Hemodialysis – Update

Hemodialysis Adequacy

연세의대

박 정 탁

Adequate dialysis

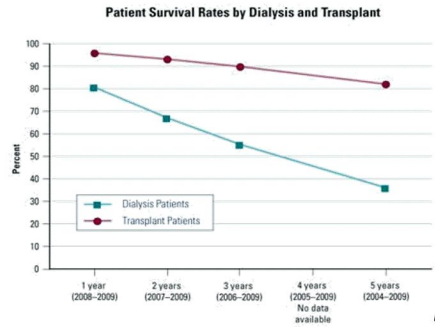
- Dialysis treatment is defined "adequate" when it permits the patients
  - To be fully rehabilitated
  - To have a satisfactory nutritional intake and a sufficient production of RBCs
  - To maintain normal blood pressure values
  - To prevent the development of neuropathy
- *Better than adequate dialysis, better than adequate doctors*

De Palma JR et al. N Engl J Med 1971,285:353-354

Introduction
Dose of dialysis and clinical outcome
Methods for quantification
Clinical guidelines

Introduction

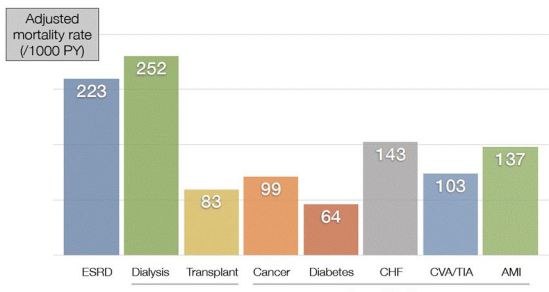
Morbidity and mortality in ESRD



USRDS, 2014

Morbidity and mortality in ESRD

- Mortality rate for persons on dialysis



USRDS, 2014

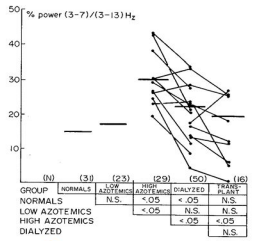
Accumulation of uremic toxins

Molecules	Molecular weight	Example
Small water-soluble compounds	<500 Da	Urea, asymmetric dimethylarginine, creatine, creatinine, guanidine, hypoxanthine, uric acid, and oxalate
Protein-bound solutes	Variable	p-cresol, phenol, 3-deoxyglucosone, hippuric acid, indoxyl sulfate, melatonin, leptin, retinol-binding protein, and homocysteine
Middle molecules	>500 Da	β_2-microglobulin, parathyroid hormone, and advanced glycosylation end products

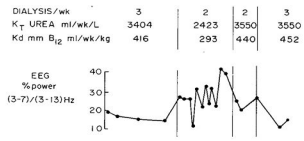
J Korean Med Assoc. 2013 Jul;56(7):583-591.

Dialysis dose and outcome

Slow-wave-associated EEG power



Dialysis prescription and neurobehavior



Uremic toxin relationship with clinical phenotype

Dialysis dose relationship with clinical phenotype

Trans Am Soc Artif Intern Organs. 1977;23:556-9.

Dose of dialysis and clinical outcome

Dose of dialysis and clinical outcome

- **1981' National Cooperative Dialysis Study (NCDS)**
- **1983' Mechanistic Analysis of the NCDS**
- **1996' United States Renal Data System (USRDS)**
- **2002'HEMO study**

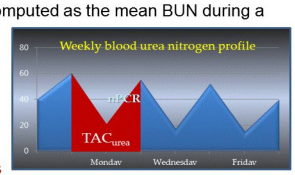
1981' National Cooperative Dialysis Study (NCDS)

- **The First Attempt to Define Adequate Hemodialysis Dose.**
- **The National Institute of Health (NIH)-sponsored conference on Adequacy of Dialysis held in 1975**
  - ✓ **Conclusion:**
    - ✓ ***"A carefully controlled multicenter cooperative study was required to determine if quantitative relationships between residual morbidity and the magnitude of dialysis prescribed could be established."***

Lowrie EG et al. N Engl J Med 1981,305:1176-1181

1981' National Cooperative Dialysis Study (NCDS)

- **TAC_{urea}: The Time-Averaged BUN Concentration**
  - An integrated parameter computed as the mean BUN during a full dialysis cycle
  - Patient characteristics
  - Urea generation
  - Dialysis time
  - Dialyzer urea clearance
  - Total number of treatments



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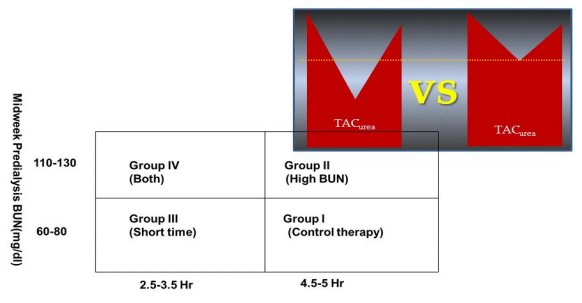

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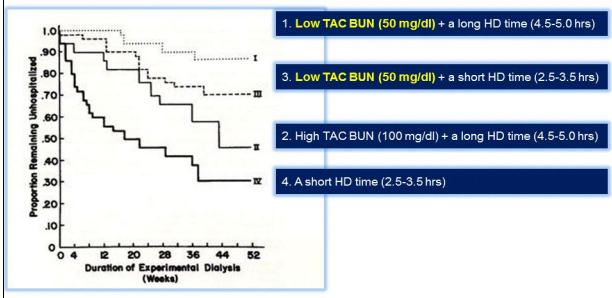


Lowrie EG et al. N Engl J Med 1981,305:1176-1181

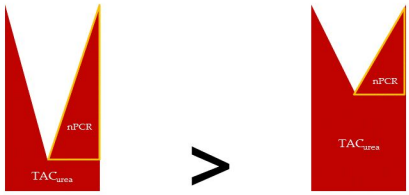
1981′ National Cooperative Dialysis Study (NCDS)

- The most important lessons from NCDS
  - ✓ *The importance of small molecule clearance, which forms the basis of current standards of adequacy*
  - ✓ *The delivered dose of dialysis can and should be quantified.*
- ***Limitations:***
  - *Interation with a computerized model.*
  - *Difficult to be applied to daily practice*
  - *A low urea value fails to distinguish the well dialyzed patients form the malnourished one.*

Laird NM et al. Kidney Int 1983,23 (Suppl 13):S101-S106.

1983′ Mechanistic Analysis of the NCDS

- **The most significant correlate with outcome was BUN (TACurea); the second most significant influence on outcome was the urea generation rate (nPCR).**



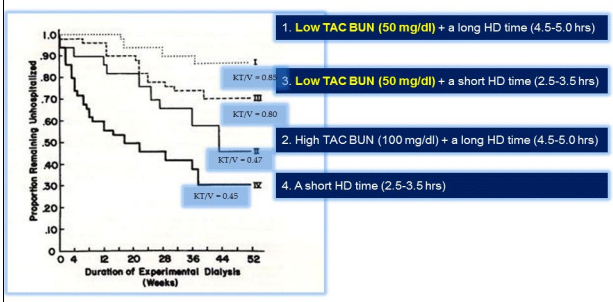
Laird NM et al. Kidney Int 1983,23 (Suppl 13):S101-S106.

1983′ Mechanistic Analysis of the NCDS

- Thus, Kt/V is a basic, generalizable dialysis parameter and serves as the basis of the mechanistic analysis reported here (formal urea kinetic modeling).
  - *Kt/V ≒ -ln[1-(0.49 X nPCR – 0.16)/pre-dialysis BUN]*

Laird NM et al. Kidney Int 1983,23 (Suppl 13):S101-S106.

1983′ Mechanistic Analysis of the NCDS



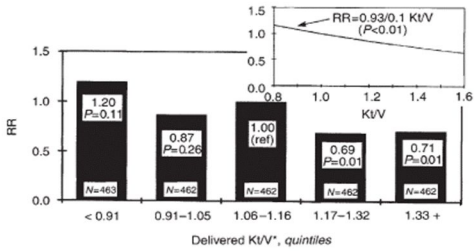
Gotch FA et al. Kidney Int 1985,28:526-534.

1996′ United States Renal Data System (USRDS)

- United States Renal Data System
- Random national sample of 2,311 patients from 347 dialysis units
- Delivered hemodialysis dose to mortality
- Adjustment for extensive comorbidity/risk factors

Kidney International, Vol. 50 (1996), pp. 550–556.

1996′ United States Renal Data System (USRDS)



Kidney International, Vol. 50 (1996), pp. 550–556.

1996′ United States Renal Data System (USRDS)

- Dialysis dose is related to mortality.
- Clearance estimated by Kt/V clearly reflects outcome.
- Mortality risk was lower by 7% with each 0.1 higher level of delivered Kt/V
- No further significant improvement in mortality above Kt/V > 1.3 (or a URR > 70%).

Kidney International, Vol. 50 (1996), pp. 550–556.

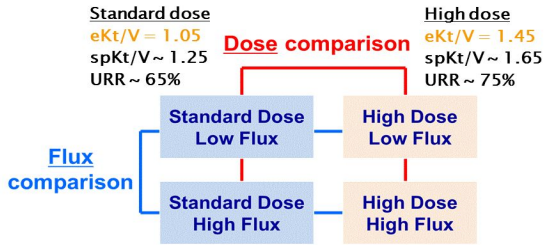
2002′ HEMO study

- Effect of dialysis dose and membrane flux in maintenance hemodialysis
- First large-scale RCT on HD adequacy target
- March 1995 to Oct 2000
- 1846 patients from 72 dialysis units in US
- Mean duration of dialysis before enrollment : 3.7years
- Mean follow up : 2.84 years

N Engl J Med. 2002 Dec 19;347(25):2010-9.

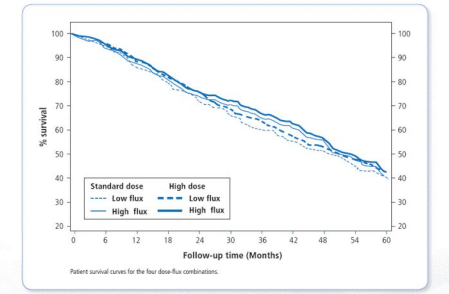
2002′ HEMO study

- Randomized 2 x 2 factorial design clinical trial



N Engl J Med. 2002 Dec 19;347(25):2010-9.

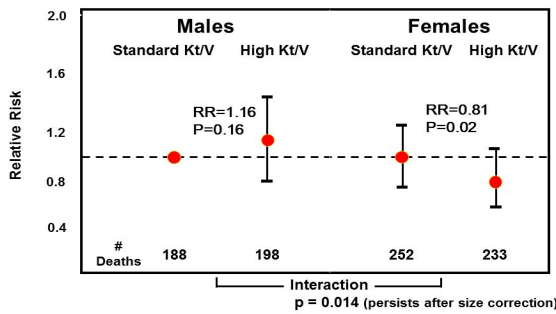
2002′ HEMO study



The primary outcome was not significantly influenced by treatment assigned for dose of dialysis or for the flux of the dialysis membranes used.

N Engl J Med. 2002 Dec 19;347(25):2010-9.

2002′ HEMO study



Depner et al, Kidney Int 2004

2002' HEMO study

- In patients receiving thrice-weekly HD a higher dose of dialysis does not significantly improved survival.
- Increase of the dialysis dose above the currently recommended minimum dose do not improve patients outcome.
- It is possible that a much higher dose of dialysis and higher convection may improve outcome.

N Engl J Med. 2002 Dec 19;347(25):2010-9.

Methods for quantification

Urea: Surrogate or toxin

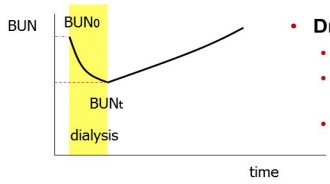
- **Ideal markers of dialysis dose.**
  - **1. Easily measured**
  - **2. Eliminated by dialysis**
  - **3. Toxicity related to renal failure**
  - **4. Representative of other potential toxins that accumulate in renal failure**
- **Urea as surrogate solute of choice**
  - Abundance in plasma
  - Technically easy to measure
  - Similar volume distribution to total body water
  - Urea clearance correlated with outcomes

Kidney International (1997) 52, Suppl. 62, S96-S100.

Urea reduction ratio

- **URR(urea reduction ratio)**

$$= \frac{\text{Predialysis BUN-postdialysis BUN}}{\text{Predialysis BUN}}$$

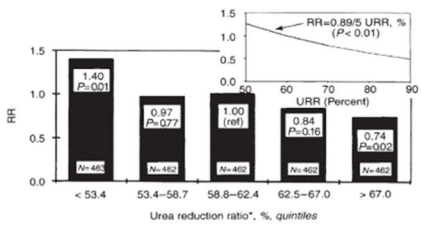


- **Draw backs**
  - **post-dialysis rebound**
  - **Intradialytic urea generation**
  - **Effect of ultrafiltration**

Kidney International (1999) 56, 754-755.

Urea reduction ratio

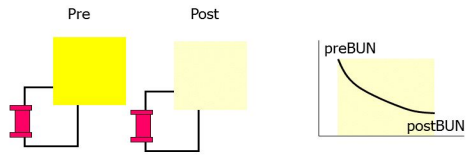
- **URR impacts on patient survival**



Kidney International, Vol. 50 (1996), pp. 550–556.

Single-pool KT/V

- **preferred method for measurement of the delivered dose**



Kidney International (1999) 56, 754-755.

Single-pool KT/V

K: the dialyzer blood water urea clearance (L/hour)

T: Treatment session length (hours)

Volume of plasma cleared (L)

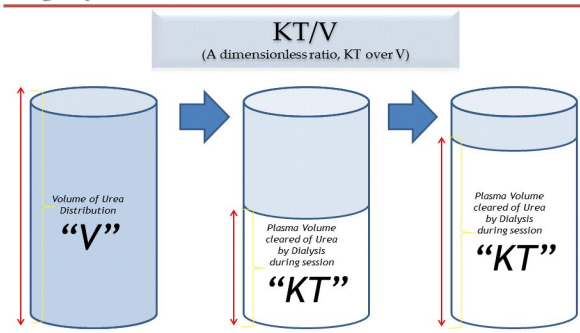
KT/V

(A dimensionless ratio, KT over V)

The distribution volume of urea (L)

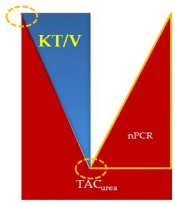
Kidney International (1999) 56, 754-755.

Single-pool KT/V



Single-pool KT/V

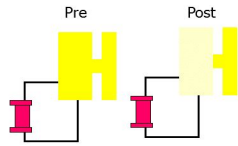
- *Kt/V = -ln(R - 0.008 X t) + (4 - 3.5 X R) X ΔBW/BW*
  - *R: the ratio of postdialysis BUN to predialysis BUN*
  - *t: time of dialysis in hours*
  - *BW: body weight.*
- **URR and spKt/V are mathematically linked**
- **Intradialytic urea generation**
- **Effect of ultrafiltration**
- **Neither URR nor Kt/V is superior as a measure of outcome**

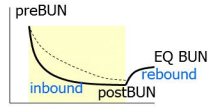


Daugirdas JT. J Am Soc Nephrol 1993,4:1208-1213

Double-pool KT/V

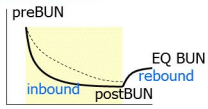
- **Equilibrated Kt/V**
- **Postdialysis rebound; urea diffuses from sequestrated tissues**



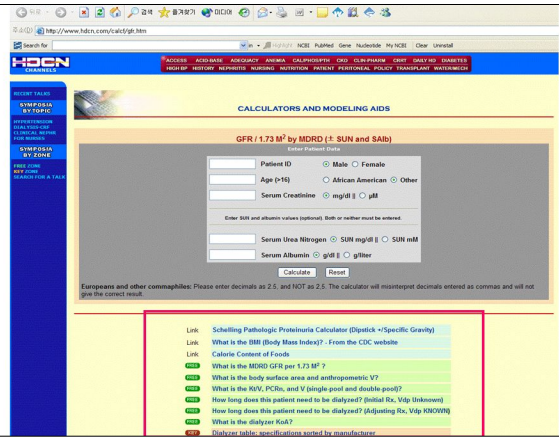


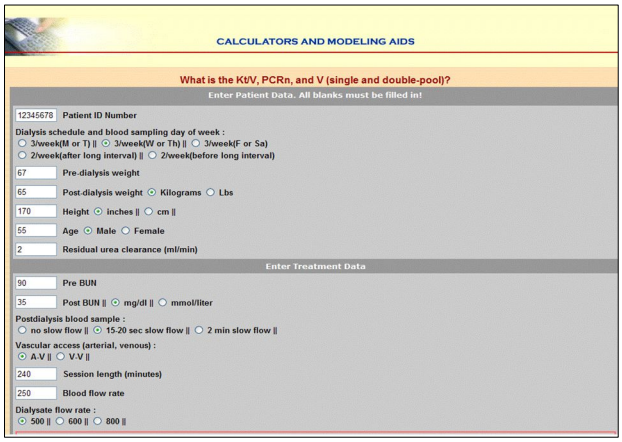
Single-pool KT/V

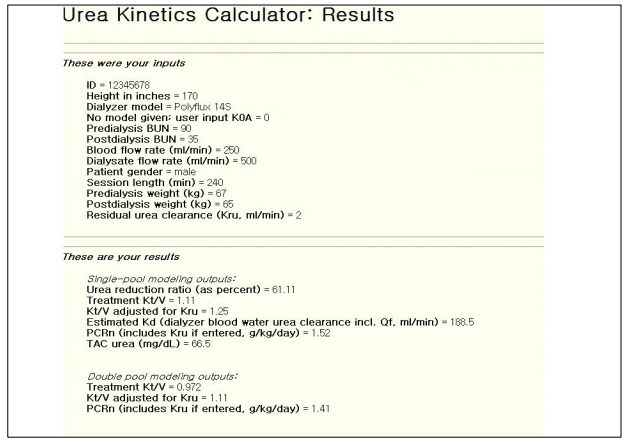
- *spKt/V = -ln(R - 0.008 X t) + (4 - 3.5 X R) X ΔBW/BW*
  - *R: the ratio of postdialysis BUN to predialysis BUN*
  - *t: time of dialysis in hours*
  - *BW: body weight*



- *eKt/V = -ln(Req - 0.008 X t) + (4 - 3.5 X R) X ΔBW/BW*
  - *Req: the ratio of equiliobrated BUN to predialysis BUN*
- **eKt/V is typically 0.2 units lower than the spKt/V**







Clinical guidelines

KDOQI Hemodialysis Adequacy Guidelines 2006

Minimally Adequate Hemodialysis

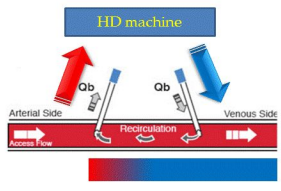
- The delivered dose of HD should be measured at regular intervals no less than monthly. (A)
- The minimally adequate dose of HD given 3 times per week to patients with Kr less than 2 mL/min/1.73 m^2 should be *an spKt/V (excluding RKF) of 1.2 per dialysis.* For treatment times less than 5 hours, an alternative minimum dose is a URR of 65%. (A)
- The target dose for HD given 3 times per week with Kr less than 2 mL/min/1.73 m^2 should be *an spKt/V of 1.4 per dialysis* not including RKF, or URR of 70%. (A)

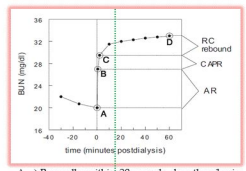
Methods for Predialysis Blood Sampling

- Both samples (predialysis and postdialysis) should be drawn during the same treatment session. (A)
- The risk of underestimating predialysis BUN level because of saline dilution or by sampling the blood after treatment has begun should be avoided. (A)

Methods for Predialysis Blood Sampling

- The risk of underestimating the postdialysis BUN level because of access recirculation (AR) should be avoided by
  - First slowing the blood flow through the dialyzer to a rate at which AR is expected to be minimal (***100 ml/min***) for a period long enough to ensure that unrecirculated blood has advanced to below the sampling port (***usually 15 seconds***). (A)





A → B: usually within 20 seconds, less than 1 min
B → C: 2 to 3 minutes after slowing the pump
C → D: 3 minutes to 30 ~ 60 minutes

Points to remember

- Measuring the clearance of solutes that accumulate in patients with uremia has become the mainstay for calculating the dose of dialysis and determining its adequacy as delivered.
- The minimally adequate dose of HD given 3 times per week to patients with Kr less than 2 mL/min/1.73 m2 should be an spKt/V (excluding RKF) of 1.2 per dialysis. For treatment times less than 5 hours, an alternative minimum dose is a URR of 65%.
  - Preferably, the target dose should be an an spKt/V of 1.4 per dialysis not including RKF, or URR of 70%.
- When dialysis adequacy is assessed by using predialysis and postdialysis BUN measurements, blood samples should be drawn by using certain acceptable procedures.