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

Adequacy of Dialysis

- Better biocompatibility: Improved membranes and ultrapure dialysate
- Blood volume monitoring for safer ultrafiltration
- Reduced clotting and inflammation: Automated regional citrate anticoagulation
- Daily and or long (nocturnal) dialysis for BP and Ca x P control
- Middle molecule removal: Hemo-diafiltration and internal filtration
- Computer-aided HD design and monitoring (Online clearance)

Focus on Cost-Control

Outcome:
- Quality of Life & Rehabilitation
- Reduced Morbidity & Mortality
HD Adequacy

1. The uremic syndrome and uremic 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. New directions after the HEMO and MPO studies
   - HEMO and MPO interventions failed to improve outcomes
   - Quality control: online clearance, computerized data collection
   - Renewed interest in home dialysis: HD duration, frequency
   - New technology: internal filtration, bio-feedback systems, citrate anticoagulation
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

<table>
<thead>
<tr>
<th>Compound</th>
<th>MW</th>
<th>Compound</th>
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<tr>
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<tr>
<td>Xanthine</td>
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<td>Phenylacetylglutamine</td>
<td>264</td>
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<tr>
<td>Urate</td>
<td>168</td>
<td>β-Endorphin</td>
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<tr>
<td>Guanidinosuccinate</td>
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<tr>
<td>Indole-acetate</td>
<td>175</td>
<td>β2-Microglobulin</td>
<td>11818</td>
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</table>

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 blood 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)

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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)
Membrane Flux and Pore Size (1)

A

B

Sivasankaran Ambalavanan, Gary Rabetoy & Alfred K. Cheung; www.kidneyatlas.org
Membrane Flux and Pore Size (2)

B: Copyright Gambro Lundia; www.gambro.com
Membrane Flux and Pore Size (3)

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**

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 $K_0A$

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

- $K_0A$ = 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 $K_0A$ to select Filters 1

<table>
<thead>
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<th>REXEED-15</th>
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<td>Qd=500 ml/min</td>
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<td>Clearance mL/min</td>
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<td>Qb=300 mL/min</td>
<td>Qb=400 mL/min</td>
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Product Brochures; Rexeed filter family; Manufacturer Asahi Kasei
B2-microglobulin clearance of this 2.5-m² filter during dialysis (QB 400, QD 800) is as high as achieved in most current hemo-diafiltration protocols.
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 $Q_i$. If the treatment consists only of ultrafiltration, $Q_d$ is zero; if the treatment consists only of dialysis, $Q_i$ 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 $Q_0$, 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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<td>$Q_v$ (mL/min)</td>
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<td>$Q_u$ (mL/min)</td>
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<td>Hct (%)</td>
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<td>bound (%)</td>
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<tr>
<td>$C_{s}$ (µM)</td>
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<td>$\Delta P_r$ (torr)</td>
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<td>Solute</td>
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### OUTPUT

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<td>$Q_s$ (mL/min)</td>
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<tr>
<td>$Q_v$ (mL/min)</td>
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<tr>
<td>$C_{so}$ (µM)</td>
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<tr>
<td>$C_s$ (µM)</td>
<td>100.0</td>
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<td>$C_u$ (µM)</td>
<td>100.0</td>
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<tr>
<td>$C_r$ (µM)</td>
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<td>bound (%)</td>
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<td>$K$ (mL/min)</td>
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Heparin Anticoagulation: Scanning Electron Micrograph of Polysulfone Dialyzer Membrane

Dialysis Machine with Online Clearance
(Sodium dialysance ≈ urea clearance)

Access Catheter
Internal Balancing Chambers
Conductivity Sensors
Dialyzer
Effluent
Treatment Data on Machine Display
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.

Online clearance measurement (1)

1. Online measured small solute clearance\(^1\)
   - Automatically measured ionic (Na\(^+\)) dialysance
   - Inexpensive, highly reproducible and accurate
   - Very robust, unlikely to malfunction
   - Clinically insignificant effect on the patient serum [Na\(^+\)]
   - 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

The Nursing Staff Documents the Online Clearance (OLC) Data

Press 1st

Press 2nd

Online Clearance Data
The National Cooperative Dialysis Study (NCDS; 1981)

1. Significance
   - First large (n=160) clinical outcomes study of hemodialysis\(^1\)
   - 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

Single Pool Fixed Volume Model

Mass Balance Equation

\[ V \frac{dC}{dt} = G - C \left( K + Kr \right) \]
Single-Compartment Fixed Volume Solute Kinetic Model

Adapted from Depner T and Garred L: Solute transport mechanisms in dialysis; in Replacement of Renal Function by Dialysis, 5th edition; p85

Eq. 1: \[ V \frac{d(C)}{dt} = G - C(K_D + K_R) \]

\( (G \approx 0) \)
\( (K_R \approx 0) \)

Eq. 2: \[ C_t = C_0 \cdot e^{-\frac{K_D \cdot t}{V}} \]
Fixed Volume, Single Pool Solute Kinetic Equation

\[
C(t) = C_0 \cdot e^{-\frac{(K_D + K_R) \cdot t}{V}} + \frac{G}{K_D + K_R} \cdot \left(1 - e^{-\frac{(K_D + K_R) \cdot t}{V}}\right)
\]

- \(C(t)\) = systemic plasma solute concentration
- \(K = \text{Sum of filter (}K_D\text{) and kidney (}K_R\text{) urea clearance during hemodialysis}\)
- \(K = \text{kidney residual clearance (}K_R\text{)}\)
- \(t = \text{time from start of modeling}\)
- \(V_0 = \text{volume of solute distribution at start of dialysis}\)
Online measurement of effective dialyzer small solute clearance and treatment effectiveness measured as Kt/V.

\[ Kt/V = \frac{(\text{dialyzer clearance} \times \text{treatment time})}{\text{patient’s water volume (L)}} \sim 0.45-75 \times \text{pt weight (Kg)} \]
The HEMO Study (2002)

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. Conclusions¹
   - “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 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

Improving Biocompatibility

1. Technology improvements
   - Novel membranes with biocompatible inner skin
   - Ultrapure dialysate generation

2. Regional citrate anticoagulation (RCA)
   - Has the potential to eliminate blood clotting 100%
   - Maintains filter performance in long dialysis
   - Blocks WBC, PLT and complement activation in the extracorporeal circuit
   - Avoids systemic bleeding tendency or true toxicity

---

Heparin versus Citrate

Online Clearance Measurement (2)

Clinical uses of online ionic dialysance (Kecn)

- Continuous, automated HD quality (adequacy) monitoring tool
- Document small solute clearance several times, every treatment
- Detect partial clotting through decline of Kecn
- Measure access flow; detect reduced clearance due to access recirculation
- Detect reverse cannulation of loop grafts
- Adjust therapy to achieve targeted URR

Troubleshooting a Low Kecn or Kt/V

Online Hemodiafiltration (olHDF)

1. Combines dialysis with (usually) post-dilution hemofiltration
   - Better middle molecule clearance
   - Replacement fluid generated online (not available in US)
   - More complex equipment with higher costs

2. DOPPS observational study (2006)
   - “After adjustment, high-efficiency HDF patients had a significant 35% lower mortality risk than those receiving low-flux HD (relative risk=0.65, P=0.01). These observational results suggest that HDF may improve patient survival independently of its higher dialysis dose.

3. Dutch Convective Transport Study (Contrast)
   - Randomized, controlled olHDF trial until 12/2010

Internal Filtration: Filter Design

- Large uniform pore size with very high Kuf and minimal resistance to the transfer of β2M\(^{1,2,3}\)
- New dialysate flow pathway design reduces stagnant dialysate layers and shunting\(^{1,2}\)
- New blood header improves flow distribution in the fiber bundle\(^1\)
- New fibers with reduced internal diameter, wall thickness and wavy structure\(^{1,2}\)
- QD can be reduced 30% without a reduction in \(K_D\) (QD≤500 ml/min)

A: from Depner T and Garred L: Solute transport mechanisms in dialysis; in Replacement of Renal Function by Dialysis, 5th edition; p85
Two-Compartment Variable Volume Solute Kinetic Model

\[
\begin{align*}
\frac{d(C_1 V_1)}{dt} &= G - C_1(K_D + K_R) + K_C(C_2 - C_1) \\
\frac{d(C_2 V_2)}{dt} &= -K_C(C_2 - C_1)
\end{align*}
\]

Adapted from Depner T and Garred L: Solute transport mechanisms in dialysis; in Replacement of Renal Function by Dialysis, 5th edition; p85
1. **Computer modeling**
   - Indispensable to visualize effects of $K_D$, frequency ($f$), duration ($t$), compartment sizes ($V_{12}$), inter-compartmental mass transfer coefficient ($K_C$), and solute generation rate ($G$)
   - Only as accurate as the model; results need clinical validation

2. **Specific solutes of interest**
   - Phosphate: multi-compartmental complex kinetics
   - B2-microglobulin: improved $K_D$ (olHDF), low $K_C$
   - Myeloma light chains: effects of dialyzer, $V$ and $K_C$
   - Cytokine mobilization with convection and adsorption
   - Creatinine and other non-protein bound plasma solutes

---

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 during hemodialysis

\( K \) = 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\textsuperscript{1}: Solute with Low $K_D$ and Low $K_C$\textsuperscript{2}

Conventional HD
3 x 3.5 hours
$K_D = 57$ ml/min

Daily Short HD
6 x 2.5 hours
$K_D = 57$ ml/min

Daily Nocturnal HD
6 x 7 hours
$K_D = 49$ ml/min

$G = 140$ mg/day
$K_C = 70$ ml/min
$V_1/V_2 = 3.5/10.5$ L

\begin{tabular}{|c|c|}
\hline
Average Clearance (mL/min) & 48.7 \\
Time-Averaged Conc. (mg/dL) & 1.11 \\
Average Peak Conc. (mg/dL) & 1.50 \\
\hline
\end{tabular}

Solute Reduction Ratios

Daily Nocturnal Hemodialysis (DNHD)

1. **Benefits**
   - Provides the best solute removal of all modalities
   - The patient can sleep through the therapy overnight
   - Excellent BP control, BP medications reduced
   - Excellent phosphate control, P-binders often stopped\(^1\)
   - Survival may be comparable to cadaveric renal Tx\(^2\)

2. **Barriers to use**
   - Requires a very motivated patient (≈ 5% of HD population)
   - Significant safety concerns limit utilization
   - Access venous connection monitoring and effective, safe anticoagulation is needed
   - A dedicated, GOOD home nocturnal HD machine should have been developed at least 10 years ago!

---


1. **Observation**
   - Cost of 3x/week in-center HD has shown explosive growth
   - No government wants to spend more per patient

2. **In-center HD cost-effectiveness study and subsequent editorial**
   1. “In conclusion, given the extraordinarily high costs of the ESRD program, the viability of more frequent hemodialysis strategies depends on significant improvements in the economic model underlying the delivery of hemodialysis.”
   2. A subsequent editorial raised the issue of even funding clinical studies for >3x/week in center HD considering the projected 75,000-125,000 USD cost/per quality life-year gained

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