
<td>≥ 1.4</td>
<td>0.67</td>
<td>0.60</td>
</tr>
</tbody>
</table>

n = 1082

691
### Cox Regression Analysis

<table>
<thead>
<tr>
<th>Kt/V</th>
<th>Relative Risk</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nondiabetic</strong>&lt;br&gt;N=1082</td>
<td>↑ 0.1</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>Diabetic</strong>&lt;br&gt;N=691</td>
<td>↑ 0.1</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Adapted from Collins, et al. AJKD 23:272, 1994
Delivered Kt/V and URR for HD Patients*
Prevalent > 1 year, 1991 and 1994

* only for thrice weekly HD
CHANGING TRENDS IN THERAPY

Distribution of Surface Area in Dialyzers Used by Hemodialysis Patients, 1991 and 1994

% of Patients

<table>
<thead>
<tr>
<th>Surface Area</th>
<th>1991</th>
<th>1994</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>1 - 1.19</td>
<td>20%</td>
<td>15%</td>
</tr>
<tr>
<td>1.2 - 1.49</td>
<td>30%</td>
<td>25%</td>
</tr>
<tr>
<td>1.5 +</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>Unknown</td>
<td>10%</td>
<td>10%</td>
</tr>
</tbody>
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CHANGING TRENDS IN THERAPY


Mean Blood Flow Rate (ml/min)

- CMA 1990/91
- DMMS 1993/94

<table>
<thead>
<tr>
<th>Dialzer Membrane</th>
<th>1991</th>
<th>1994</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unmodified Cellulose</td>
<td>295</td>
<td>324</td>
</tr>
<tr>
<td>Modified Cellulose</td>
<td>328</td>
<td>343</td>
</tr>
<tr>
<td>Synthetic</td>
<td>369</td>
<td>373</td>
</tr>
</tbody>
</table>
CHANGING TRENDS IN THERAPY

Mean Treatment Time for Hemodialysis Patients*, 1991 and 1994

- CMA Study (1991): 195.1 minutes
- DMMS - Wave 1 (1994): 194.9 minutes

* Only patients on 3 times/week schedule
Mortality by Delivered Kt/V, 1990-93

Linear RR = 0.93 / Δ 0.1 Kt/V (p = <0.01)

Patients > 1 year
Bicarbonate only
Stratified by region
Adj. for comorbid

USRDS Case Mix Adequacy Study, 1990/91, n = 2,410
MEMBRANE FLUX: A POTENTIAL CONFOUNDING VARIABLE

• CHANGES IN $K_t/V$ WERE IN PART ACCOMPLISHED BY USE OF HFM

• POTENTIAL BENEFITS OF HFM
  – IMPROVED PROTEIN CATABOLIC RATE
  – IMPROVED TG METABOLISM
  – IMPROVED EPO RESPONSE
  – IMPROVED BETA$_2$-MICROGLOBULIN REMOVAL

• HOWEVER, BECAUSE OF LOW $T_D$, THE FULL EFFECT OF HFM IS NOT EVIDENT. REMOVAL OF HIGH MW SUBSTANCES ARE ALSO TIME DEPENDENT.
INFLUENCE OF DOSE AND DIALYZER CHOICE ON NUTRITION

GOAL: HEMO-Kt/V > 1.2
PD-Kt/V > 2.1 (week)

DIALYSIS DOSE

nPCR

Low Kt/v & Cellulosic

High Kt/V, Cellulosic

High Kt/V, Synthetic
# ADEQUACY AND NUTRITIONAL STATUS

<table>
<thead>
<tr>
<th>N</th>
<th>Yearly Average Kt/V</th>
<th>Albumin</th>
<th>Transferrin</th>
<th>PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>&lt; 0.86</td>
<td>3.5 ± 0.3</td>
<td>220 ± 34</td>
<td>0.83 ± 0.19</td>
</tr>
<tr>
<td>16</td>
<td>&gt; 1.21</td>
<td>3.9* ± 0.2</td>
<td>257* ± 64</td>
<td>1.00* ± 0.19</td>
</tr>
</tbody>
</table>

* P < 0.05
ADEQUACY AND ALBUMIN LEVEL
HEMODIALYSIS TIME: THE UNRESOLVED PARAMETER

• $K_D$ IS A MERE TECHNICAL ISSUE
• MINIMUM $T_D$ HAS ITS BASIS ROOTED IN PHYSIOLOGY
• SHORT TIME MAKES HEMODIALYSIS UNFORGIVING:

<table>
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<th>Calculated Kt/V</th>
<th>Delivered Kt/V</th>
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<tbody>
<tr>
<td></td>
<td>1.56 ± 0.28</td>
<td>1.50 ± 0.28</td>
<td>1.37 ± 0.23</td>
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</table>

• EXCEPT FOR TASSIN, NO MODERN STUDIES HAS EXAMINED LONG (>5 HOURS) TIME AND OUTCOME
# THE NCDS POPULATION

## Table 5. NCDS Inclusion/Exclusion

- Age, 18-70 years (mean, 49.0 ± 12.7)
  - (US 1988 mean, 57 years)
  - (US 1988 median, 60 years)
- Average time on dialysis, 4.2 ± 2.3 years
- No diabetes
  - (1988 US acceptance rate, 30%)
- No malignancy
- No significant cardiovascular disease
- No hospitalization for past 6 months
- T_d range, 2.5-5.5 hours during study
  - (mean before participation, 4.3 hours)
- Cooperative
- Compliant
FACTORS RELATED TO DIALYSIS ADEQUACY

- **HEMODIALYSIS RELATED FACTORS**
  - DOSE
    - LOW MW SOLUTES
    - HIGH MW SOLUTES
    - DIALYSIS TIME
  - MEMBRANE
    - FLUX
    - BIOCOMPATIBILITY
    - REUSE

- **PATIENT RELATED FACTORS**
  - NUTRITION
  - ACIDOSIS
  - CA x P
  - BLOOD PRESSURE
  - LIPIDS
  - CARDIOVASCULAR MORBIDITY
  - INFLAMMATION
ALTERNATIVES FOR THE HEMO STUDY

HEMO STUDY

**Choice**

- Dialysis Dose
- Dialysis Time
- Biocompatibility
- Flux
- Nutrition

**Controversy**

- We know the answer
- Does not reflect U.S. practice
- Confounded by reuse techniques
- Definition
- Prohibitive cost

Remember: Limited Funds Dictates 2 x 2 Design
THE HEMODIALYSIS (HEMO) STUDY

AN NIH-NIDDK SPONSORED RANDOMIZED, MULTI-CENTER CLINICAL TRIAL
THE CHOICE: OBJECTIVES OF THE HEMO STUDY

In patients undergoing 3x/week maintenance hemodialysis, to determine whether
higher dose, or
high-flux membrane
affect
mortality (primary outcome), or
morbidity (secondary outcome)
DOUBLE POOL KINETICS
THE RATE EQUATION

Rate equation

eKt/V = spKt/V - 0.6(K/V) + 0.03

(K/V in hours⁻¹)
RELATIONSHIP OF $Kt/V_{SP}$ TO $Kt/V_{DP}$ AND AS A FUNCTION OF REBOUND
RATE EQUATION AS A FUNCTION OF TIME
THE DIALYSIS CYCLE
Standard dose
- eKt/V = 1.05
- spKt/V ≈ 1.25
- URR ≈ 65%

High dose
- eKt/V = 1.45
- spKt/V ≈ 1.65
- URR ≈ 75%
Flux

Low-flux dialyzers: $\beta_2$M clearance < 10 ml/min

High-flux dialyzers: $\beta_2$M clearance > 20 ml/min
Time to Death by Kt/V Group

Adjusted RR for High Kt/V: 0.96 (0.84 - 1.09), p = 0.52
Time to Death by Flux Group

Adjusted RR for High Flux: 0.92 (0.81 - 1.06), p = 0.24
Interactions of Treatments with Baseline Characteristics

Did treatment effects differ between subgroups for seven pre-specified baseline factors?

<table>
<thead>
<tr>
<th>Age</th>
<th>Years of dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Comorbidity</td>
</tr>
<tr>
<td>Race</td>
<td>Albumin</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
</tbody>
</table>
Predictors of Mortality by Cox Regression

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Relative Risk</th>
<th>95% Confidence</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose</td>
<td>0.96</td>
<td>(0.84, 1.09)</td>
<td>0.52</td>
</tr>
<tr>
<td>High flux</td>
<td>0.92</td>
<td>(0.81, 1.06)</td>
<td>0.24</td>
</tr>
<tr>
<td>Age (per 10 yrs increase)</td>
<td>1.44</td>
<td>(1.35, 1.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>0.86</td>
<td>(0.74, 0.99)</td>
<td>0.03</td>
</tr>
<tr>
<td>Race (African American)</td>
<td>0.76</td>
<td>(0.65, 0.89)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.24</td>
<td>(1.06, 1.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Years of dialysis</td>
<td>1.04</td>
<td>(1.02, 1.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline serum albumin (per 0.5 g/dL increment)</td>
<td>0.51</td>
<td>(0.43, 0.62)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Model also includes 2 other sig. variables: ICED, albumin x time
Analysis stratified by clinical center
Effect of High Dose on Primary and Pre-specified Secondary Outcomes

( ) indicate 95% confidence interval
Effect of High Flux on Primary and Pre-specified Secondary Outcomes

( ) indicate 95% confidence interval
Time to Death by Kt/V Group
Females (484 Deaths)

Adjusted RR for High Kt/V: 0.81 (0.67 - 0.97), p = 0.02
Time to Death by Flux Group
Duration of Dialysis > 3.7 Years (298 Deaths)

Adjusted RR for High Flux:
0.68 (0.53 - 0.86), p = 0.001
Effects of High Flux on Primary and Secondary Outcomes

% Risk difference

-40 -30 -20 -10 0 10 20 30

( ) indicate 95% confidence interval

- All-cause mortality
- Cardiac composite
- Infectious composite
- Albumin composite
- Non-access hosp.
- Cardiac death
- Cardiac hosp. or cardiac death
- Infectious death
- Infect. hosp. or infect. death

HEMO Study
HEMO STUDY SUMMARY

1) THE HIGHER DOSE OF HEMODIALYSIS THRICE WEEKLY DID NOT:
   IMPROVE SURVIVAL,
   REDUCE HOSPITALIZATIONS, OR
   MAINTAIN SERUM ALBUMIN

2) USE OF A HIGH FLUX MEMBRANE DID NOT:
   IMPROVE SURVIVAL,
   REDUCE HOSPITALIZATIONS, OR
   MAINTAIN SERUM ALBUMIN
3) HOWEVER, EFFECTS MAY VARY AMONG CERTAIN SUBSETS OF PATIENTS:

A) IN WOMEN, THE HIGHER DOSE OF DIALYSIS MAY BE ASSOCIATED WITH INCREASED SURVIVAL

B) IN PATIENTS WITH > 3.7 YEARS ON DIALYSIS, USE OF A HIGH FLUX MEMBRANE MAY BE ASSOCIATED WITH INCREASED SURVIVAL

C) THE RESULTS ON THESE SUBSETS SHOULD BE INTERPRETED CAUTIOUSLY AND BE FURTHER INVESTIGATED
Relative Risk of Mortality vs. Mean Achieved $eKt/V$

Within Dose Groups

- **Standard Dose**
  - q1: 64.0
  - q2: 65.4
  - q3: 66.1
  - q4: 66.8
  - q5: 69.2

- **High Dose**
  - q1: 71.9
  - q2: 74.5
  - q3: 75.6
  - q4: 76.4
  - q5: 77.7

*Reference Group*

Median URR by quintile

- q1: 64.0
- q2: 65.4
- q3: 66.1
- q4: 66.8
- q5: 69.2
- q1: 71.9
- q2: 74.5
- q3: 75.6
- q4: 76.4
- q5: 77.7
MORTALITY BY ACHIEVED DOSE

DOSE TARGETING SELECTION BIAS

• IN THE SETTING OF INTENSE DOSE TARGETING A STRONG SELECTION BIAS WAS APPARENT, I.E., PATIENTS WITH CONDITIONS PREDISPOSING TO DEATH TENDED ALSO TO HAVE LOWER eKT/V RELATIVE TO THEIR TARGETED DOSE.

• SIMILAR TRENDS WERE FOUND WITHIN BOTH RANDOMIZED DOSE GROUPS.

• THIS COULD NOT BE EXPLAINED ON THE BASIS OF A TRUE DOSE EFFECT.

• THE CAUSE(S) REMAIN(S) SPECULATIVE; ASSOCIATION OF ACCESS DIFFICULTIES WITH LOWER-THAN-TARGET ACHIEVED DOSES ACCOUNTS FOR SOME OF THIS EFFECT.
PATIENT AND TREATMENT EFFECTS ASSOCIATED WITH COMPARATIVELY LOW ACHIEVED EKT/V

• FACTORS ASSOCIATED WITH LOWER ACHIEVED EKT/V AND HIGHER MORTALITY:
  – INCREASE IN KINETIC VOLUME
  – VENOUS CATHETERS
  – ACCESS PROCEDURES
  – HOSPITALIZATIONS
  – DECLINE IN SERUM ALBUMIN
  – REDUCTION IN TREATMENT TIME

• STRONGER IN HIGH DOSE GROUP, BUT OBSERVED IN STANDARD DOSE AS WELL
DOSE TARGETING SELECTION BIAS - IMPLICATIONS FOR OBSERVATIONAL STUDIES

• MAGNITUDE OF DOSE TARGETING BIAS SEEN HERE IS MUCH GREATER THAN EFFECTS OF ACHIEVED EKT/V IN OBSERVATIONAL STUDIES

• WIDER RANGE OF TARGET DOSES, LESS INTENSE DOSE TARGETING, IN OBSERVATIONAL STUDIES

• HYPOTHESIS: BIAS DUE TO DOSE-TARGETING EFFECT MAY MAKE IT DIFFICULT TO ANSWER THE QUESTION, “WHAT IS THE OPTIMAL DIALYSIS DOSE?” BY CROSS-SECTIONAL STUDIES
ARE WE CONFOUNDING DETERMINATION OF ADEQUACY BY THE USE OF Kt/V?

Kt/V
Kt = AMOUNT OF DIALYSIS, A GOOD THING
V = VOLUME~WEIGHT~MUSCLE MASS, A GOOD THING

A GOOD THING/A GOOD THING
UREA VOLUME AND SURVIVAL

OPTIMAL $Kt = 45L$
THEREFORE: $P = 45/L$

$P$ IS THE POINT OF INFLECTION TO 0 SLOPE

RELATIVE RISK OF DEATH
MINEFIELDS AVOIDED BY THE HEMO STUDY

- DESPITE ITS LENGTH, WE AVOIDED BEING ECLIPSED BY CHANGES IN COMMUNITY PRACTICE PATTERNS
  - $T_D$, $Q_B$, $Q_D$ SIMILAR TO USRDS
  - MEMBRANES SIMILAR
  - STANDARD LEVEL Kt/V DELIVERED WAS BETTER OR EQUAL TO COMMUNITY PRACTICE THROUGHOUT THE STUDY. THE COMMUNITY RECOMMENDATIONS EXCEEDED HEMO STANDARD Kt/V FOR ONLY A SHORT TIME

- DOSE AND FLUX GOALS ACHIEVED
- MORTALITY NOT OVERESTIMATED
- ADEQUATELY POWERED
- WHAT WAS PILOTED IS WHAT WAS STUDIED
WHY THE HEMO STUDY WAS NEEDED

- Rapidly growing ESRD population
  - 10%/year growth rate, costing $billions
  - Worsening comorbidity
  - Majority treated by hemodialysis
- US annual gross mortality of 21-23%
- Observational and correlational studies demonstrating improved survival following treatment changes
  - Higher dose as measured by Kt/V or URR
  - Biocompatible membranes
  - Removal of high MW substances (flux)
IMPLICATIONS OF THE HEMO STUDY

What situations require clinical guidelines to be updated?

- Changes in evidence on the existing benefits and harms of interventions
- Changes in outcomes considered important
- Changes in available interventions
- Changes in evidence that current practice is optimal
- Changes in values placed on outcomes
- Changes in resources available for health care

BMJ 2001;323:155-157

ADAPTED FROM MUJ AIS; ADEMEX STUDY
PLACES TO GO NEXT

- Changing a number?
- Changing an approach:
  - Cardiovascular Risk Reduction
  - Control of Co-morbid Conditions
  - Solute Removal: beyond small solutes
  - Volume Control
  - Nutrition
  - Anemia Correction
  - Bone Disease

ADAPTED FROM MUJ AIS; ADEMEX STUDY
LARGE MOLECULE REBOUND
MEMBRANE FLUX: A POTENTIAL CONFOUNDING VARIABLE

• CHANGES IN \( K_t/V \) WERE IN PART ACCOMPLISHED BY USE OF HFM

• POTENTIAL BENEFITS OF HFM
  – IMPROVED PROTEIN CATABOLIC RATE
  – IMPROVED TG METABOLISM
  – IMPROVED EPO RESPONSE
  – IMPROVED BETA\(_2\)-MICROGLOBULIN REMOVAL

• HOWEVER, BECAUSE OF LOW \( T_D \), THE FULL EFFECT OF HFM IS NOT EVIDENT: REMOVAL OF HIGH MW SUBSTANCES ARE ALSO TIME DEPENDENT-
  LONGER TIMES ARE NECESSARY TO SHOW BENEFITS OF HFM
HEMODIALYSIS TIME: THE UNRESOLVED PARAMETER

• $K_D$ IS A MERE TECHNICAL ISSUE
• MINIMUM $T_D$ HAS ITS BASIS ROOTED IN PHYSIOLOGY
• SHORT TIME MAKES HEMODIALYSIS UNFORGIVING:

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• EXCEPT FOR TASSIN, NO MODERN STUDIES HAS EXAMINED LONG (>5 HOURS) TIME AND OUTCOME
POTENTIAL PARAMETERS TO CONSIDER WITH NOCTURNAL AND DAILY HD

IS IT INCREASED TIME OR INCREASED QUANTITY?
FACTORS THAT MAY INFLUENCE MORBIDITY AND SURVIVAL ON HEMODIALYSIS

- MEMBRANES: SYNTHETIC, FLUX
- DIALYSATE: SODIUM, BICARBONATE
- PHOSPHATE, Ca x P, Ca
- EPO
- DIALYSIS KINETICS
- DIALYSIS TIME
- NUTRITION

ALTERNATE DIALYSIS SCHEDULES
ISSUES TO BE CONSIDERED

• DEFINITIONS OF THE MODALITIES
• INDIVIDUAL STUDIES OF EACH OF THE MODALITIES
• DAILY HEMODIALYSIS vs NOCTURNAL HEMODIALYSIS
ALTERNATIVES TO STANDARD HEMODIALYSIS TREATMENTS

• SLOW LONG-DURATION HEMODIALYSIS
  – THRICE WEEKLY; BIOINCOMPATIBLE MEMBRANE; 6-8 HOURS; $Q_B = 200-220 \text{ mL/min}; \textit{Kt/V}>1.8$

• SHORT DURATION DAILY DIALYSIS
  – 5-6 TIMES EACH WEEK; HIGH FLUX BIOCOMPATIBLE MEMBRANE; 1.5-2.5 HOURS; $Q_B>400 \text{ mL/min}; \textit{Kt/V-.2-.8}$

• NOCTURNAL HEMODIALYSIS
  – 5-7 TIMES EACH WEEK; BIOCOMPATIBLE MEMBRANE; 6-8 HOURS; $Q_B=250-300 \text{ mL/min}; \textit{K-0.9-1.2}$
Elevated Serum Phosphorus Increases Mortality Risk


**PP = 0.03  ^PP = 0.0001  (n=6407)**
SERUM PHOSPHORUS DURING DIALYSIS

(DeSoi CA, Umans JG: JASN 4:1214-8, 1993)
NOCTURNAL HD AND PHOSPHATE CONTROL

KI 1998; 53:1399-1404
DIETARY PHOSPHATE INTAKE: CONVENTIONAL vs NOCTURNAL HD

KI 1998; 53:1399-1404
CONVENTIONAL HD vs NOCTURNAL HD: PHOSPHATE CONTROL

• PHOSPHATE LEVELS
  – 2.1 mmol/L (~6 mg/dL) DECREASED TO 1.3 mmol/L (~3.9 mg/dL) WITH THE START OF NOCTURNAL HD

• BY THE 4th MONTH OF NOCTURNAL HD, NONE OF THE PATIENTS WERE USING PHOSPHATE BINDERS

KI 1998; 53:1399-1404
NOCTURNAL vs DAILY SHORT HEMODIALYSIS

• NOCTURNAL HD
  – LONG TREATMENTS
  – PHOSPHATE CONTROL IMPROVED
  – BLOOD PRESSURE CONTROL IMPROVED
  – ALBUMIN IMPROVED
  – HOME THERAPY

• DAILY SHORT HD
  – SHORT TREATMENTS
  – PHOSPHATE CONTROL NOT IMPROVED
  – BLOOD PRESSURE CONTROL IMPROVED
  – ALBUMIN IMPROVED
  – HOME OR IN-CENTER THERAPY
PRINCIPLE BEHIND THE USE OF STANDARD Kt/V

• UREA IS REMOVED IN A MORE EFFICIENT MANNER AT THE SAME WEEKLY KT/V AS YOU INCREASE DIALYSIS FREQUENCY.

• REMOVAL OF LESS DIFFUSIBLE SOLUTES IS EVEN MORE EFFICIENT AT THE SAME WEEKLY KT/V.
STATUS OF DAILY DIALYSIS

- NO PROSPECTIVE STUDIES OF INCIDENT PATIENTS
- PATIENT SELECTION IS NOT RANDOM
- PATIENTS NUMBER IN THE 100’S
- NO STANDARDIZATION OF REGIMENS
- NO OUTCOME STUDIES
- NOCTURNAL vs DAILY
- ACCESS FUNCTION NOT COMPROMISED
THE DIALYSIS CYCLE

- Influence of Dialysis
- Influence of Diet/Nutritional Status
- UREA GENERATION

Pre$_1$ BUN

KT

Pre$_2$ BUN

Area Under Curve

TAC

TIME
As you increase the frequency, on the x axis here, and maintain the same time average BUN, the need for dialysis diminishes, the dose of dialysis expressed on a weekly basis is less.
RATIONALE FOR USING THE STANDARD Kt/V

- Predicts the currently accepted minimum standard for continuous urea clearance.
- Predicts the approximate level of native kidney urea clearance requiring dialysis intervention.

DEPNER
STANDARD Kt/V

\[
\text{Standard Kt/V} = \frac{\text{continuous removal rate}}{\text{average peak concentration}}
\]

In a steady state, removal is equal to generation (G).

\[
\text{Standard Kt/V} = \frac{G}{\text{average peak concentration}}
\]

For a continuous therapy, peak = mean.
CONTINUOUS VS INTERMITTENT THERAPY
STANDARD WEEKLY Kt/V MODEL

- CAPD
- IHD
- SDHD
- NHHD
## RELATIONSHIP BETWEEN WEEKLY AND STANDARD Kt/V

<table>
<thead>
<tr>
<th>MODALITY</th>
<th>WEEKLY Kt/V</th>
<th>STANDARD Kt/V</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHORT DAILY DIALYSIS</td>
<td>3.5-4.5</td>
<td>2.7-3.2</td>
</tr>
<tr>
<td>NOCTURNAL HEMODIALYSIS</td>
<td>5.0-6.0</td>
<td>3.7-4.2</td>
</tr>
</tbody>
</table>

LEYPOLDT, SEMINAR DIAL, 2004
SUMMARY AND CONCLUSIONS

• MULTIPLE LINES OF EVIDENCE SUGGEST DAILY TREATMENTS IMPROVE:
  – ADEQUACY
  – BLOOD PRESSURE CONTROL
  – HOSPITALIZATION RATE
  – NUTRITION

• TRIALS OF THE MODALITIES ARE REQUIRED

• NOCTURNAL HD NEEDS TO BE INCLUDED IN SUCH TRIALS
FREQUENT HEMODIALYSIS STUDY

• 250-300 ESRD PATIENTS RANDOMIZED
  – 12 MONTHS
• PRIMARY OUTCOMES
  – SF-36 PHYSICAL HEALTH COMPOSITE
  – Δ LEFT VENTRICULAR MASS BY MRI
• SECONDARY OUTCOMES
  – DEPRESSION
  – NUTRITION
  – COGNITIVE FUNCTION
  – HYPERTENSION
  – RENAL OSTEO DysTROPHY
CONVENTIONAL VS SHORT DAILY HEMODIALYSIS

I) CONVENTIONAL HEMODIALYSIS OF 3 SESSIONS PER WEEK. SUBJECTS MAY REMAIN ON THEIR USUAL DIALYSIS PRESCRIPTION SUBJECT TO A MINIMUM EKT/V OF 1.1 PER SESSION AND A MINIMUM TREATMENT TIME OF > 2.5 HOURS PER SESSION;

II) DAILY HEMODIALYSIS OF 6 SESSIONS PER WEEK, TO MAINTAIN A TARGET EKT/(V_N)* OF 0.90 PER SESSION, AND A TREATMENT TIME OF 1.5 HOURS TO 2.75 HOURS

\[ V_N = 3.271V^{2/3} \]
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Conventional HD Regimen</th>
<th>Daily HD Regimen</th>
<th>% Difference in medians; Daily HD vs. Conventional HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sessions per week</td>
<td>3</td>
<td>6</td>
<td>100%</td>
</tr>
<tr>
<td>Target prescription</td>
<td>Unspecified: subject to a minimum eKt/V of 1.10</td>
<td>eKt/(V_n) = 0.90</td>
<td>-</td>
</tr>
<tr>
<td>Hours per session</td>
<td>≥ 2.5 (median = 3.50)</td>
<td>1.50 to 2.75 (median = 2.36)</td>
<td>-33%</td>
</tr>
<tr>
<td>Maximum interdialytic interval during treatment week (median, hours)</td>
<td>68.5</td>
<td>45.6</td>
<td>-33%</td>
</tr>
<tr>
<td>Average interdialytic interval during treatment week (median, hours)</td>
<td>52.5</td>
<td>25.6</td>
<td>-51%</td>
</tr>
<tr>
<td>Hours per week (median, 5th – 95th percentile)</td>
<td>10.5 (9.0 – 13.1)</td>
<td>14.2 (11.5 – 16.5)</td>
<td>+35%</td>
</tr>
<tr>
<td>eKt/V urea per treatment (median, 5th – 95th percentile)</td>
<td>1.39 (1.12 – 1.75)</td>
<td>0.92 (0.74 – 1.05)</td>
<td>-34%</td>
</tr>
<tr>
<td>Weekly stdKt/V urea (median, 5th – 95th percentile)</td>
<td>2.46 (2.16 – 2.80)</td>
<td>3.82 (3.32 – 4.17)</td>
<td>+55%</td>
</tr>
<tr>
<td>Weekly eKR β₂-microglobulin (ml/min/35 L) (median, 5th – 95th percentile)</td>
<td>12.8 (10.7 – 15.2)</td>
<td>17.6 (14.6 – 19.8)</td>
<td>+38%</td>
</tr>
<tr>
<td>Standardized phosphorus removal (mg/day) (median, 5th – 95th percentile)</td>
<td>299 (254-374)</td>
<td>415 (338 – 497)</td>
<td>+39%</td>
</tr>
</tbody>
</table>
Achieved eKt/V for different V’s when eKt/(V_n) = 0.90

<table>
<thead>
<tr>
<th>Patient Weight (kg) (assuming weight = V/0.6)</th>
<th>Patient V (L)</th>
<th>eKt/(V_n)</th>
<th>eKt/V</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>25</td>
<td>0.90</td>
<td>1.01</td>
</tr>
<tr>
<td>50</td>
<td>30</td>
<td>0.90</td>
<td>0.95</td>
</tr>
<tr>
<td>58</td>
<td>35</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>67</td>
<td>40</td>
<td>0.90</td>
<td>0.86</td>
</tr>
<tr>
<td>75</td>
<td>45</td>
<td>0.90</td>
<td>0.83</td>
</tr>
<tr>
<td>83</td>
<td>50</td>
<td>0.90</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Relationship of treatment time, eKt/V, and eKt/(V_n) to patient volume (V)*

<table>
<thead>
<tr>
<th>Patient V (L)</th>
<th>Treatment Time (min)</th>
<th>eKt/V</th>
<th>eKt/(V_n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 27.5</td>
<td>189</td>
<td>1.51</td>
<td>1.35</td>
</tr>
<tr>
<td>27.5 – 32.5</td>
<td>202</td>
<td>1.43</td>
<td>1.36</td>
</tr>
<tr>
<td>32.5 – 37.5</td>
<td>212</td>
<td>1.35</td>
<td>1.34</td>
</tr>
<tr>
<td>37.5 – 42.5</td>
<td>224</td>
<td>1.29</td>
<td>1.35</td>
</tr>
<tr>
<td>&gt; 42.5</td>
<td>240</td>
<td>1.21</td>
<td>1.34</td>
</tr>
</tbody>
</table>

*N=3285 from RRI database

\[ V_N = 3.271V^{2/3} \]
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PLACES TO GO NEXT

TIME!!

DAILY/ NOCTURNAL TREATMENT REGIMENS
THE REAL KEY TREATMENT VARIABLE

\[ MD \times t \]

COMORBIDITY

AFTER DR. C RONCO
THE EYE OF GOD
STANDARD Kt/V: A CONTINUOUS CLEARANCE EQUIVALENT