Hemodialysis Prescription & Adequacy Monitoring

Annual Dialysis Conference
March 3rd, 2023

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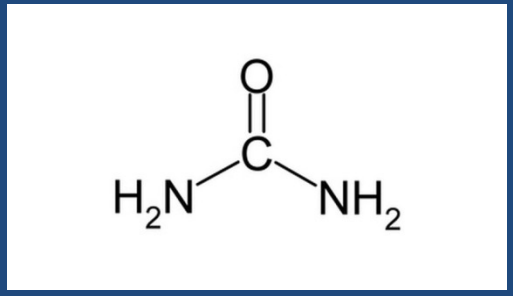
Objectives

- 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/QA) and reimbursement may be based on your performance

Urea as a marker of small solute clearance

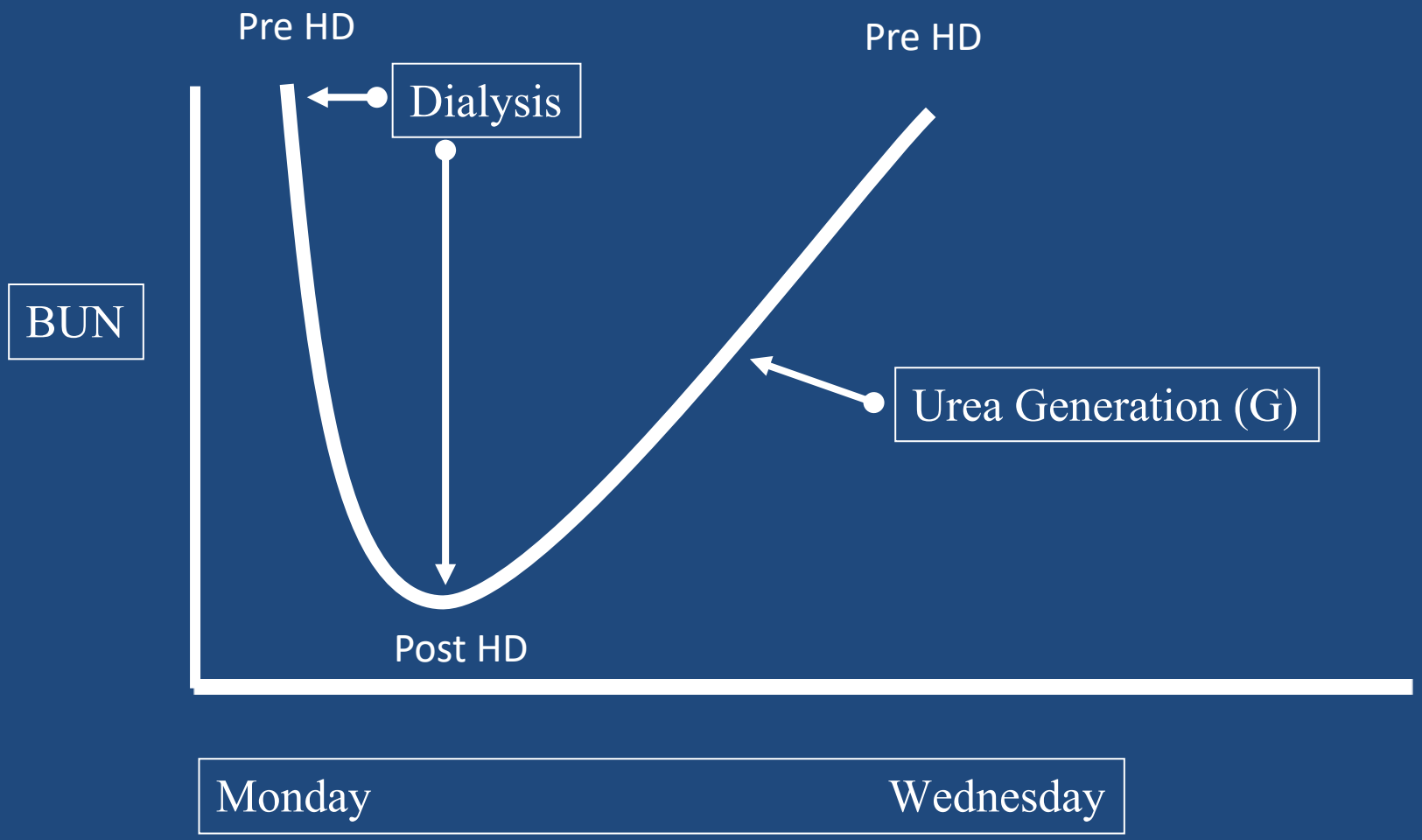


- Most abundant of organic solutes accumulating in renal failure
- Easily measured at a low cost
- Easily removed by the dialyzer
  - 60Da (small), water soluble, & uncharged
- Urea distribution volume = total body water
  - Estimated at 55-60% of body weight
  - Anthropometric equations
    - Mellits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

Mellits ED Monogr Soc Res Child Dev 1970

Morgenstern BZ JASN 2006

BUN Levels & HD Adequacy



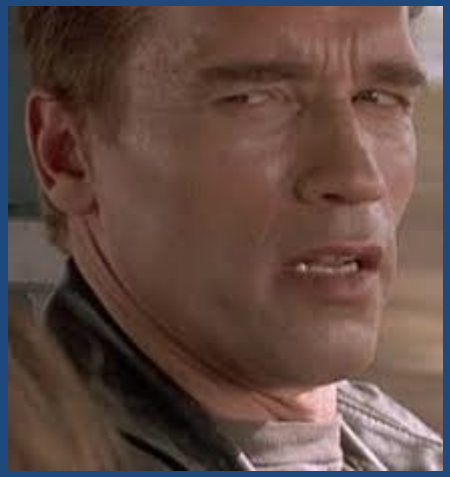
Hemodialysis Adequacy: Urea Clearance Measurements

- **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)

- **$(C_0-C_1)/C_0 * 100\%$**
- C_0 = pre-dialysis BUN (mg/dL) or urea (mmol/L)
  C_1 = post-dialysis BUN (mg/dL or urea (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

$$\frac{\text{K (dialyzer urea clearance) x t (time)}}{\text{V (urea volume of distribution)}}$$

- Kt/V has no units

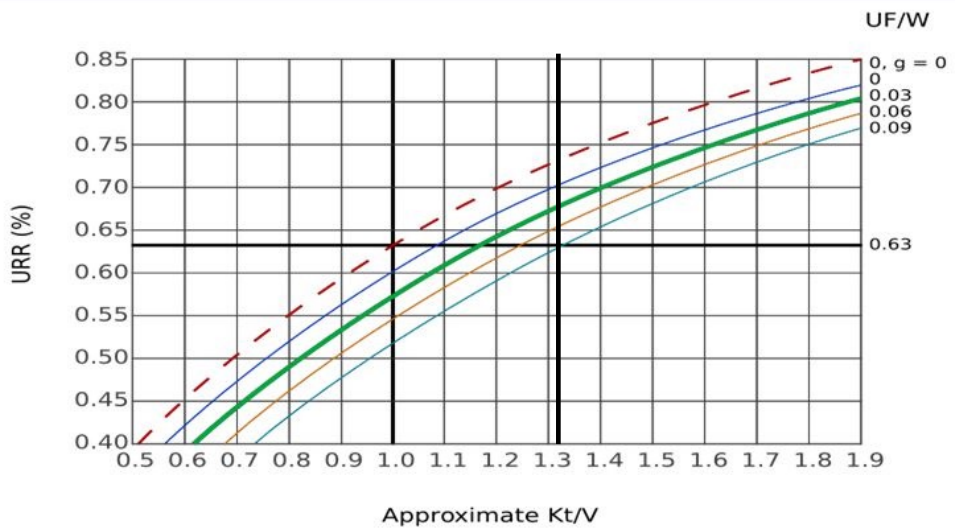
  K x t = L/hr x hr = L

  V = L

  (K x t)/V = L/L = dimensionless ratio

- What does a Kt/V of 1.0 mean?
  - Implies K x t, or the total volume of blood cleared of urea during the HD session, is equal to V

URR & Kt/V



(Reproduced with permission from Daugirdas JT. Urea kinetic modeling.Hypertens Dial Clin Nephrol [HDCN] http://www.hdcn.com)

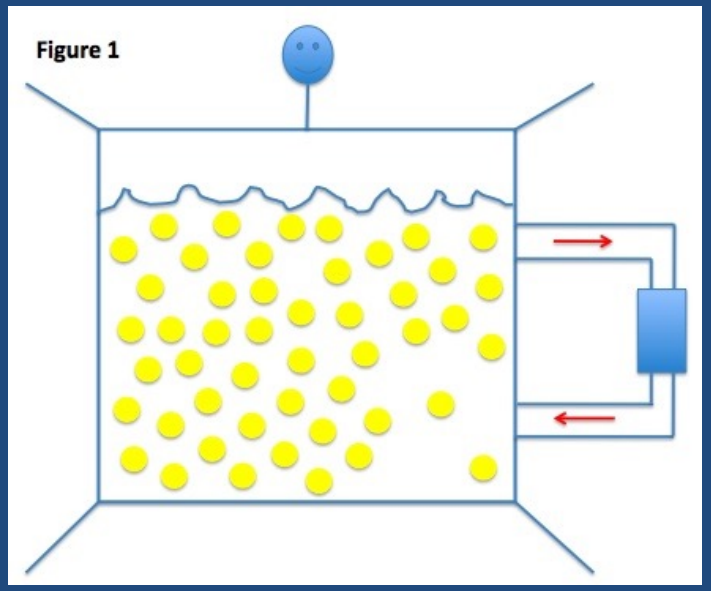
$$Kt/V \sim -\ln (1-URR)$$

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

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



Urea Kinetic Modelling (UKM) Fundamentals

- UKM uses advanced computational software to solve for *two factors* using an 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

1. Goldstein SL, Sorof JM and Brewer ED: *AJKD* 33:518-22, 1999
2. KDOQI HD Adequacy Guidelines. 2000, 2006, 2015 Update
3. CMS-TEP, NQF

spKt/V: Daugirdas' Approximation Formula

$$Kt/V = -\ln(C1/C0 - 0.008*t) + (4 - 3.5*C1/C0)*UF/W$$

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

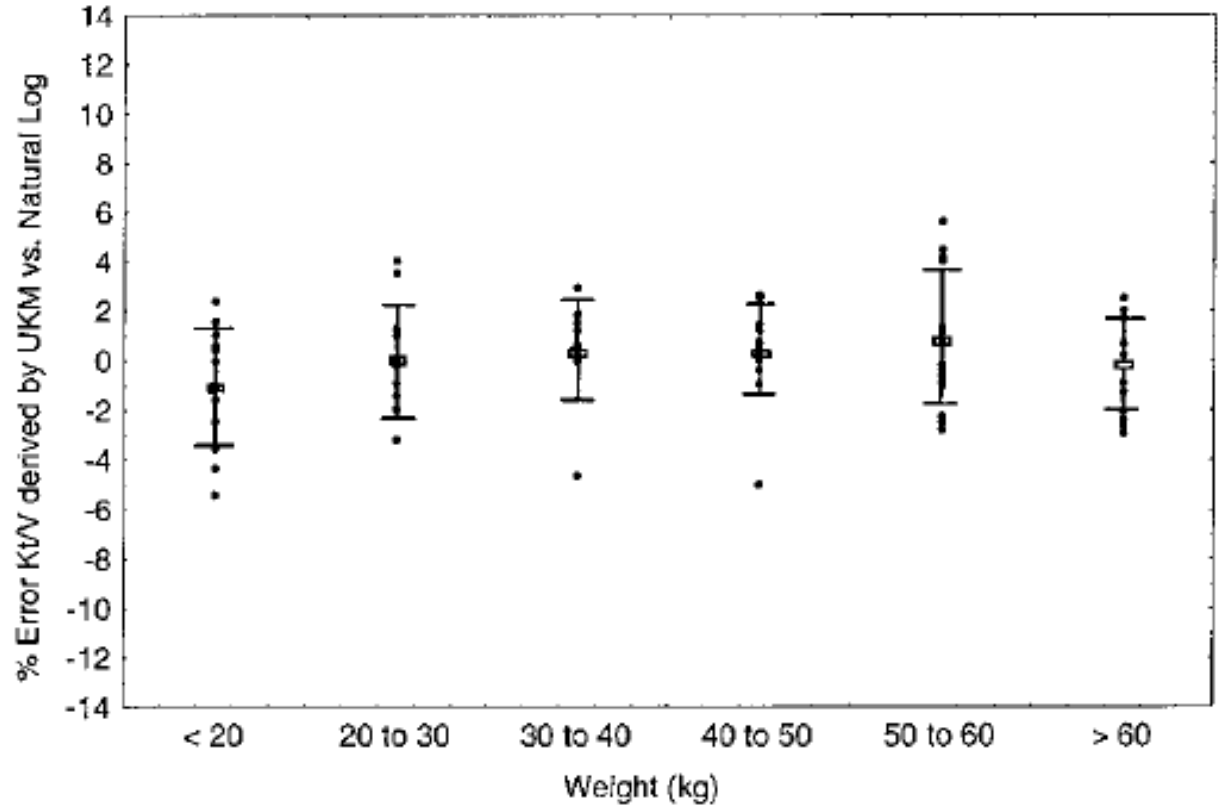
KDOQI Target: spKt/V 1.4 per HD session for pts treated thrice weekly, with a minimum delivered spKt/V of 1.2

Daugirdas JT: J Am Soc Nephrol 4: 1205-1213, 1993

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

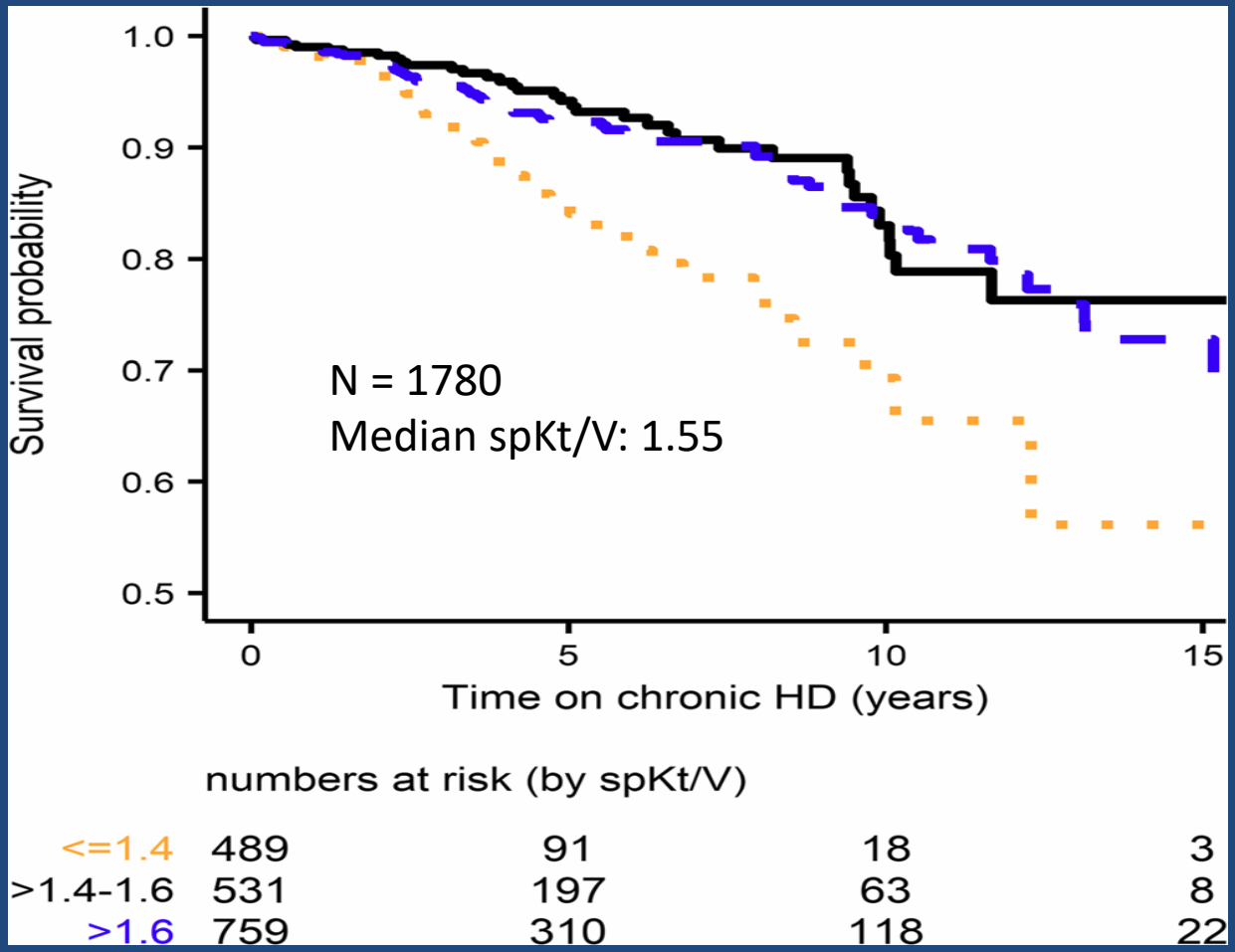
Stuart L. Goldstein, MD, Jonathan M. Sorof, MD, and Eileen D. Brewer, MD

American Journal of Kidney Diseases, Vol 33, No 3 (March), 1999: pp 518-522



spKt/V & Patient Survival

Retrospective cohort of patients <30 yrs on 3x/week HD since childhood (<19 yrs)



Gotta V et al Pediatr Nephrol 2021

spKt/V & Hospitalizations

Table 3. Unadjusted Rates and Rate Ratios of Hospitalization and Days Hospitalized in 613 Adolescent HD Patients

Outcome (/100 patient-y)	Total (N = 613)	spKt/V < 1.2 (n = 116)	spKt/V ≥ 1.2 (n = 497)	Rate Ratio (95% CI)	*P*
Admissions	39	53	36	1.45 (1.00-2.05)	0.04
Days hospitalized	232	400	198	2.02 (1.77-2.31)	<0.0001
Deaths	2.0	4.4	1.5	2.86 (0.75-9.51)	0.08

Table 4. Analyses Examining the Incidence Rate Ratio of Hospital Admission by spKt/V Less Than 1.2 Versus 1.2 or Greater in 613 Adolescent HD Patients

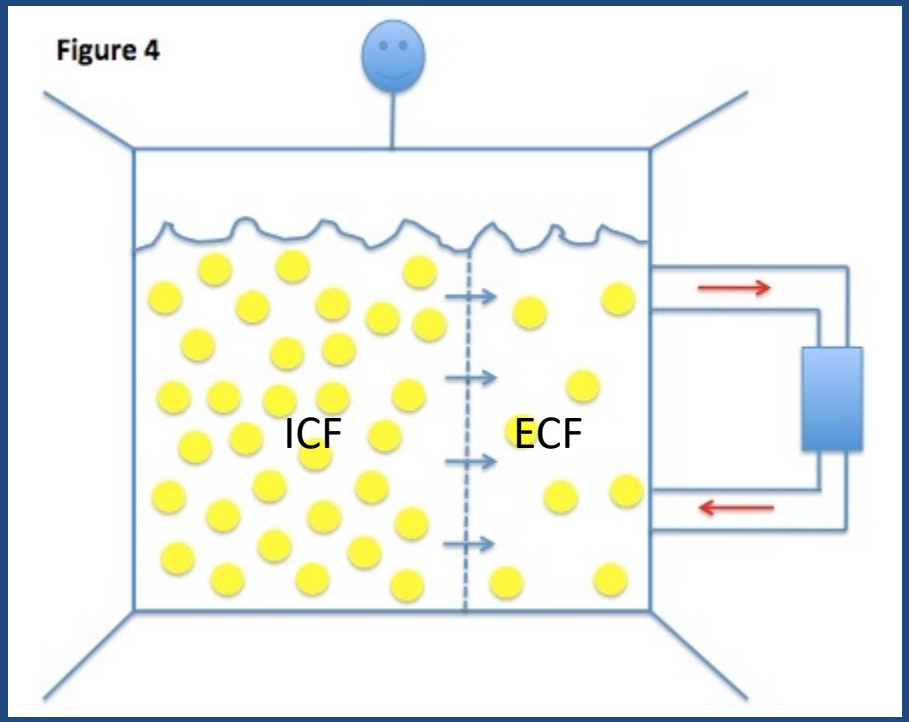
Analysis	Incidence Rate Ratio	95% CI	*P**
Unadjusted (n = 613)	1.45	1.03-2.04	0.04
Model 1 (n = 613)†	1.59	0.98-2.56	0.06
Model 1, weighted for transplantation (n = 613)	1.55	0.96-2.50	0.07
Model 1, excluding outliers (n = 609)	1.67	1.02-2.74	0.04

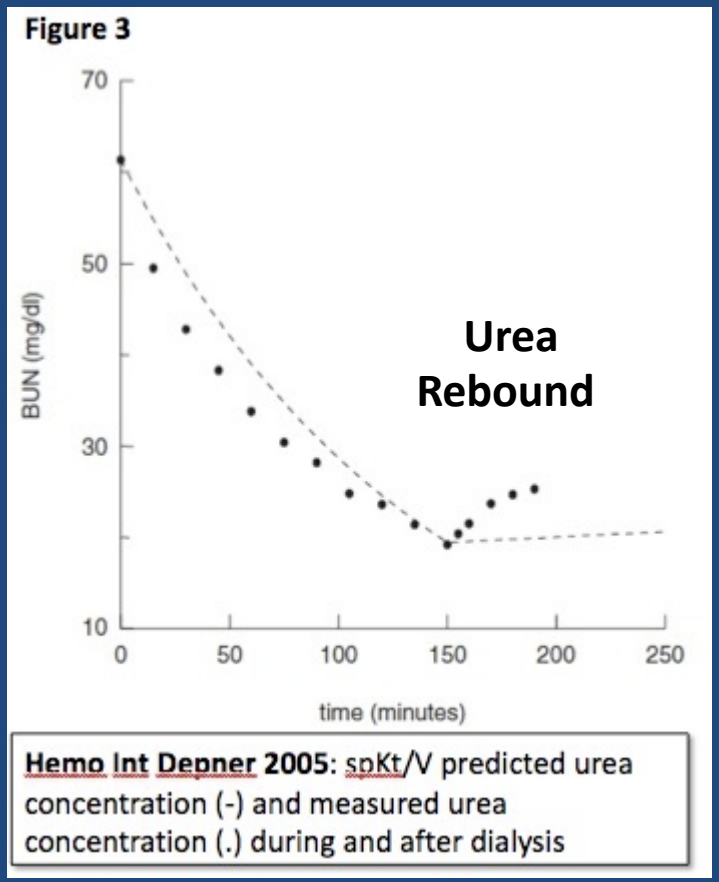
**P* derived by means of Poisson log-linear regression with observations clustered by patient.

†Adjusted for albumin level, hemoglobin level, time since dialysis therapy initiation, short stature (height *z* score < −1.88), and dialysis access.

Gorman G et al Am J Kidney Dis 2006

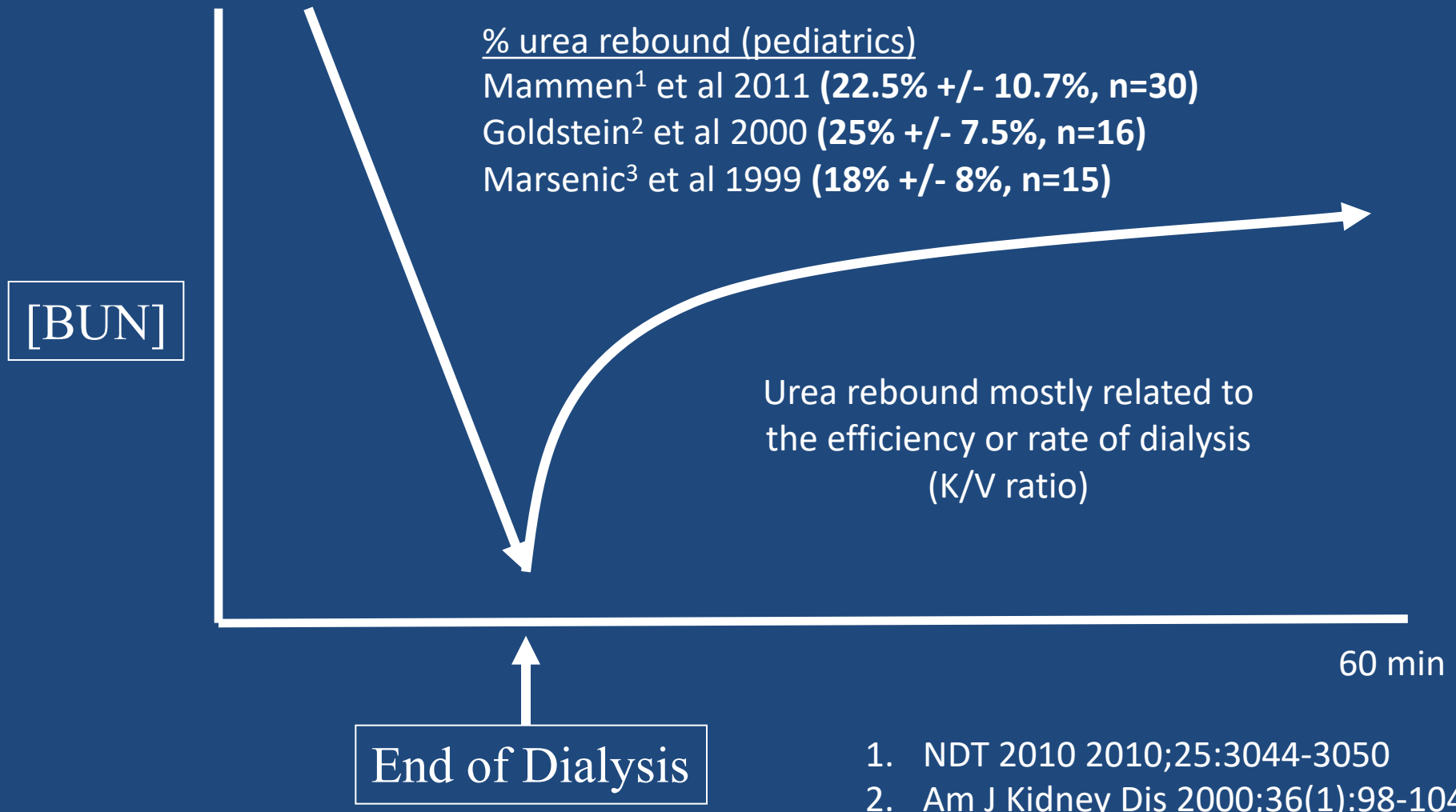
Double Pool Kinetics & eKt/V





eKt/V generally 0.2 units less than spKt/V

Urea Rebound after Hemodialysis



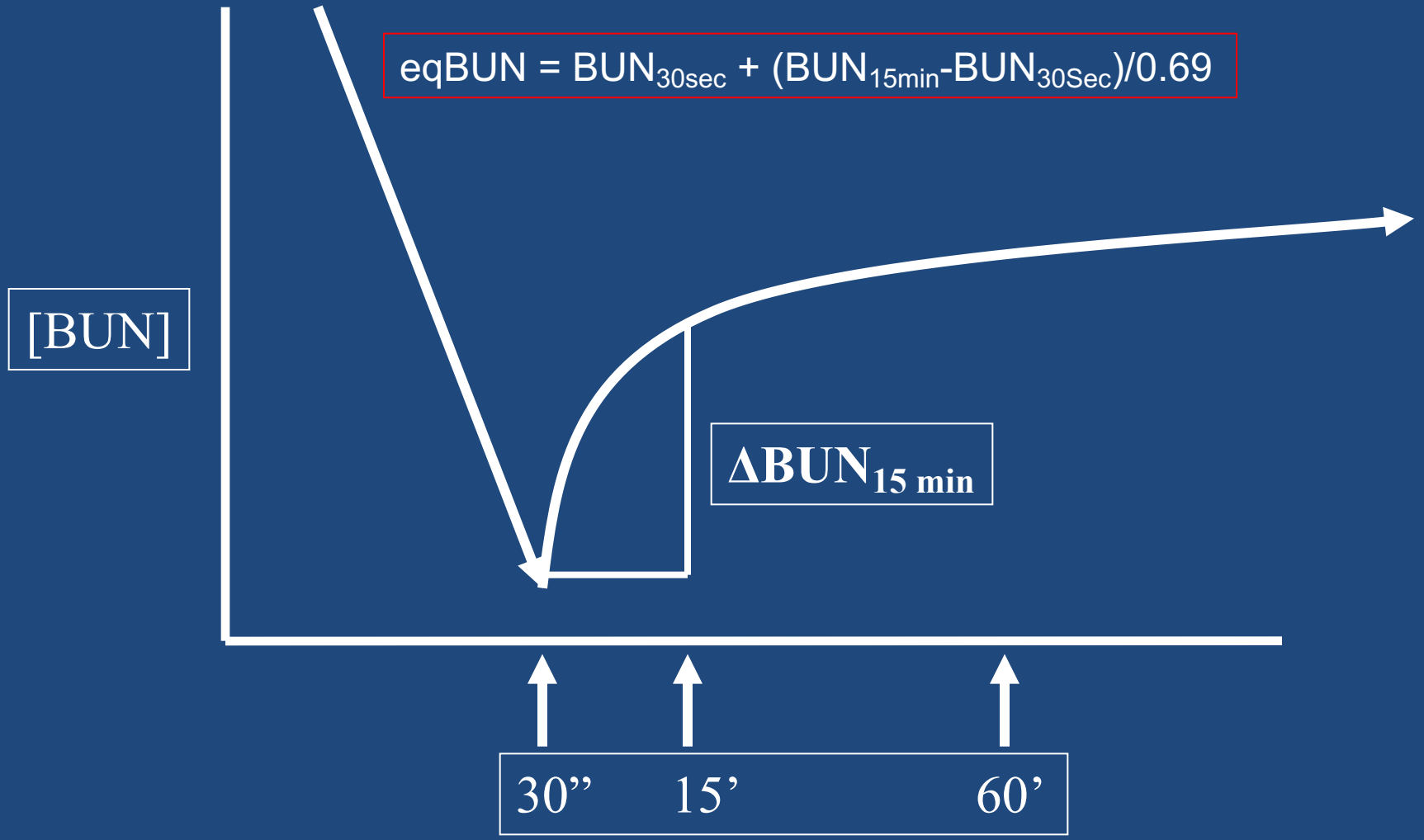
1. NDT 2010 2010;25:3044-3050
2. Am J Kidney Dis 2000;36(1):98-104
3. Pediatr Nephrol 1999;13:418-422

Equilibrated Kt/V Estimation Methods

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

1. Kidney Int 1997 Nov;52(5):1395-405
2. Clin Phys Physiol Meas. 1992 Feb;13(1):51-62
3. Am J Kidney Dis. 2000 Jul;36(1):98-104
4. ASAIO J 2000 May-Jun;46(3):283-7

Utilizing 30 sec & 15 min BUN (Goldstein)



Equilibrated Kt/V Estimation Methods: Pediatric Study

Method	*Total % error*
Daugirdas (Rate equation)	11.3% to 25.6%[1,2]
Smye (Mid-Dialysis)	46%[1]
Goldstein (Log extrapolation)	8%[2]
Marsenic (Linear Regression)	26.5%[3]

1. Kidney Int 1997 Nov;52(5):1395-405
2. Am J Kidney Dis. 2000 Jul;36(1):98-104
3. ASAIO J 2000 May-Jun;46(3):283-7

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

$$\text{std}Kt/V = 168 * (1 - \exp[-Kt/V])/t/[(1 - \exp[-Kt/V])/(Kt/V) + 168/(N * t) - 1], \quad (3)$$

t = treatment time in hours
Kt/V in stdKt/V calculation is eKt/V
N=number of treatments/week

Jaber BL et al: Blood Purif. 2004 22:481-9

Standard Kt/V thresholds to accurately predict single-pool Kt/V targets for children receiving thrice-weekly maintenance haemodialysis

Cherry Mammen[1], Stuart L. Goldstein[2], Ruth Milner[3] and Colin Thomas White[1]

- 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

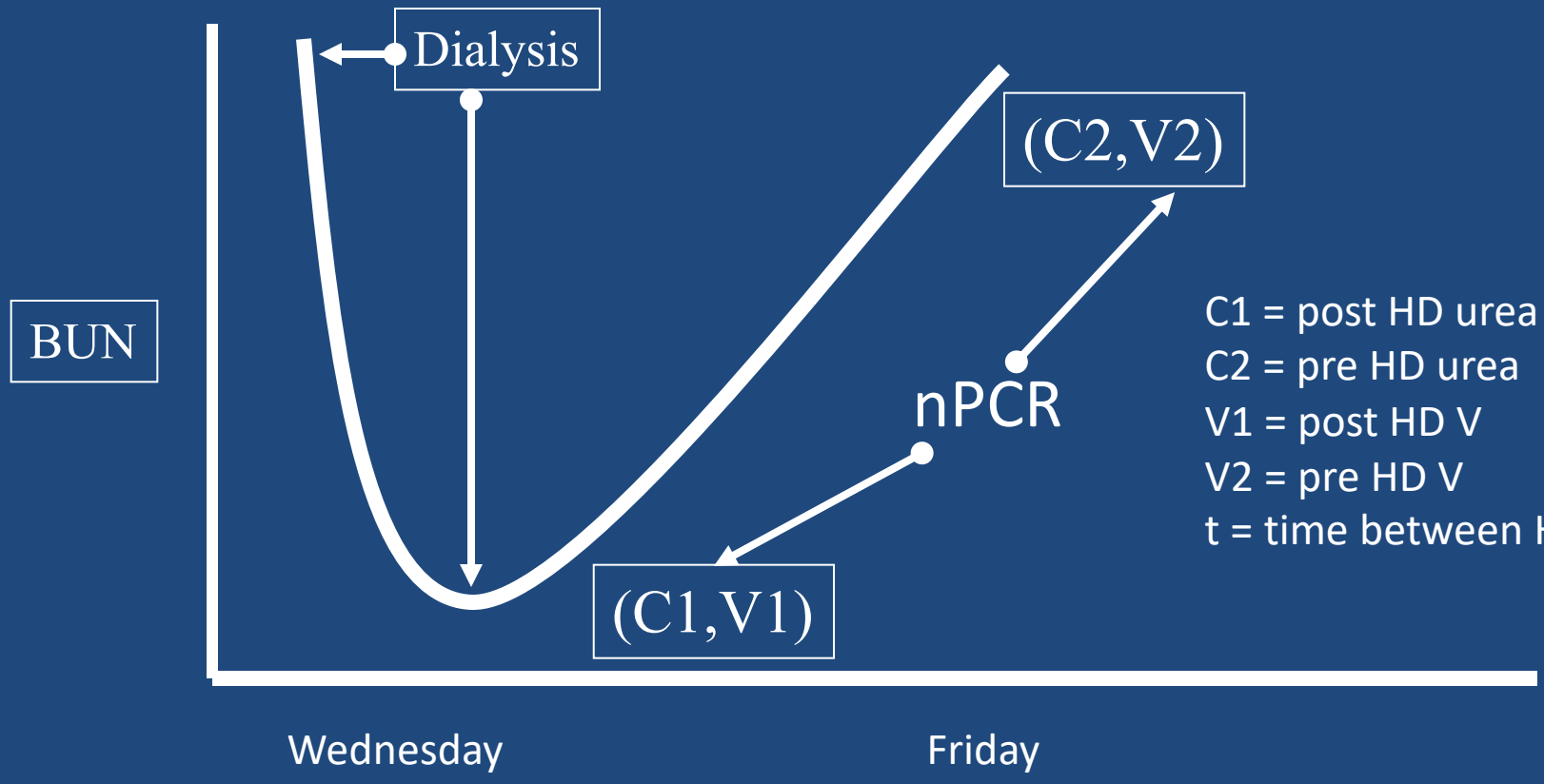
Nephrol Dial Transplant (2010) 25: 3044–3050

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



C1 = post HD urea
C2 = pre HD urea
V1 = post HD V
V2 = pre HD V
t = time between HD in min

nPCR Estimation for Children

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

$$\mathbf{estG = [(C2 * V2) - (C1*V1)]/t}$$

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

$$\mathbf{nPCR_{est} = 5.42 * estG/V1 + 0.17}$$

Goldstein SL: *Adv Ren Rep Ther* 2001 8:173-9.

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

Stuart L. Goldstein · Shannon Baronette
Tywanna Vital Gambrell · Helen Currier
Eileen D. Brewer

nPCR assessment and IDPN treatment of malnutrition in pediatric hemodialysis patients

Table 1. Nutrition and hemodialysis adequacy parameters before and during intradialytic parenteral nutrition (IDPN) (*BMI* body mass index, *nPCR* normalized protein catabolic rate)[a]

	Pre IDPN	IDPN	*P*
% Weight change	–0.6±2.70	1.8±2.1	<0.02
% BMI change	–1.3±2.7	1.3±2.1	<0.02
nPCR (g/kg per day)	1.05±0.36	1.35±0.37	<0.05
Serum albumin (g/dl)	3.7±0.8	3.8±0.6	NS
spKt/V	1.49±0.29	1.43±0.18	NS

[a] All values mean monthly±SD

Pediatr Nephrol (2002) 17:531–534

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 3. WL2% in Three Consecutive Months: Child and Adolescent Subgroups

	Lose Weight (n)	Maintain Weight (n)	*P* Value*
nPCR: adolescents	1.03 ± 0.29 (67)	1.15 ± 0.27 (407)	<.002
nPCR: child-aged	1.30 ± 0.31 (46)	1.28 ± 0.33 (223)	.68
Serum albumin: adolescents	4.24 ± 0.59 (67)	4.20 ± 0.40 (406)	.40
Serum albumin: child-aged	4.26 ± 0.38 (46)	4.09 ± 0.52 (223)	<.03

nPCR, normalized protein catabolic rate; WL2%, 2% monthly weight loss.
*As assessed by unpaired *t* test.

Weight loss: 2% monthly weight loss for 3 consecutive months

Journal of Renal Nutrition, Vol 17, No 4 (July), 2007: pp 269-274

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: Example

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 1.3m^2 is chosen.
(K_{urea}= 210 ml/min @ Qb of 250 ml/min)
Patient pre-dialysis weight is 42 kg.
How long should we dialyze for the 1st run?

Equation: **Kt/V ~ -ln (post/pre BUN) or –ln(1-URR)**

210 ml/min * t / (60% of 42 kg x 100) = -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: **Kt/V = -ln (C1/C0)**

210ml/min*83min/V = -ln (65/94)

leading to **V = 47.2 liters**
(Previous estimated V = 25.2 litres)

Plug in new V and start process again for desired removal

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

Weight (kg)	*SpKt/V*	*nPCR*
34.3	1.40	1.20
35.2	1.32	1.15
36.1	1.21	1.18

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

Maintenance HD Scenario #2
Fluid Weight Gain

Weight (kg)	*SpKt/V*	*nPCR*
34.3	1.40	1.20
35.2	1.32	0.89
36.1	1.21	0.65

- 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

Weight (kg)	*SpKt/V*	*nPCR*
34.3	1.40	1.20
32.5	1.32	1.65
31.6	1.35	1.7

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

Conclusions

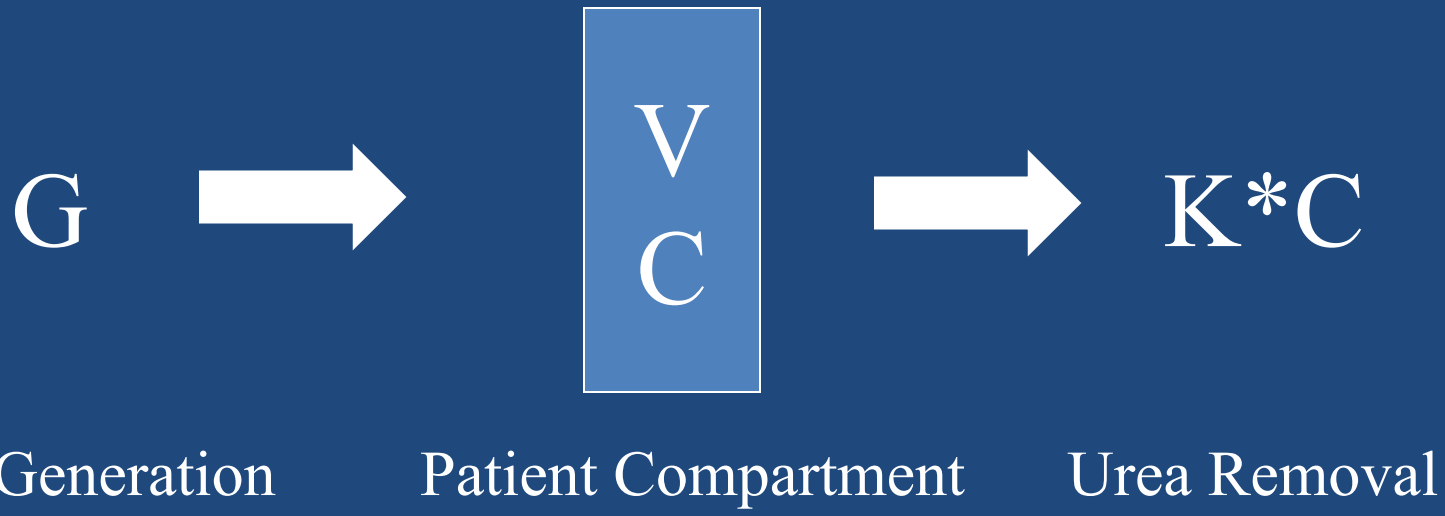
- HD adequacy measurements are an essential component of hemodialysis care delivery
- Understanding hemodialysis & nutrition adequacy can improve patient care
- HD adequacy calculations are not that complex
- Adequacy of dialysis is not equivalent to adequacy of patient care
  - Anemia, phosphate control,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

Thank You

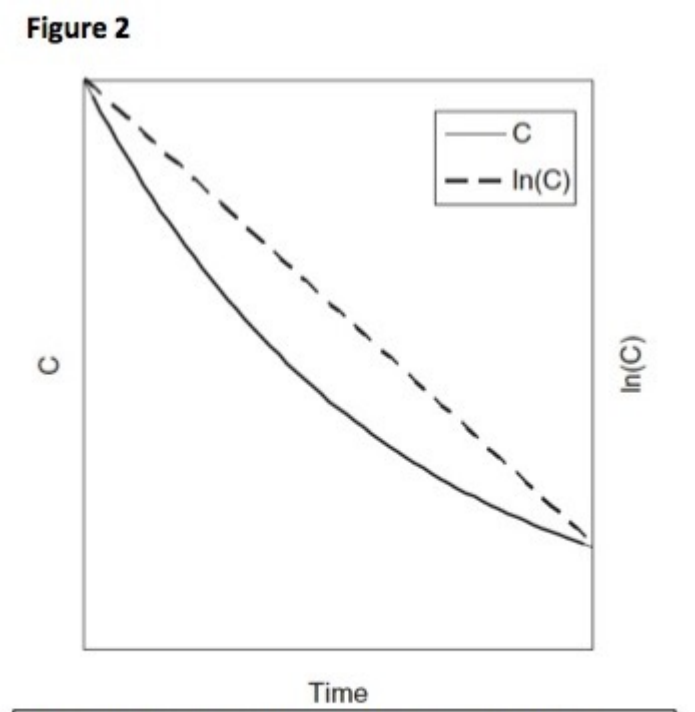
- Email me for Excel spreadsheet calculators

- mammencherry@gmail.com

Urea Clearance During Hemodialysis: Single-Pool Model

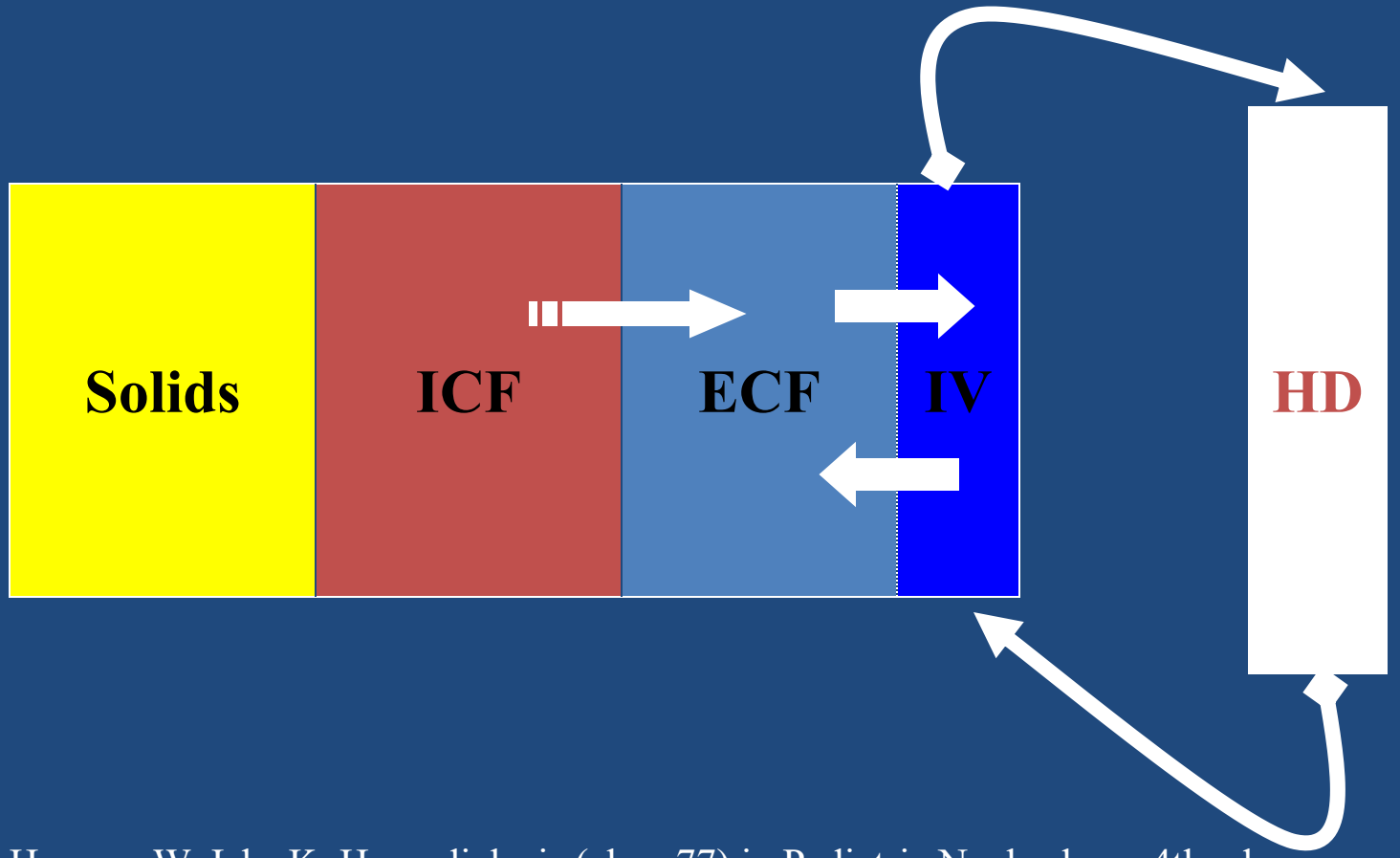


Urea kinetics (single pool)



- 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 -K/V (efficiency)

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

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

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 i three-point r

value

=0.0001

=0.0000

Values expr

BUN blood normalize pr

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

	Total patient sample cohort (n=76)	Percent of samples
Two-point model incorrectly categorizes nPCR as >1	7	9.2 %
Two-point model incorrectly categorizes nPCR as <1	1	1.3 %
Two-point and three-point nPCR calculations agree	68	89.5 %

Pediatr Nephrol (2013) 28:797–801

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

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

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.

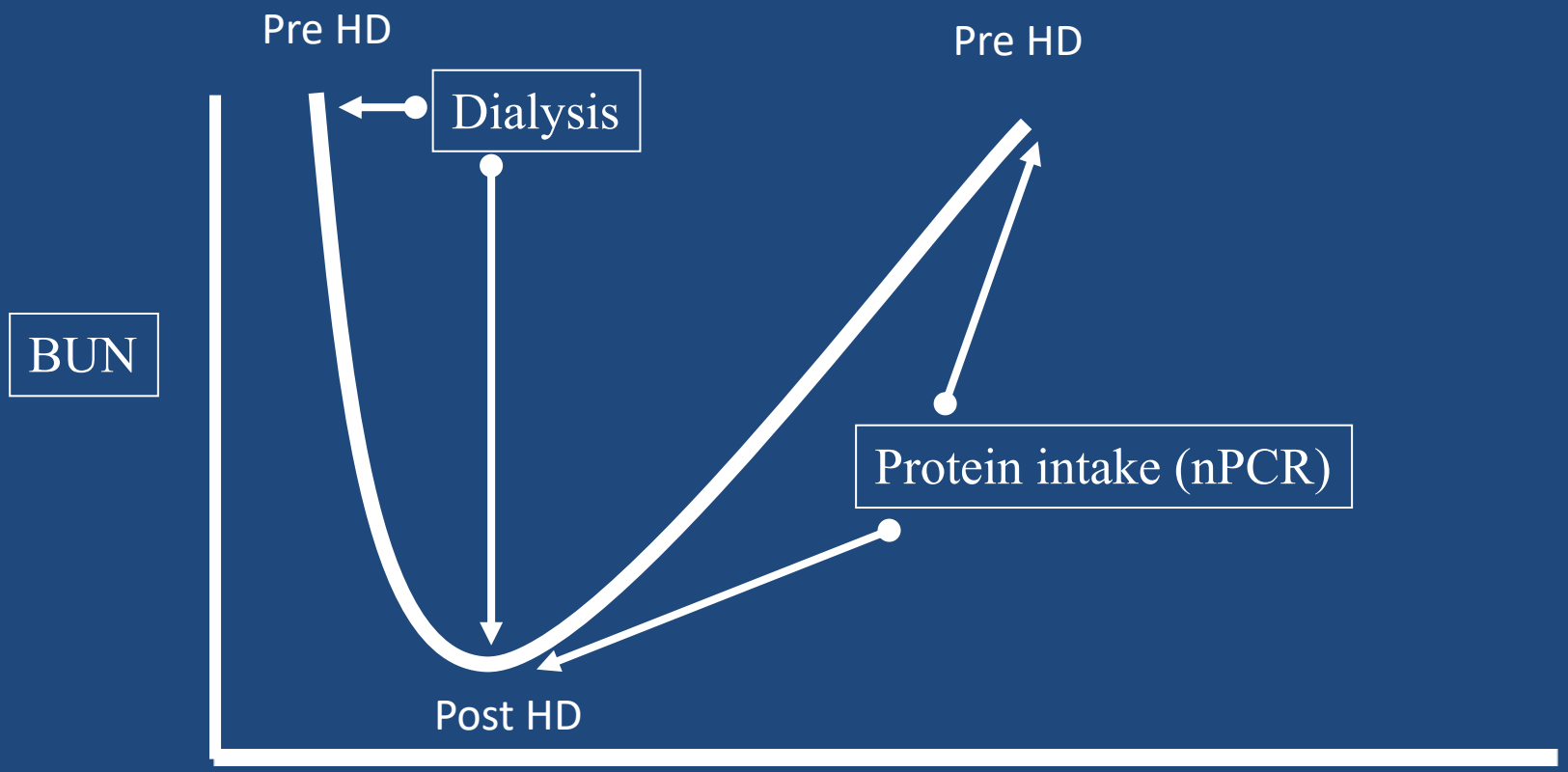
Journal of Renal Nutrition, Vol 17, No 4 (July), 2007: pp 269-274

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_{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**

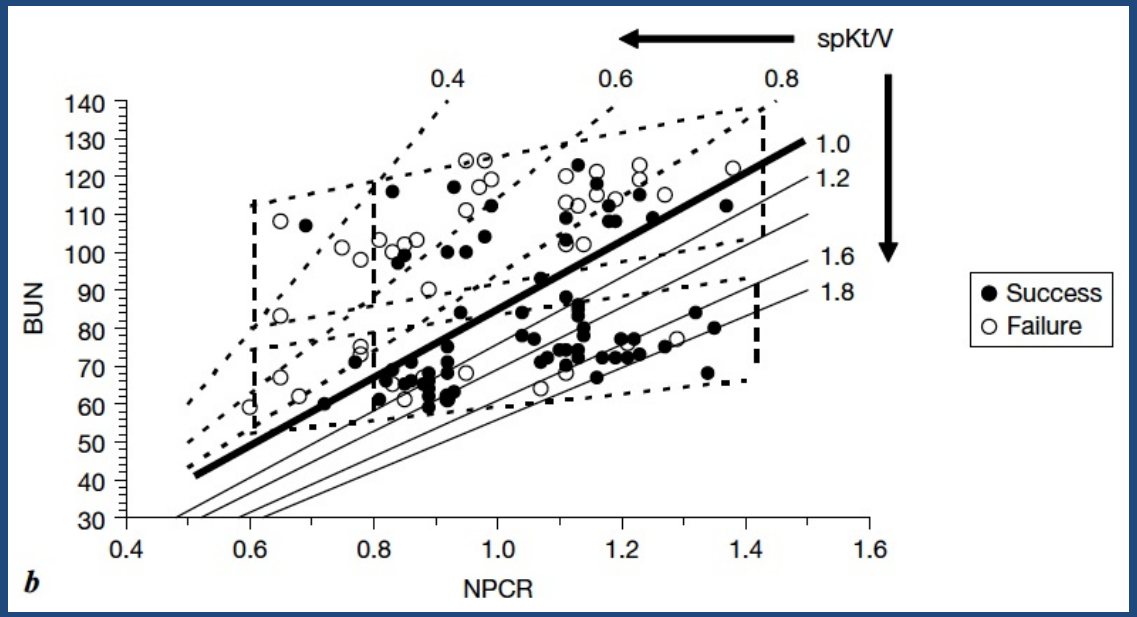
Lowrie EG et al N Eng J Med 1981

BUN Levels & Nutrition Adequacy



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



Gotch FA Kidney Int 1985

HEMO Study (2002)

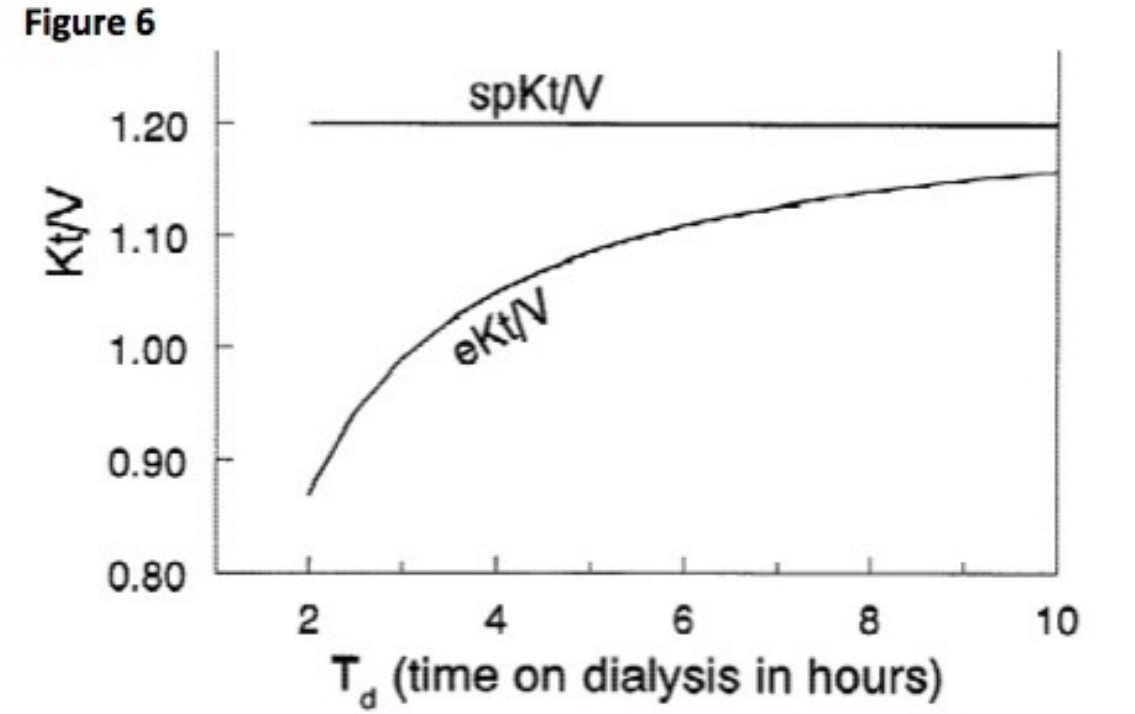
- 1846 adult pts randomized to high or low flux HD and standard or high dose 3x/week HD
- Dose targets: eKt/V calculated from spKt/V
  - Standard dose: 1.05
  - High dose: 1.45
- Achieved mean eKt/V in both groups:
  - 1.16 (standard) & 1.53 (high dose)
  - No difference in morbidity & mortality from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



Initial Hemodialysis Prescription & Refinement: Iterative Process

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

(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