Mini-Lecture 4

Hemodialysis Adequacy

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What is "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*

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

- Until 1974, nephrologists frequently prescribed hemodialysis (HD) based on clinical judgment, often paying more attention to fluid balance than to the need to remove metabolic waste product.
  - ✓ *Although still valid, this approach is subjective and has the drawback of a possible late diagnosis of underdialysis.*
- Until 1974, practice varied widely from center to center, with treatment times varying from as little as 6 to as many as 48 hours per week.

A 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."*
- A National Cooperative Dialysis Study (NCDS, conducted from 1978 to 1980) was undertaken subsequently as a large-scale, carefully controlled study with comprehensive monitoring of multiple treatment and outcome variable.

160 patients
- 1. Low TAC BUN (50 mg/dl) + a long HD time (4.5-5.0 hrs)
- 2. High TAC BUN (100 mg/dl) + a long HD time (4.5-5.0 hrs)
- 3. Low TAC BUN (50 mg/dl) + a short HD time (2.5-3.5 hrs)
- 4. A short HD time (2.5-3.5 hrs)

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

A National Cooperative Dialysis Study (NCDS)
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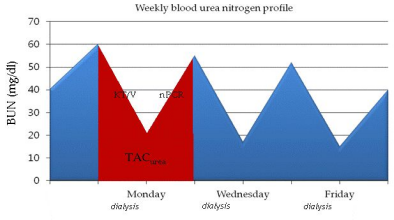
- Independent variables:
  - Urea nitrogen averaged with respect to time (TAC_{urea})
    - An integrated parameter computed as the mean BUN during a full dialysis cycle



  - The length of the dialysis treatment

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A National Cooperative Dialysis Study (NCDS)
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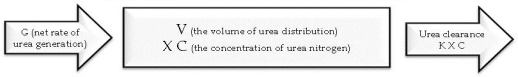
Diagrammatic representation of the single-pool model for urea nitrogen



- G ≒ ∆(ΔC X V)/2,646 [interdialytic time interval (mins)]
  - *G: net urea generation rate (mg/min)*
  - *ΔC: the change in BUN during dialysis [(pre-dialysis BUN) - (post-dialysis BUN)]*
  - *V: urea distribution volume*
- Protein catabolic rate (PCR, g/day) is calculated directly from G
  - *PCR = 9.35 X G + 0.00029 X V (ml)*
- $TAC_{urea} = \{C_0(1 + exp [-Kd X Td/V]\}/2$
  - *C_0: pre-dialysis BUN (mg/ml)*
  - *Kd: dialyzer clearance*
  - *Td: dialysis time*
  - *V: urea distribution volume*

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A National Cooperative Dialysis Study (NCDS)
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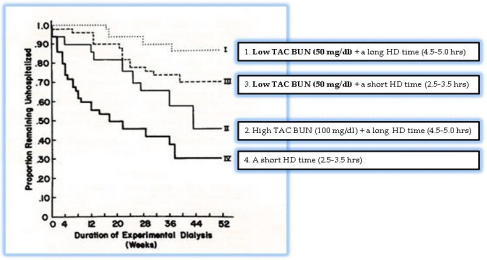

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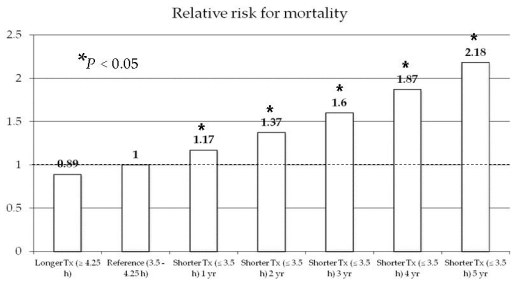
Mortality and Duration of Hemodialysis Treatment



Held PJ et al. JAMA 1991;265:871-875

A National Cooperative Dialysis Study (NCDS)
: *A Mechanistic Analysis of the NCDS*

- The most important lessons from NCDS are summarized as
  - ✓ *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.*

$$TAC_{urea} = \frac{(C_{11} + C_{02})(2T - td) + (C_{12} + C_{03})(2T - td) + (C_{13} + C_{04})(3T - td)}{14T - 6td} + \frac{1}{td}\int_0^{td} Cdt + \frac{1}{td}\int_{2T}^{2T+td} Cdt + \frac{1}{td}\int_{4T}^{4T+td} Cdt.$$

- ***Limitations:***
  - *Iteration 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.*

Kidney International, Vol. 28 (1985), pp. 526–534

A mechanistic analysis of the National Cooperative Dialysis Study (NCDS)

FRANK A. GOTCH and JOHN A. SARGENT

Ralph K. Davies Medical Center and Consultant to Kinetic & Treatment Control Section of the NCDS, San Francisco, California, and Quantitative Medical Systems, Inc., Co-Principal Investigator, Kinetics & Treatment Control Section of the NCDS, Emeryville, California, USA

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

A National Cooperative Dialysis Study (NCDS)
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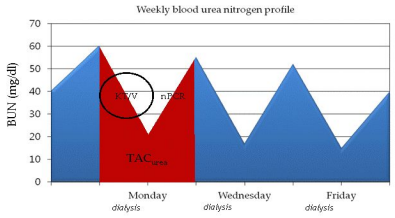
- Kt/V can be considered to be a more fundamental mechanistic parameter of the level of dialysis prescribed compared to BUN which represents the concentration of a single relatively non-toxic solute.



BUN = Nutrition/Treatment = *F*[PCR/Kt/V]

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A National Cooperative Dialysis Study (NCDS)
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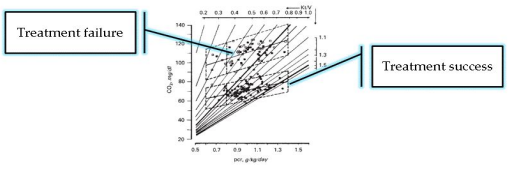
- Thus, Kt/V is a basic, generalizable dialysis parameter and serves as the basis of the mechanistic analysis reported here (formal urea kinetic modeling).
  - *Kt/V ≒ -ln[1-(0.49 X nPCR - 0.16)/pre-dialysis BUN]*
- The probability of dialysis failure was a constant step function of Kt/V: it was higher when Kt/V was ≤ 0.8 and abruptly decreased when it was ≥ 0.9.



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A National Cooperative Dialysis Study (NCDS)
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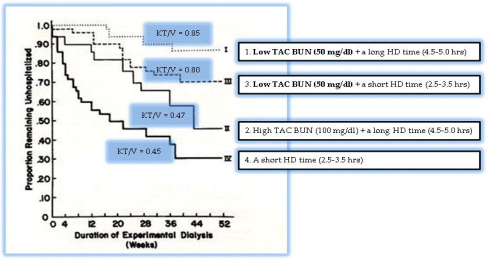
- The concept of Kt/V_{urea} as an index of dialysis evolved from the NCDS but is essentially a part of the first order kinetic expression describing the fall in urea concentration during dialysis.



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A National Cooperative Dialysis Study (NCDS)
: Second Generation Logarithmic Estimates of Single-Pool Variable Volume Kt/V

- The preferred method for measurement of the delivered dose is *formal urea kinetic modeling (UKM)*. Other methods may be used provided they give similar results and do not significantly overestimate the modeled dose.
- However, formal UKM requires accurate measures of:
  - *Predialysis and postdialysis BUN for the first dialysis treatment of the week and the predialysis BUN for the second dialysis session of the week in a thrice weekly hemodialysis schedule.*
  - Predialysis and postdialysis weights at the time of the first hemodialysis treatment of the week.
  - The actual treatment time, ie, the exact number of minutes during which the hemodialysis treatment was delivered on the first dialysis treatment of the week
  - *The effective clearance of the dialyzer as measured in the hemodialysis unit (not the in vitro clearance value reported by the manufacturer alone).*

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$$Vr = Qf \times t \left[\left[1 - \left[\frac{G - C\theta(K + Kr - Qf)}{G - C\theta(K + Kr - Qf)} \right]^{\frac{Qf}{K+Kr-Qf}} \right]^{-1} - 1 \right] \quad (1)$$

$$G = \frac{(Kr + \alpha)\left[C\theta - Cf\left(\frac{Vf + \alpha\theta}{Vf}\right)^{-\frac{Kr+\alpha}{\alpha}} \right]}{\left(1 - \left(\frac{Vf + \alpha\theta}{Vf}\right)^{-\frac{Kr+\alpha}{\alpha}}\right)} \quad (2)$$

$$C = C_0\left[\frac{V - B \cdot t}{V}\right]^{\left(\frac{K_r + K_d + B}{B}\right)} + \frac{G}{K_r + K_d + B}\left[1 - \left[\frac{V - B \cdot t}{V}\right]^{\left(\frac{K_r + K_d + B}{B}\right)}\right]$$

A National Cooperative Dialysis Study (NCDS)
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- The preferred method for measurement of the delivered dose is *formal urea kinetic modeling (UKM)*. Other methods may be used provided they give similar results and do not significantly overestimate the modeled dose.
- More simpler, alternative methods were also accepted.
  - Second generation logarithmic estimates of single-pool variable volume Kt/V by Daugirdas JT.
    - *Daugirdas JT. J Am Soc Nephrol 1993,4:1208-1213*
  - *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.*

The Meaning of KT/V as a Marker of Dialysis Adequacy

K: the dialyzer blood water urea clearance (L/hour) X T: Treatment session length (hours)

Volume of plasma cleared (L)

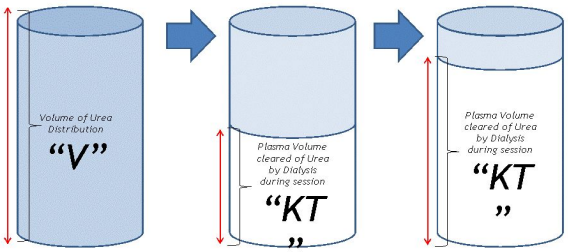
KT/V

(A dimensionless ratio, KT over V)

The distribution volume of urea (L)

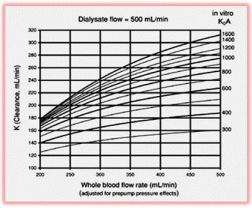
The Meaning of KT/V as a Marker of Dialysis Adequacy

KT/V
(A dimensionless ratio, KT over V)



The Meaning of KT/V as a Marker of Dialysis Adequacy

- Factors affecting the blood urea water urea clearance (K)
  - ✓ Effect of the blood flow rate
  - ✓ Effect of dialysis solution flow rate
  - ✓ Effect of dialyzer efficiency
    - The dialyzer mass transfer area coefficient, K_oA: *the efficiency of a given dialyzer in removing any solute can be described by a constant K_oA*
      - *K_o: the permeability constant of the membrane material for a given solute*
      - *A: the effective surface area*



- *Dialyzers with K_oA values > 700 are used for "high-efficiency" dialysis*
  - *A high efficiency dialyzer is basically a big dialyzer that by virtue of its larger surface area has a high ability to remove urea.*
  - *These membranes may have either small or large pores*
- *Dialyzers with KUF (coefficient of ultrafiltration) values > 10 mL/hr/mmHg, and usually 20 mL/hr/mmHg are used for "high-flux" dialysis*
  - *These membranes have large pores*

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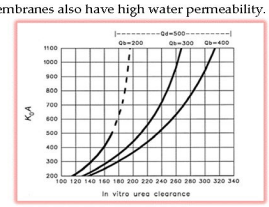
  - High-flux membranes have large pores
  - High-flux membranes also have high water permeability.



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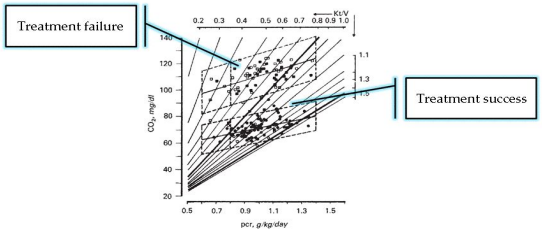
Hemodialysis												
UF=0 ml/min, Q_d=500 ml/min												
Q_b(ml/min)	200	300	400	500	200	300	400	500	200	300	400	500
Urea	193	262	309	-	196	270	321	-	-	281	339	378
Creatinine	181	232	266	-	186	243	281	-	-	259	303	334
Phosphate	174	220	250	-	180	232	266	-	-	249	289	317
Vitamin B_{12}	128	149	163	-	137	162	178	-	-	163	203	218
Inulin	91	102	109	-	100	113	121	-	-	131	143	151
Hemodiafiltration												
UF=60 ml/min, Q_d=500 ml/min												
Q_b(ml/min)	200	300	400	500	200	300	400	500	200	300	400	500
Urea	198	277	332	-	199	283	343	-	-	290	359	406
Creatinine	191	252	292	-	194	262	306	-	-	274	327	363
Phosphate	187	242	277	-	191	252	292	-	-	266	314	347
Vitamin B_{12}	152	177	193	-	159	189	208	-	-	208	232	249
Inulin	120	133	141	-	128	143	153	-	-	161	174	183
KoA for Urea	993				1165				1450			
Ultrafiltration* (ml/min) +/- 10%, measured at Q_b=300 ml/min and TMP=300 mmHg	113				127				144			
UF-coefficient* (ml/h, mmHg) +/-20%	60				70				85			
Priming volume (ml)	94				115				125			
Fluid volume for priming (ml)	> 500				> 500				> 500			
Residual blood volume (ml)	< 1				< 1				< 1			
Maximum TMP (mmHg)	600				600				600			
Recommended Q_b (ml/min)	200-400				250-500				300-500			

Which Targets of Dialysis Dose Should Be Achieved?

- In the secondary mechanistic analysis of the NCDS data, the probability of dialysis failure was a constant step function of Kt/V_{urea}
  - It was higher when Kt/V_{urea} was ≤ 0.8 and abruptly decreased when it was ≥ 0.9.
  - As a consequence, Kt/V_{urea} >1.0 per HD treatment was considered of no apparent clinical value.



Which Targets of Dialysis Dose Should Be Achieved?

- Does more than 1.0 of Kt/V provide further benefits in outcomes of HD patients?
  - Keshaviah suggested that benefit of a ***Kt/V > 1.2*** *(1983)*.
  - An increase in the quality-adjusted life expectancy of HD patients with increasing ***Kt/V up to a value of 2.0*** *(1993)*.
  - In the diabetic patients, ***Kt/V ≥ 1.4*** was associated with a lower risk of death even compared with the Kt/V range of 1.2–1.4 *(1994)*.
  - A progressively decreasing risk of death with increasing ***single-pool Kt/V values up to 1.8*** has been reported by a survey of the Japanese Patient Registration Committee from data of over 50,000 HD patients *(1997)*.
  - The recent preliminary results of the DOPPS study are in line with the theory of a progressive benefit from increasing dialysis dose, by showing that increasing Kt/V is beneficial up to a double-pool Kt/V of 1.4 (roughly corresponding to ***a single-pool Kt/V of 1.6)*** *(2000)*.

The HEMO study (2002)

- Guidelines until 2002 target urea-reduction ratio of at least 65 percent or a single-pool Kt/V of at least 1.20.
  - The NCDS was performed prior to the widespread dissemination of current hemodialysis technologies as followings
    - ➢ Ultrafiltration control
    - ➢ Bicarbonate dialysate
    - ➢ Variable dialysate sodium programming
    - ➢ Biocompatible dialysis membrane materials.
  - Diabetics and patients over the age of 70 were excluded from the NCDS.
  - Uncontrolled retrospective studies suggested an improved survival with greater delivered doses of hemodialysis (up to Kt/V 1.2 and URR of 65%).
- Therefore, this landmark study was planned to determine whether increasing the dose of dialysis or using a high-flux dialyzer membrane alters survival or morbidity among patients undergoing HD (total 1,846 patients)
  - Standard-dose HD vs. high dose HD (***spKt/V of 1.32 vs. Kt/V of 1.71***)
  - Low flux HD vs. high flux HD

Eknoyan G et al. N Eng J Med 2002;347:2010-2019

The HEMO study (2002)

- Methods
  - The target equilibrated Kt/V was achieved by manipulating
    - ➢ The duration of the treatment session
    - ➢ The dialyzer clearance commensurate with ultrafiltration requirements.
  - Dialysis was provided in as short a time as possible but not less than 2.5 hours.

TABLE 2. MEAN CHARACTERISTICS OF TREATMENT DURING FOLLOW-UP.*

TREATMENT VARIABLE	STANDARD-DOSE GROUP (N=926)	HIGH-DOSE GROUP (N=920)	LOW-FLUX GROUP (N=925)	HIGH-FLUX GROUP (N=921)
Duration of dialysis session (min)	190±23	219±23	206±28	203±27
Rate of blood flow (ml/min)	311±51	375±32	344±53	341±54
Rate of urea clearance (ml/min)	218±25	251±18	233±27	236±28
Total urea clearance/dialysis session (liters)	41.4±7.0	55.1±7.6	48.2±10.1	48.2±9.9
Single-pool Kt/V	1.32±0.09	1.71±0.11	1.51±0.22	1.52±0.22
Equilibrated Kt/V†	1.16±0.08	1.53±0.09	1.34±0.21	1.34±0.21
Urea-reduction ratio (%)	66.3±2.5	75.2±2.5	70.6±5.1	70.9±5.1
Blood urea nitrogen before dialysis (mg/dl)	62.1±13.6	54.3±11.8	58.6±13.5	57.9±13.1
Rate of beta$_2$-microglobulin clearance (ml/min)	18.9±19.0	18.3±16.8	3.4±7.2	33.8±11.4
Total beta$_2$-microglobulin clearance/dialysis session (liters)	3.5±3.6	4.0±3.6	0.7±1.5	6.8±2.3

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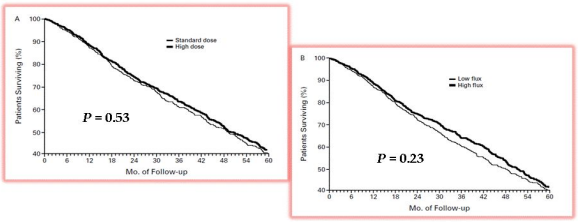

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KDOQI Hemodialysis Adequacy Guidelines 2006
- *Minimally Adequate Hemodialysis*

- 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)

KDOQI Hemodialysis Adequacy Guidelines 2006
- *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)

Table 5. Recommended Predialysis Blood-Drawing Procedure

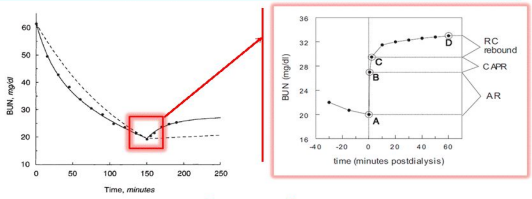
A. When using an AV fistula or graft
1. Obtain the blood specimen from the arterial needle prior to connecting the arterial blood tubing or flushing the needle. Be sure that no saline and/or heparin is in the arterial needle and tubing prior to drawing the sample for BUN measurement.
2. Do not draw a sample for use as a predialysis measure of BUN if HD has been initiated.
B. When using a venous catheter
1. Using sterile technique, using a 5 mL syringe, withdraw any heparin and saline from the arterial port of the catheter, along with blood, to a total volume of 5 mL.[87,88] Discard the contents of this syringe.
2. Connect a new syringe or collection device and draw the sample for BUN measurement.
3. Complete initiation of HD per dialysis clinic protocol.

$Kt/V = ln(C_0/C_t)$

- Assuming zero ultrafiltration and no urea generation during the dialysis

KDOQI Hemodialysis Adequacy Guidelines 2006
- *Methods for Postdialysis 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)



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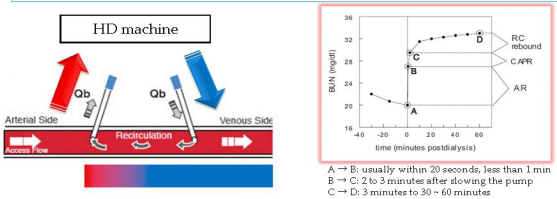

A → B: usually within 20 seconds, less than 1 min
B → C: 2 to 3 minutes after slowing the pump
C → D: 3 minutes to 30 ~ 60 minutes

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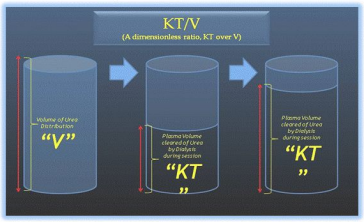
Table 6. Slow-Blood-Flow Method for Obtaining the Postdialysis Sample

A. Drawing the sample from the blood line sampling port
1. At the completion of HD, turn off the dialysate flow and decrease the UFR to 50 mL/hr, to the lowest TMP/UFR setting, or off. If the dialysis machine does not allow for turning off the dialysate flow, or if doing so violates clinic policy, decrease the dialysate flow to its minimum setting.
2. Decrease the blood flow to 100 mL/min for 15 s (longer if the bloodline volume to the sampling port exceeds 15 mL). To prevent pump shut-off as the blood flow rate is reduced, it may be necessary to manually adjust the venous pressure limits downward. At this point, proceed to obtain your sample. You can either shut off the blood pump before sampling, or leave it running at 100 mL/min while the sample is being drawn.
3. After the sample has been obtained, stop the blood pump (if not already stopped) and complete the patient disconnection procedure as per dialysis clinic protocol.
B. Method that avoids use of an exposed needle: Drawing the sample from the arterial needle tubing using a syringe or vacutainer device.
1. Proceed with steps (1) and (2) as per A above.
2. After the 15 s slow-flow period (a slow-flow period is still required to clear the small volume in the arterial needle tubing of recirculated blood), stop the blood pump. Clamp the arterial and venous blood lines. Clamp the arterial needle tubing. Disconnect the blood line tubing from the inlet bloodline, and attach either a syringe or a Vacutainer with a Luer-Lok type connection to the arterial needle tubing (or arterial port of the venous catheter). Release the clamp on the arterial needle tubing and obtain the blood sample.
3. Proceed with step (3) as in section A above.

TMP: Transmembrane pressure; UFR: Ultrafiltration rate

Take-Home Messages (1)

- 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.
  - Precise standards and goals of dialysis adequacy are based on
    - Clearance of urea, a byproduct of protein catabolism, which can be readily and accurately measured, and represented as **"KT"**
    - The volume of distribution of urea, which is neither lipophilic nor highly protein-bound, reflects total body water **"V"**.



Take-Home Messages (2)

- 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%.
  - 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.
  - Postdialysis BUN sampling is more important and sensitive procedure for an accurate estimation of dialysis adequacy than predialysis BUN sampling.