Hemodialysis Adequacy: A Complex and Evolving Paradigm

Balazs Szamosfalvi, MD
Saturday, 08/29/2009 12:15-12:45
Adequacy 1943 - 1970

- The patient survived the dialysis session
- Uremia improved
- Volume status improved
- Patient survival to recovery of kidney function or transplant

Source: http://www.homedialysis.org/learn/museum/
Adequacy 1970 - 2000

- Safe dialysis sessions in large numbers
- Good control of uremia
- Focus on small solute (urea) kinetics
- Volumetric ultrafiltration
- Patient survival on dialysis for years
- Large clinical studies and guideline development

Source: http://www.homedialysis.org/learn/museum/
Adequacy 2000 – into the future

Computer-Aided HD design and monitoring (Online Clearance)

Reduced Inflammation: Better Biocompatibility and Ultrapure dialysate

Adequacy of Dialysis

Middle Molecule Removal: Hemo-diafiltration and Internal Filtration

Blood volume monitoring for safer ultrafiltration

Daily and or long (nocturnal) dialysis for BP and Ca x P control

Increasing Focus on Cost-control

OUTCOME:
Quality of life Rehabilitation
Morbidity & Mortality
HD Adequacy

1. Definition of uremic syndrome and toxins
   - Uremic toxin removal
   - Volume homeostasis

2. Kinetic studies of solute movement
   - Solute flux studies on the dialyzer
   - Online dialyzer flux measurements and computer modeling
   - Solute flux studies in the patient
   - Computer modeling of patient solute fluxes and levels

3. Large clinical studies
   - Validate kinetic analyses
   - Inform guideline development for best dialysis practices
   - Databases: Observational evaluation of novel therapies
   - Questionnaires: Incorporate “user acceptance” into guideline development (e.g. forget 30 minute post-HD urea sampling)
Uremic toxins

I. Small (< 500 D); water soluble
   - Surrogate marker urea or sodium (ionic dialysance)
   - Rapidly produced in intracellular fluid compartment
   - Large variability in intra-patient kinetics (e.g. phosphate)

II. Middle-molecules (500 – 40,000 D); water soluble
   - B2-microglobulin, PTH, some cytokines (IL-6, TNF)
   - Optimized filter design and convection for removal
   - Complex intra-patient kinetics (generation, compartments)

III. Small (< 500 D); protein-bound
   - Poorly removed with traditional dialysis
   - Resin adsorption-based therapies are in development

European Uremic Toxin Work Group (Eutox; http://EUTox.info)
Examples of uremic toxins

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CMPF, carboxymethylpropylfuranpropionic acid; ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine.
Solute fluxes on the dialyzer

1. Nomenclature
   • Clearance and dialysance
   • Efficiency and flux (membrane area and pore size)
   • Diffusion and or convection (plus adsorption)

2. Analytical mathematical models and solutions
   • Concept of $K_0A$ and the classic diffusive clearance equation
   • Limitations of $K_0A$: effect of internal filtration and shunting
   • Bio-fouling: albumin coating, progressive clotting

3. Computer models and online measurements
   • More precise modeling of mathematically complex treatments
   • Online, multiple measurements of delivered ionic dialysance
     (precise surrogate for effective urea clearance)

Depner T and Garred L: Solute transport mechanisms in dialysis; in Replacement of Renal Function by Dialysis, 5th edition; p73-93
Nomenclature

1. Dialysance and Clearance
   - The volume of blood cleared from the concentration difference of a solute between the fresh blood and the fresh dialysis fluid entering the filter
   - Clearance: special case of dialysance when the fresh dialysate solute concentration is zero

2. Efficiency and Flux
   - Efficiency: ability to achieve large small solute clearance with high blood flows (all filters are high efficiency these days)
   - Flux: ability to achieve high middle molecule clearance and ultrafiltration rate (determined by the average pore size)

3. Diffusion and Convection
   - Diffusion: solutes move by diffusion between blocks of fluid separated by the membrane
   - Convection: solutes move en mass with a block of fluid across the membrane (more effective for moving large molecules)
B: Copyright Gambro Lundia; www.gambro.com
Diffusion and Convection 1

Figure 1. Mechanisms of solute removal in different blood purification techniques

Ronco et al: Continuous renal replacement techniques; in Replacement of Renal Function by Dialysis, 5th edition; p700
Diffusion and Convection 2

From Cheung: Hemodialysis and Hemofiltration; in Primer On Kidney Diseases, 4th edition; p465
Clearance as a function of dialysate and effective blood water flow rates and $K_0A$

$$K_D = Q_B \cdot \frac{K_0A \cdot \left(\frac{Q_D - Q_B}{Q_D Q_B}\right)}{e^{K_0A \cdot \left(\frac{Q_D - Q_B}{Q_D Q_B}\right)} - 1}$$

- $K_0A$ = mass transfer area coefficient
- $Q_B$ = effective blood water flow:
  $$Q_{Bw} = Q_B \left[0.72\gamma(Hct) + 0.93(100 - Hct)\right]/100$$
- $\gamma$ = fraction of RBC volume containing the solute
- $Hct$ = hematocrit in %
- $Q_D$ = dialysis fluid flow rate
Concept of $K_0A$

1. Mathematical construct which predicts filter clearance with clinically good accuracy
   - Incorporates solute properties
   - Incorporates fluid layer resistance to diffusion on both the blood and dialysate side of the membrane
   - Incorporates membrane resistance to diffusion

2. Limitations
   - Bio-fouling and partial clotting changes $K_0A$
   - $K_0A$ may change with blood and dialysate flow depending on filter geometry (effect of shunting, internal filtration)
   - Hemodiafiltration, partially protein-bound solutes require more complex equations
Solute Clearances by $K_0A$: Low Flux Filter

Robert W. Hamilton ; www.kidneyatlas.org
Using Clearance and $K_0$A to select Filters 1

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Product Brochures; Rexeed filter family; Manufacturer Asahi Kasei
Using Clearance and $K_0A$ to select Filters 2

The BAD Marketing Trick

The GOOD Feature

B2-microglobulin clearance of this 2.5-m² filter during dialysis (QB 400, QD 800) is as high as achieved in most hemo-diafiltration protocols.

Product Brochures; Rexeed filter family; Manufacturer Asahi Kasei
Downloadable computer models for renal replacement therapy

Figure 1 | Diagram illustrating the approach used to model solute clearances. Plasma enters (upper left) at a flow of $Q_p$. If predilution is employed, the plasma is diluted by the replacement fluid flow $Q_r$ before entering the kidney. Dialysate enters (lower right) at a flow of $Q_d$. Within the kidney, fluid is ultrafiltered from the plasma compartment to the dialysate compartment at the rate given by $Q_f$. If the treatment consists only of ultrafiltration, $Q_d$ is zero; if the treatment consists only of dialysis, $Q_f$ is zero. The problem is how to determine the rate at which solute, represented by the stippling, is transported from the plasma to the dialysate compartment. The program described here uses the common technique of assigning the kidney an arbitrary length of one unit and dividing it into a large number of parallel slices, as illustrated in the figure. The location of each slice is specified by the variable $x$, which ranges from 0 at the blood inlet to 1.0 at the blood outlet. The fluid transport rate $J_{d,x}$ in each slice is first determined based on the hydraulic pressure gradient across the kidney membrane. The local solute transport rate $J_{s,x}$ is then calculated from $J_{v,x}$ and from the membrane permeability $k$ and local solute concentrations in the plasma and dialysate compartments, $C_{p,x}$ and $C_{d,x}$. Solute transport in the kidney as a whole is determined by adding the values for $J_{s,x}$ in the individual slices.

Figure 2 | Diagram showing different patterns of ultrafiltration within the kidney. The horizontal arrows depict the direction and magnitude of the transmembrane hydraulic pressure $\Delta P$. The variation in $\Delta P$ is assumed to be linear from one end of the kidney to the other, and values for $\Delta P$ at any point can therefore be calculated from values for $\Delta P_0$ and $\Delta P_1$. The membrane is assumed to have uniform hydraulic permeability, so that the fluid transport is proportional to the transmembrane hydraulic pressure. In each of the cases illustrated, the average transmembrane hydraulic pressure is the same, so that $Q_d$, which is the sum of fluid transport along the length of the kidney, is also the same. In (a), the transmembrane pressure is uniform. Our program assumes a uniform transmembrane pressure if specific values for $\Delta P_0$ and $\Delta P_1$ are not entered. (b) The more realistic assumption that $\Delta P$ is greater at the blood inlet than at the blood outlet. Convective transport is therefore most prominent near the blood inlet and the clearance of small free solutes is very slightly higher than with uniform $\Delta P$. In (c), the change in $\Delta P$ along the kidney has increased to the point where $\Delta P_1$ is negative, so that there is ‘back filtration’ of dialysate toward the blood outlet. Back

Addis Filter Clearance Calculator

**INPUT**

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**OUTPUT**

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Heparin Anticoagulation: Scanning Electron Micrograph of Polysulfone Dialyzer Membrane

Dialysis Machine with Online Clearance

- Dialysis Machine
- Internal Balancing Chambers
- Access Catheter
- Dialyzer
- Treatment Data on Machine Display
- Conductivity Sensors
- Effluent
Online clearance measurement 1

1. Online measured small solute clearance
   - Automatically measured ionic (Na⁺) dialysance
   - Inexpensive, highly reproducible and accurate
   - Very robust, unlikely to malfunction
   - Clinically insignificant effect on the patient
   - Excellent agreement with measured urea clearance

2. Limitations
   - Slow acceptance into clinical practice
   - Has not been implemented for low (< 300 ml/min) dialysate flow
   - Does not provide urea generation or nPCR data

Fig. 1. (A) A schematic depiction of the on-line clearance monitor. (B) Typical dialysate inlet and outlet conductivity profiles and a stable blood inlet profile. The three basic conductivity dialysance equations are shown.

Obtaining the Online Clearance (OLC) Data

Press 1st

OLC Data

Press 2nd
Two-compartment variable volume solute kinetic model

\[
\frac{d(C_1 V_1)}{dt} = G - C_1(K_D + K_R) + K_C(C_2 - C_1)
\]

\[
\frac{d(C_2 V_2)}{dt} = -K_C(C_2 - C_1)
\]

Adapted from Depner T and Garred L: Solute transport mechanisms in dialysis; in Replacement of Renal Function by Dialysis, 5th edition; p85
Variable volume, single pool solute kinetic equation

\[
C(t) = C_0 \cdot \left( \frac{V_0 + \beta t}{V_0} \right)^{-\frac{K + \beta}{\beta}} + \left( \frac{G}{K + \beta} \right) \cdot \left[ 1 - \left( \frac{V_0 + \beta t}{V_0} \right)^{-\frac{K + \beta}{\beta}} \right]
\]

\(C(t)\) = systemic plasma solute concentration

\(K\) = Sum of filter (\(K_D\)) and kidney (\(K_R\)) solute clearance

\(K\) = kidney residual clearance (\(K_R\)) between dialyses

\(t\) = time from start of modeling

\(V_0\) = volume of solute distribution at start of dialysis

\(\beta\) = rate of fluid gain between and during dialyses
Coplone Dialysis Simulator 1

Dialysis Parameters
- Duration (hours): 4
- Blood Flow (mL/min): 350
- Dialysate Flow (mL/min): 500
- Koa (mL/min): 1000
- Sigma (L ± 2.1): 1
- UF to offset Fluid Gain (L/treatment): 3.5
- Additional UF (L/treatment): 0
- Postdilution (L/treatment): 0

Patient Parameters
- Hematocrit (%): 35
- Fluid Gain (L/day): 1.5
- Endogenous Clearance (mL/min): 0
- Recirculation (%): 2
- Solute Type: Urea
- Generation Rate (mg/day): 9000
- Protein Binding (%): 0

Model Parameters
- Model Type: Two Comp Ad Lib
- Volume of Distribution: Comp 1 (L): 14
- Volume of Distribution: Comp 2 (L): 28
- Intercompartmental KC (mL/min): 800
- Fluid Gain to Compartment 1 (%): 100
- Fluid Gain to Compartment 2 (%): 0

Results
- Average Clearance (mL/min): 291.1
- Time-Averaged Conc. (mg/dL): 39.65
- Average Peak Conc. (mg/dL): 61.58
- Solute Reduction Ratios: 0.77, 0.75, 0.76

The patient’s small solute kinetic volume of distribution is entered manually.
European Renal Association–European Dialysis and Transplantation Association (ERA–EDTA) QUality European STudies (QUEST) questionnaire on HD adequacy (2008)

1. Background
   - European Best Practice Guidelines 2002, 2007: eKt/V ≥ 1.2
   - NKF K-DOQI 2006: spKt/V ≥ 1.2; target spKt/V ≥ 1.4
   - European national and regional registries surveyed with about 25% response rate on HD adequacy assessment

2. Findings:
   - URR alone 37%, spKt/V 25%, eKt/V 10%, OLC 4%
   - “the results of our study show that 5 years after the publication of EBPG, there still appears to be a great variability in the procedures to measure urea removal in European HD patients. In general, with regard to this aspect, the EBPG are not well implemented.”

The National Cooperative Dialysis Study (NCDS; 1981)

1. Significance
   - First large (n=160) clinical outcomes study of dialysis\(^1\)
   - Urea TAC 100 versus 50 mg/dL
   - Treatment time = 2.5-3.5 h versus 4.5 – 5.5 h
   - Good nutrition and lower urea TAC together better
   - Showed pre-HD BUN cannot assess adequacy alone
   - Fostered urea kinetic modeling after secondary analysis\(^2\)

2. Limitations
   - Excluded diabetics, hypertensives and the elderly
   - Low power to define optimal spKt/V, missed effect of time

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1. Significance

- Large, randomized clinical outcomes study for 3x/week intermittent HD
- Compared eKt/V 1.16±0.08 versus 1.53±0.09
- Compared low-flux versus high-flux dialysis (Kβ2M 3±7 versus 34±11 ml/min)

2. Conclusions

- Patients undergoing hemodialysis thrice weekly appear to have no major benefit from a higher dialysis dose than that recommended by current U.S. guidelines or from the use of a high-flux membrane.

The HEMO (2002) Study 2

1. Subsequent commentary and analyses
   - Improved RR of mortality in women with high dose\(^1\)
   - Better outcomes with high flux for patients on HD longer
   - Trends for high dose and high flux being better noted\(^2\)

2. Various bias effects alleged and disputed
   - Prevalent HD patients used (prior treatment influence)\(^2,3\)
   - Large >100 Kg or malnourished patients excluded\(^2,3\)
   - Younger patients and more blacks included\(^2,3\)

The MPO Study (2009)

1. Significance
   - Large, randomized clinical outcomes trial for 3x/week intermittent HD for incident patients
   - Compared low versus high flux filters (Kuf, β2M-sieving coefficient) with equal urea Kt/V
   - Stratified patients based on albumin (≥4 g/dL or <4 g/dL)

2. Conclusions
   - “In summary, we did not detect a significant survival benefit with either high-flux or low-flux membranes in the population overall, but the use of high-flux membranes conferred a significant survival benefit among patients with serum albumin <4 g/dl.”¹
   - “the results of the MPO Study can be interpreted as a supporting rationale for the use of high-flux dialysis membranes if they are financially affordable.”²