# Hemodialysis Adequacy

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### In centre 3x per week remains the dominant form of haemodialysis











**UK Renal Registry 19th Annual Report** 

- Survival in patients with end-stage renal disease (ESRD) is made possible by removal of uremic solutes by dialysis.
- The amount of dialysis that a patient receives and the amount of uremic toxin removal can impact morbidity and mortality.
- All methods used to measure dialysis dose are based upon urea clearance. Although the best method is not known, the Kt/V is used by most nephrologists

- Two central issues in the management of patients undergoing maintenance hemodialysis include:
  - determining the optimal amount of dialysis that should be prescribed and quantifying the amount of
  - dialysis that is actually delivered to individual patients

# Measure of urea removal

- Urea reduction ratio (UUR)
- Single pool Kt/V (spKt/V)
- Equilibrated Kt/V (eKt/V)
- Weekly standard Kt/V (stdKt/V)

#### **EFFECT OF THE HEMODIALYSIS PRESCRIPTION ON PATIENT MORBIDITY**

#### Report from the National Cooperative Dialysis Study\*

E. G. LOWRIE, M.D., N. M. LAIRD, PH.D., T. F. PARKER, M.D., AND J. A. SARGENT, PH.D.

- Effect of hemodialysis prescription of patients morbidity: Report of NCDS
- 151 patients
- 4 treatment groups
  - Long dialysis
  - Short dialysis
  - High time-average urea concentration
  - Low time-average urea concentration
- Protein intake was not restricted

## Predialysis urea 38 vs 26 mmol. Dialysis 2.5-35h vs 4.5-5 h





. Withdrawal of patients from the high-BUN groups for medical reasons was significantly greater than withdrawal from the low-BUN groups. Hospitalization was also greater in the high-BUN groups, but dialysis treatment time had no significant effects

# **NCDS Conclusion**

 Thus, according to NCDS patient morbidity and treatment failure are related to the dialysis dose

# Kt/V Definition and calculation

- Kt/V is the preferred method for measuring the dialysis dose.
- The correction of total urea removal (Kt) for volume of distribution is important since the rate of urea removal depends on the total body burden of urea;

in a large patient, a given degree of urea loss represents a lower rate of removal of the total body burden of urea (and presumably of other small uremic toxins)

### Kt/VDaugirdas = -In((BUNPost / BUNPre) - (0.008 \* Hours)) + ((4 - (3.5 \* BUNPost / BUNPre)) \* UFVol / WeightPost)



## TABLE

Minimum<sup>*a*</sup> spKt/V Values for Various Frequency Schedules of Dialysis (Achieving an Estimated stdKt/V = 2.1)

Schedule <sup>b</sup>	$K_{\rm r}$ ,2 mL/min per 1.73 m <sup>2</sup>	$K_{\rm r}$ .2 mL/min per 1.73 m <sup>2</sup>
Two times per week	Not recommended	2.0
Three times per week	1.2	0.9
Four times per week	0.8	0.6

sp <i>Kt/V</i>	<i>t</i> (hr)	sp <i>Kt</i> /V per hour	Rebound	e <i>Kt/V</i>
1.2	6	0.2	0.09	1.11
1.2	3	0.4	0.17	1.03
1.2	2	0.6	0.24	0.96

As is evident from the table, eKt/V can be significantly less than spKt/V, especially during short dialysis treatments. Perhaps for this reason, the European Best Practices guidelines set their minimum recommended dialysis Kt/V of 1.2 in terms of eKt/V rather than spKt/V.

#### Once upon a time in dialysis: the last days of Kt/V?

Raymond Vanholder<sup>1</sup>, Griet Glorieux<sup>1</sup> and Sunny Eloot<sup>1</sup>

<sup>1</sup>Nephrology Section, Department of Internal Medicine, Ghent University Hospital, Ghent, Belgium

# Table 1 | Negative aspects of $Kt/V_{urea}$ as an index of dialysis adequacy and outcomes

- In clinical studies Kt/V urea is not often the sole and the most consistent determinant of dialysis outcomes
- Raising Kt/V urea above standard in randomized trials does not improve outcomes
- Proof of the toxic effect of urea is scarce
- Clinical studies supporting the toxicity of urea are almost nonexistent
- Dialysis kinetics of urea are dissimilar to the kinetics of many other uremic retention solutes
- Concentration pattern during dialysis of many solutes can be dissociated from that of urea by applying alternative strategies to standard dialysis

- Urea kinetics overlook partially or entirely the effect on removal of applying large pore dialyzers or convection
- Urea kinetics overlook partially or entirely the effect on removal of extending dialysis
- Urea kinetics do not account for intestinal or metabolic generation of uremic toxins
- Kt/V urea insufficiently takes into account the effect of residual renal function on solute removal
- Kt/V urea incompletely takes into account the effect of dialysis length on solute removal
- Kt/V urea does not reflect technical aspects of dialysis with potential impact on outcomes—e.g., ultrafiltration rates
- Kt/V does not reflect the impact of dialysis on electrolyte balance and volume status
- Vurea as an index of body water may be inaccurate in people with divergent body composition

# Limitation of adequacy

- The ultimate goal of treatment for patients with chronic kidney disease stage 5 is improvement in quality of life, with prolongation of life often an additional goal.
- This requires more than the dialysis treatment itself.
- In recent literature, adequacy of dialysis is sometimes confused with adequacy of other aspects of patient management, with the erroneous assumption that having achieved dialysis adequacy, the goal of dialysis has been accomplished.

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## Kt/V (and especially its modifications) remains a useful measure of hemodialysis dose

# SCALING

- The Kt/V urea adequacy measure scales dialysis dose to total body water, into which urea is dissolved.
- However, glomerular filtration rate in healthy subjects scales better to body surface area than total body water
- The net result of scaling to body surface area is to give a substantially larger dose of dialysis to women, especially when continuous measures of adequacy, such as standard Kt/V, are considered, and also to small patients, and importantly, much larger doses to small children

### Kt/V (and especially its modifications) remains a useful measure of hemodialysis dose

Table 1 | Hypothetical ability of various hemodialysis adequacy metrics to reflect uremic toxins, fluid overload, and high UF rates

Toxin or adverse element	Standard Kt/V <sup>a</sup>	Equivalent Kt/V <sup>a</sup>	Hemodialysis product	Weekly dialysis time	Square- meter-hour	Weekly time× solute-specific clearance	Convective volume (HDF)	Sodium protein, phosphorus, meat in diet
Urea	++	++++	++	+	++	++	+	++
High-rebound dialyzable	++++	+++	++	++	+++	+++	+	0
solute								
β2-M <sup>b</sup>	++	++	++	++	++	++++	++	0
Protein-bound toxins	+	+	+	++	++	++++	++	+++
Phosphorus	++	+	++	+++	+++	++++	+	++++
ECF overload <sup>c</sup>	+++	++	+++	+++	+++	+++	0	++++
UF rate	++	+	++	++++	++	++	0	++++
Avoid long interdialytic interval	0	+	0	0	0	0	0	+++?

Toxin or adverse			
element	Advantages	Disadvantages	Scaling
Urea Kt/V	Easy to measure NCDS data support minimum dose	Urea not toxic Small, easily dialyzable	Kt/V scaling scales to body water that may be suboptimal
StdKt/V	May reflect removal of important class of sequestered uremic toxins; measure gives LOTS of weight to frequency; may have a volume impact as well	Removal of larger molecules may be strictly time related with little benefit of added frequency; does not penalize for long interdialytic intervals	StdKt/V scaling to body water may be suboptimal
HD product	Gives added weight to frequency	Essentially the same as stdKt/V but without accounting for clearance	No scaling to any measure of body size
Weekly time	May reflect salt and water control; ensures that small patients get sufficient dialysis	No clearance term; so removal of some toxins may be suboptimal; may need to be adjusted for sodium intake and residual urine output	No scaling to body size
Square-meter-hour	Salt water control, helps ensure small patients get sufficient dialysis, has a clearance term	Does not reflect benefit of increased frequency	No scaling to body size
Weekly time × solute- specific clearance	Focuses on removal of specific solutes, and can be adapted to protein-bound uremic toxins	Not clear which solutes are key to follow.	No scaling to body size
Substitution fluid volume (HDF)	Some <i>post hoc</i> evidence that volumes > 21 l/treatment result in better outcomes	Evidence from randomized trials that convective volume is important, comes from secondary analyses only; possible confounding (patient selection, circuit temp)	May be scaled to body size, either V or S
Maximum target UFR	Observational evidence and common sense that high UFR is detrimental	No randomized evidence; not clear how best to achieve the target (longer dialysis vs. lower Na intake vs. maintaining residual urine volume)	Unscaled UFR targets may be more robust than UFR/kg or UFR/S
Maximum interdialytic interval	Evidence from 3/week dialysis that 3-day interval is detrimental	May not be a critical factor in patients with substantial residual urine volume	Not applicable

#### Table 2 | Potential advantages and disadvantages of various proposed hemodialysis adequacy metrics

# ALTERNATIVES TO K†/V

Urea reduction ratio

Solute removal index:(SRI)

# **Urea Reduction Ratio**

- The urea reduction ratio (URR) is closely related to Kt/V.
- The URR is the fractional reduction of urea (blood urea nitrogen [BUN]) during a single dialysis.
- It is simple to calculate but less accurate than Kt/V since it assumes that urea volume of distribution
- remains constant during dialysis (ie, no ultrafiltration)

 $URR = (C_0 - C)/C_0$ 

# Limitation of URR

- Urea clearance determined by any method may not represent the behavior of other potentially toxic molecules.
- URR reflects clearance during a single session and does not account for missed treatments or shortened dialysis that may occur during other sessions.
- Errors in timing of post dialysis BUN determination affect URR value.
- URR cannot be used to compare treatments among patients when dialysis frequency is delivered more than three times weekly



Approximate Kt/V

UF/W

# Solute removal index

- Solute removal index:(SRI) is a measure of the total amount of urea removed during dialysis and is determined by multiplying the urea concentration in the dialysate by the volume of spent dialysate.
- Since the SRI does not rely upon changes in the BUN, it is unaffected by the timing of the post dialysis blood sample

- Limitations of the SRI include the following :
  - Few studies have correlated patient outcomes with the SRI.
  - It is impractical to collect the total spent dialysate.
- The calculated hemodialysis dose obtained using SRIs is relatively inaccurate compared with that calculated from equilibrated BUN

# **RESIDUAL KIDNEY FUNCTION**

# Role of Residual Renal Function

Residual renal function in <u>either</u> modality is associated with a lower risk of death. Peritoneal Dialysis

NECOSAD-2 Study (based on renal kt/V)

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JASN (2004); 15: 1061-1070
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Haemodialysis

Shemin et al. (Based on Measured Creatinine Clearance) AJKD (2001) 38: 85-90.

Several surrogate markers also associated with RRF e.g. Phosphate Control / Anaemia CONTRAST Study CJASN (2011)

#### AUXILIARY DISEASES Official Journal of the National Kidney Foundation"

# Residual renal function and mortality risk in hemodialysis patients

#### Douglas Shemin, MD, Andrew G. Bostom, MD, Priscilla Laliberty, RD, Lance D. Dworkin, MD

Renal Division, Rhode Island Hospital; Brown University School of Medicine, Providence; and the Rhode Island Renal Institute, Warwick, Rl.

Abstract Full Text Images References

cardiovascular disease, serum albumin level, and urea reduction rate. In conclusion, the presence of residual renal function, even at a low level, is associated with a lower mortality risk in HD patients. © 2001 by the National Kidney Foundation, Inc.

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minority of patients with end-stage renal disease treated with peritoneal dialysis. This issue generally has not been examined in patients treated with HD. This prospective observational study of all 114 patients at a single community-based freestanding HD center is designed to examine the impact of residual renal function (defined as renal urea clearance and renal creatinine clearance derived from 24-hour urinary volumes) on mortality over a 2-year period. During that period, 50 deaths occurred in 114 patients. The presence of residual renal function was protective against mortality (odds ratio for death, 0.44; 95% confidence interval, 0.24 to 0.81; P = 0.008), even after adjustment for duration of dialysis treatment, age, smoking, presence of diabetes, presence of cardiovascular disease, serum albumin level, and urea reduction rate. In conclusion, the presence of residual renal function, even at a low level, is associated with a lower mortality risk in HD patients. © 2001 by the National Kidney Foundation, Inc.



KDOQI Clinical Practice Guideline Hemodialysis Update

Update of the KDOQI<sup>™</sup> Clinical Practice Guideline for Hemodialysis Adequacy Running head: Hemodialysis Guideline Update

# Questions should be answered

- In patients with end stage kidney disease, does more frequent hemodialysis (> 3 times a week) improve outcomes compared to less frequent hemodialysis ?
- What harms result from more frequent hemodialysis?
- In patients with end stage kidney disease, does extended duration hemodialysis improve outcomes compared to usual length hemodialysis?
- What harms result from extended hemodialysis?

# THE OPTIMAL AMOUNT OF DIALYSIS

# Is a URR of 65 percent or a Kt/V of 1.2 good enough?

## HEMO Study

The New England Journal of Medicine

### EFFECT OF DIALYSIS DOSE AND MEMBRANE FLUX IN MAINTENANCE HEMODIALYSIS

GARABED EKNOYAN, M.D., GERALD J. BECK, PH.D., ALFRED K. CHEUNG, M.D., JOHN T. DAUGIRDAS, M.D., TOM GREENE, PH.D., JOHN W. KUSEK, PH.D., MICHAEL ALLON, M.D., JAMES BAILEY, M.D., JAMES A. DELMEZ, M.D., THOMAS A. DEPNER, M.D., JOHANNA T. DWYER, D.SC., R.D., ANDREW S. LEVEY, M.D., NATHAN W. LEVIN, M.D., EDGAR MILFORD, M.D., DANIEL B. ORNT, M.D., MICHAEL V. ROCCO, M.D., GERALD SCHULMAN, M.D., STEVE J. SCHWAB, M.D., BRENDAN P. TEEHAN, M.D., AND ROBERT TOTO, M.D., FOR THE HEMODIALYSIS (HEMO) STUDY GROUP<sup>#</sup>

## HEMO STUDY

## 1846 pts

- 65 dialysis units associated with 15 centers
- 2 x 2 design
  - Low dose (eKt/V=1.05) vs high dose (eKt/V=1.45)
  - Low vs high flux
  - No treatments > 4.5hrs
- 3/95 10/2000
- Primary outcome-mortality
- Secondary outcomes-hospitalizations due to CVD or infection, albumin

#### JOURNAL & MEDICINE

# Landmark trial : HEMO study

RCT 1846 USA patients; 4 groups 2x2 factorial design
High flux/Low flux and Standard/High dose

- Low flux mean β2M clearance < 10 ml/min</li>
   High flux mean β2M clearance > 20 ml/min
- Standard dose eqKt/V 1.05, spKt/V 1.25, URR 65%
   High dose eqKt/V 1.45, spKt/V 1.65, URR 75%

#### N Engl J Med (Dec)2002;347:2010-9



HEMO study group. N Engl J Med. 2002;347(25):2010-9.



# High-flux vs Low-flux

- The Hemodialysis (HEMO) study
  - not find a difference between low- and high-flux membranes

**Effects of high-flux hemodialysis on clinical outcomes:** Results of the HEMO Study. J Am Soc Nephrol 2003 14:3251-3263.

- MPO study (Membrane Permeability Outcome)
  - High-flux benefits in DM and low serum albumin levels ( < 4 g/dl)</li>
  - No significant survival benefit

Membrane Permeability Outcome (MPO) Study Group Effect of membrane permeability on survival of hemodialysis patients. J Am Soc Nephrol 2009 20:645-654



Both the Hemodialysis (HEMO) study and the Membrane Permeability Outcome (MPO) study compared low-fl ux hemodialysis with high-fl ux hemodialysis. Neither study showed a difference in mortality risk between the treatment arms.

In HEMO, High-flux HD was associated with an 8% nonsignificant reduction of mortality compared with low-flux HD

Secondary analyses in the HEMO and MPO studies suggested a survival benefit of high-flux hemodialysis in patients with a dialysis vintage >3.7 years, patients with diabetes, and if serum albumin < 40 g/L at baseline.

# **Conclusions Of HEMO**

 Dialysis prescription of KT/V Values less than 1.2 may carry a high mortality and morbidity

 Increasing the dose of dialysis of a KT/V more than 1.4 does not carry any significant benefit

 Recommended dose is a KT/V which lies between 1.3 and 1.4 (single pool)

No benefit from the use of high Flux dialyzers

# Minimum dialysis frequency and time

# What is the frequent Dialysis

Until 2015 recently no standard definition



- KDOQI 2015:
  - Frequent ≥ 5 sessions per week
  - Duration: short = <3hrs per session, long >5hrs

(Long usually performed at home overnight)





# Outcomes with frequent dialysis

#### Three RCTs, plus multiple observational reports

CVD



chanaed due to slow recruitment

<sup>1</sup>Chertow NEJM 2010;363:2287-2300 <sup>2</sup>Rocco Kidney Int 2011;80:1080-1091

# FHN Daily Trial (in-center vs in-center)

- 11 US centres
- Prevalent HD patients (70% anuric)
- 12M follow up
- Mean age ~50
- Recruitment rate <10%</li>
- Adherence in intervention arm: 78% of patients attended ≥80% of planned sessions
- Two co-primary endpoints
- Improvements in:

CKR Killer

- QoL (PHC +3.2)
- LV mass (-13.8g)
- BP with fewer meds
- Phosphate control
- Increased access procedures but not access loss
- Lower IDH <u>rate</u> but higher <u>total number</u> of events



Chertow NEJM 2010:363:2287-2300

# FHH daily trial extended follow up

- Mortality analysis extended beyond the initial 12-months
- Status of patients was determined over a median of 3.6 years after randomization
- Mortality was 20 of 125 patients (16%) with frequent HD versus 34 of 120 patients (28%) with conventional HD
- Mortality hazard for frequent versus conventional HD: 0.56 (95% CI 0.32 to 0.99)





## FHN Nocturnal Trial (home vs home)

- Mean age ~53
- Lower LV mass at baseline
- Higher % incident patients (30% anuric)
- Recruitment target 250, actual 87
- Adherence in intervention arm: 72% of pts. had ≥80% of planned sessions

- QoL (PHC) increased in <u>both</u> arms
- Trend towards reduced LV mass (-11g, p=0.09)
- Lower pre dialysis BP
- Lower serum phosphate
- Trend towards more access procedures and greater loss of RRF
- Less IDH
- No significant difference in co-primary endpoints





Rocco Kidney Int 2011;80:1080-1091

## Alberta Trial (home vs in-center)

- 2 Canadian centres
- Prevalent HD patients (mean vintage ~5Y)
- 6M follow up
- Mean age ~54

CKR Kighey

- Improvements in:
  - LV mass (-15.3g); primary outcome
  - BP with fewer meds
  - Phosphate control
- No change in QoL (EQ5D) but were differences in kidney specific domains
- No difference in access procedures or hospital admissions





Cullerton JAMA 2007;298:1291-1299

## Summary of what the evidence tells us

Definite benefits	Lower blood pressure Reduced LV mass Lower serum phosphate Reduction in medications
Likely benefits	Improved Quality of life measures Lower IDWG, reduced ECF Nutrition Intradialytic cardiac injury (stunning)
Possible/uncertain benefit	Mortality Cognitive functioning Depression Anaemia/ESA dose Hospitalisation rates Intra-dialytic hypotension
Reported risks	Increased access events (but not access loss) Burden of care Loss of RRF?

Dialysis procedure	(My) opinion-based recommendation
2/Week hemodialysis	Consider for incident patients with substantial residual kidney function (for example, daily urine volume >600 ml and residual urea clearance >2–3 ml/min per 1.73 m <sup>2</sup> ). Set session length to limit UFR to <800 ml/h. No target solute clearance.
3/Week hemodialysis	Target small solute clearance would be a surface area adjusted standard Kt/V $\ge$ 2.45 (average value in high-dose arm of HEMO study for women and conventional-dose arm in men). Adjust session length to keep UFR < 800 ml/h.
Fourth session (4/week schedule)	Add for patients with baseline LVH, with UFR > 800 ml/h during dialysis session after weekend interval, and/or who have high predialysis serum K before Mon/Tues session.
Every other day schedule	Consider for all home patients as initial therapy.
Short daily schedule	Consider for all home patients with baseline LVH, or problems with controlling fluid or blood pressure.
In-center 3/week nocturnal schedule	Consider for patients who prefer this schedule for lifestyle, and also for patients who have baseline LVH or problems with blood pressure, volume, or phosphorus control.
High-flux hemodialysis	Consider for all patients, especially those with long expected remaining lifespan, to avoid problems with $\beta$ 2-microglobulin amyloid deposition.
Hemodiafiltration	Some data suggest lower cardiovascular risk.
Protein-bound uremic toxins	Consider dietary manipulations (somewhat speculative); low-meat diet, keeping short gastrointestinal transit time. Hemodiafiltration and long weekly dialysis time using a high dialysate flow rate may increase removal but effect on blood levels not established.
Phosphorus	Best controlled by increasing weekly dialysis time; hemodiafiltration lowers plasma levels in some but not all studies.

#### Table 3 Opinion-based adequacy recommendations

# Why does more not lead to better?



## Any disadvantages of more frequent or longer dialysis sessions ?

More frequent and longer dialysis

Disadvantages

# Repeated exposure to dialysis circuit

- inflammatory response
  - ✤ platelets
  - Ieukocytes
- o consequence
  - \* access
    - ✓ thrombosis
    - $\checkmark$  infection
  - immune response



1









Month	spKT/V	Modeled V
May	1.5	43
Jun	1.43	45
Jul	1.7	38
Aug	1.8	36
Sep	1.1	58

# CAUSES OF INADEQUATE DIALYSIS

- Fistula integrity
- Treatment duration
- Method of obtaining blood urea nitrogen (BUN) samples
- Dialysis machine and patient-specific variables
- Inadequate fluid removal

Month	spKT/V	Modeled V
Jul	1.2	54
Aug	1.15	56
Sep	1,35	48
Oct	1,18	55
Nov	1.5	43
Dec	1.43	45
Jan	1.5	43
Feb	1.43	45

- Increase blood flow through a dialyzer
- Increase time on dialysis
- Identify and eliminate the circulatory problems
- Removal of chronic overhydration
- Loss of lean body mass

# What are some factors that can cause a discrepancy between prescribed and delivered dose?

- Actual treatment time is less than prescribed (treatment interruptions, frequent alarms stopping pump, early termination, elective termination)
- Access recirculation (access stenosis, clotting, central stenosis, needle placement)
- Blood flow rate lower than prescribed due to problems with dialysis access.
- Blood pump problems (inaccurate calibration, inadequate occlusion of rollers on tubing, error in setting flow rate)
- Dialyzer clotting (loss of dialyzer surface area)
- Dialysate flow problems (inaccurate calibration, error in setting flow rate)

- Dialysate flow problems (inaccurate calibration, error in setting flow rate)
- Error in draw of pre or post dialysis BUN (saline in line, pre sample drawn after hemodialysis started, needles reversed, fistula recirculation, post sample drawn too early or too late, lab error)
- Overestimation of prescribed dose by use of manufacturer in vitro KoA values: clearance data for dialyzers is based on in vitro data that overestimates in vivo clearance.

