Dialysis Dosing: Kinetics Versus Physiology

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Disclosure of Interests

- NxStage European Medical Advisory Board
Estimated number of patients undergoing RRT from 2010 to 2030 **worldwide (A)** and by region (B)

Expected remaining lifetime (years) of the general population (cohort 2011-2015) and of prevalent dialysis and transplant patients (cohort 2011-2015)
Unadjusted percentages of deaths in 2014 by cause, excludes missing/unknown causes of death data among dialysis patients

Cardiovascular disease > 50%

Abbreviations: ASHD, atherosclerotic heart disease; AMI, acute myocardial infarction; CHF, congestive heart failure; CVA, cerebrovascular accident.
Dialysis Therapy

**SOLUTES CLEARANCE**
- Uremic Toxins
- Electrolites Regulation
- Acid–base Balance
- Calcium–phosphate control

**HORMONE PRODUCTION**
- Red blood cell mass regulation
- Vitamin D regulation
- Others

**VOLUME HOMEOSTASIS**
- Fluid Overload
- Blood pressure control
Dialysis Therapy

SOLUTES CLEARANCE
- Uremic Toxins
- Electrolites Regulation
- Acid–base Balance
- Calcium–phosphate control

VOLUME HOMEOSTASIS
- Fluid Overload
- Blood pressure control

Ability for solute clearance, frequency and therapy duration

Convensional Hemodialysis
Peritoneal dialysis
Hemodiafiltration technologies
Intensive Hemodialysis

KDIGO
“From an **idealistic** clinical perspective, an **adequately** treated **dialysis patient** is physically active, well nourished, euvolemic and normotensive, with a maintained good quality of life and a life expectancy that is **not inferior** to that of **healthy** patients”\(^1\)

The marker of dialysis adequacy has been typically determined just by measuring small solute clearance, based on urea removal.

Urea kinetics modeling has been taken as a paradigm of all uremic toxins; but now it is clear, that urea removal is not very similar to kinetics of other retention solutes.

Calculation of the index of urea clearance (Kt/Vurea) has been the principal tool to estimate dialysis dose, correlated with clinical outcomes for more than 30 years.
Relevant studies have changed dialysis adequacy over the years

Dialysis sessions were long procedures 20-40 h/week

- Time was a “prime measure” in the concept of dialysis adequacy

First serious approach to quantify dialysis

- Wolf et al

Hypothesis “Square meter hour”

- Babb et al

Equilibrated Kt/v

- by Daugirdas

URR

- by Lowrie

CANUSA Study

HEMO Study

NECOSAD EAPOS Study

Alberta Nocturnal Trial

FHN Trials


RRF and total UF important factors in PD adequacy

More attention has turned to alternative dialysis schedules

Adequacy HD target spKt/v 1.4 until now!!!

Adequacy PD target weekly Kt/v 1.7 until now!!!

Time on dialysis was less important, as long as urea clearance reached the target

Urea clearance index (Kt/Vurea) became the marker of dialysis adequacy until today!

1949

First HD in North America Performed by Murray

1983

NCDS Study

2002

ADEMEX Trial

2003

Hong Kong Study (Lo et al)

2008

MPO Study

2012

CONTRAST

- Technological improvements
- New convective modalities

2018

KDIGO

KDIGO

KDIGO

KDIGO

MEDICARE ESRD

ESHOL Turkish HDF

2015

2018
Adequacy Guidelines

Kt/Vurea
Dialysis Adequacy

Where are we Now?
Prescription - Actual Situation

Achieved dialysis session length, continuous
National sample

Prescribed dialysis sessions per week
National sample

USRDS Annual Data Report 2017
US-DOPPS Practice Monitor, August 2017; http://www.dopps.org

Facility sample transitioned from DOPPS 4 to 5 in Jan-Apr 2012 (see “Study Sample and Methods”).
Facility sample transitioned from DOPPS 5 to 6 in Mar-Jul 2013 (see “Study Sample and Methods”).
Percentage of prevalent hemodialysis and peritoneal dialysis patients meeting clinical care guidelines for dialysis adequacy, by modality

- Percentage of patients with HD Kt/V >=1.2: > 80%
- Percentage of patients with PD Kt/V >=1.7: > 80%
Adequacy - Actual Situation

Single-pool Kt/V, continuous
National sample

Among patients with >365 days on dialysis
Facility sample transitioned from DOPPS 4 to 5 in Jan-Apr 2012 (see "Study Sample and Methods").
Facility sample transitioned from DOPPS 5 to 6 in Mar-Jul 2015 (see "Study Sample and Methods").

Guidelines
spKt/v 1.2-1.4

US-DOPPS Practice Monitor, August 2017; http://www.dopps.org
Sudden Cardiac Death - Actual Situation

From the 2016 Peer Kidney Care Initiative Report

Annual rates of all-cause cardiovascular mortality and sudden cardiac death in maintenance dialysis patients.

From the 2016 Peer Kidney Care Initiative Report

Annual rates of hospitalizations with primary discharge diagnosis of heart failure/cardiomyopathy or fluid overload for incident and prevalent maintenance dialysis patients.

Blood Pressure Control - Actual Situation

Pre-dialysis systolic blood pressure, remained relatively unchanged from 2010 to 2017

Pre-dialysis systolic blood pressure, categories
National sample

Facility sample transitioned from DOPPS 4 to 5 in Jan-Apr 2012 (see "Study Sample and Methods"). Facility sample transitioned from DOPPS 5 to 6 in Mar-Jul 2015 (see "Study Sample and Methods").

US-DOPPS Practice Monitor, August 2017; http://www.dopps.org
Serum phosphate levels remained relatively unchanged from 2010 to 2017

Serum phosphorus (most recent), categories
National sample

Most recent (single) monthly value
Facility sample transitioned from DOPPS 4 to 5 in Jan-Apr 2012 (see "Study Sample and Methods"). Facility sample transitioned from DOPPS 5 to 6 in Mar-Jul 2015 (see "Study Sample and Methods").
Health-related Quality of life – Actual Situation

No significant improvements in Mental and Physical Component of HRQL.

SF-12 Mental Component Summary score, categories
National sample

SF-12 Physical Component Summary score, categories
National sample

All DOPPS participants are asked to complete a questionnaire once a year. Participants who complete the questionnaire tend to be somewhat younger and healthier compared to non-respondents. Therefore results may not be representative of the US hemodialysis population overall.

Facility sample transitioned from DOPPS 4 to 5 in Jan–Apr 2012 (see "Study Sample and Methods"). Facility sample transitioned from DOPPS 5 to 6 in Mar–Jul 2015 (see "Study Sample and Methods").

US-DOPPS Practice Monitor, August 2017; http://www.dopps.org
Adjusted mortality (deaths per 1,000 patient-years) by calendar year, treatment modality, and comorbidity among ESRD patients and comorbidity-specific Medicare populations aged 65 & older, 1996-2015
Is \( \text{Kt/V}_{\text{urea}} \) an \textbf{adequate} marker of dialysis adequacy?
Once upon a time in dialysis: the last days of Kt/V?

Raymond Vanholder, Griet Glorieux, and Sunny Eloit

Evidence

Does the Adequacy Parameter Kt/V_{urea} Reflect Uremic Toxin Concentrations in Hemodialysis Patients?

Sunny Eloit, Wim Van Biesen, Griet Glorieux, Nathalie Neirynck, Annemieke Dhondt, Raymond Vanholder

A broader concept of adequacy is required!!

Kt/V_{urea} alone is not enough!!

KDIGO

Effect of Treatment Duration and Frequency on Uremic Solute Kinetics, Clearances and Concentrations

John K. Leyboldt and Björn K. I. Meljster

The Use of a Multidimensional Measure of Dialysis Adequacy—Moving beyond Small Solute Kinetics

Jeffrey Perl, Laura M. Demer, Joanne M. Bargman, Teri Browne, David M. Charytan, Jennifer E. Flythe, LaTonya J. Hickson, Adriana M. Hung, Michel Jaffee, Timmy Chang Lee, Klemens B. Meyer, Hamid Moradi, Tariq Shali, Isaac Teitelbaum, Leslie P. Wong, and Christopher T. Chan, and on behalf of the American Society of Nephrology Dialysis Advisory Group

Personal viewpoint: Limiting maximum ultrafiltration rate as a potential new measure of dialysis adequacy

John W.M. Agar

Department of Renal Medicine Barwon Health, University Hospital, Geelong, Victoria, Australia
Evidence

Kt/Vurea alone is not enough!!

A broader concept of adequacy is required!!

Seminars in Dialysis

A Sad but Forgotten Truth: The Story of Slow-Moving Solutes in Fast Hemodialysis

Sunny Eloot, Wim Van Biesen, and Raymond Vanholder
Nephology Section, Department of Internal Medicine, Ghent University Hospital, Gent, Belgium

2012

Progress in Dialysis Practice

Dialysis Dosing for Chronic Hemodialysis: Beyond Kt/V

John T. Daugirdas
Department of Medicine, University of Illinois, Chicago, Illinois

2014

The International Journal of Artificial Organs / Vol. 27 / no. 6, 2004 / pp. 452-466

Review

2004

Short, thrice-weekly hemodialysis is inadequate regardless of small molecule clearance

Z.J. TWARDOWSKI
Division of Nephrology, Department of Medicine, University of Missouri, Columbia, Missouri - USA


Survival as an index of adequacy of dialysis

BERNARD CHARRA, EDOUARD CALEMARD, MARTIAL RUFFET, CHARLES CHAZOT, JEAN-CLAUDE TERRAT, THIERRY VANEL, and GUY LAURENT

Centre de rein artificiel, Tassin, France
Acid–base Balance

Electrolyte Regulation
Key: Blue box = VOLUME HOMEOSTASIS
Key: Green box = Uremic Toxins

SOLUTES CLEARANCE

Kt/Vurea

HORMONE PRODUCTION

Red blood cell mass regulation
Vitamin D regulation
Others

Fluid Overload
Blood pressure control

Calcium–phosphorus control
Major Unmet Clinical Needs

1. High risk of **cardiovascular morbidity and mortality**
   - Persistent hyperphosphatemia
   - Left ventricular hypertrophy and heart failure
   - Persistent hypertension
   - Limited tolerability of conventional hemodialysis treatment
   - Arrhythmias & Sudden Death

2. Diminished **quality of life**
   - More uremic toxins than urea
   - Persistent volume overload
   - Persistence Long Interdialytic Interval
“It is important to distinguish adequacy of the dialysis from adequacy of patient care”.

We should focus on the patient, and focus on other dialysis parameters, if we want to increase dialysis adequacy and improve our patients’ outcomes.

1. KDOQI. Am J Kidney Dis. 2015
Which other parameters could be important to measure dialysis adequacy in order to improve our patients’ outcomes?
The high incidence of cardiovascular morbidity and mortality in dialysis patients is multifactorial.
The **uremic syndrome** is the consequence of the retention of more molecules than urea alone.

Retention solutes of middle molecular size, play an important role in the pathogenesis of the uremic state which contributes to the high mortality of dialysis patients.

- **High-flux membranes**
- **Convection therapies**
- **Increasing dialysis duration**

Leypoldt JK et al. Seminars in Dialysis 2016
Ronco C. Expanded Hemodialysis. Basel, Karger, 2017
The **uremic syndrome** is the consequence of the retention of **more molecules than urea** alone.

Retention solutes of **middle molecular size**, play an **important role** in the **pathogenesis** of the **uremic state** which contributes to the **high mortality** of dialysis patients.

**We are not measuring other Uremic Toxins**

**Kt/Vurea as adequacy target**
The kinetics of intradialytic phosphate removal, differ significantly from classic urea kinetics.

- Despite low molecular weight, its elimination is similar to a middle molecule:
  - Large distribution space, and its difficulty moving from the intracellular space

- At the beginning of dialysis session there is a decrease in serum levels, but then because of mobilization of phosphate from the intracellular space, serum phosphate reaches a constant level

Phosphate needs more time than urea to decrease in serum levels and its removal is directly related to dialysis duration and frequency

Kuhlmann M. Blood Purif 2010.
Daugirdas J.T, Seminars in Dialysis, 2015
Gutzwiller, JP et al.. Nephrol Dial Transplant 2017
The **kinetics** of intradialytic **Beta-2-microglobulin** removal **differ significantly** from **urea kinetics**, and is the **general marker** for **middle molecules**

- **Middle molecules removal** is limited in **short sessions**, because of their **slower** inter-compartmental equilibration rates

- **Residual renal function** is the most important factor that **increases its elimination**

In **anuric patients**: The **dialyzer clearance** and the **weekly treatment duration** are the most important factors related to **its removal**
Dialysis Adequacy

Kt/v Urea Clearance
Small Molecules

Adequacy Parameters

Kt/v B2 $^1$
Clearance
Middle Molecules

Phosphate Serum
Normal levels

Surrogate parameters of middle molecules clearance

Cardiovascular Morbidity

The high incidence of **cardiovascular morbidity and mortality** in dialysis patients is **multifactorial**.

**Risk Factors for Cardiovascular Disease in Chronic Kidney Disease**

- **Traditional Risk Factors**:
  - Age
  - Male sex
  - Hypertension
  - Smoking
  - Left ventricular hypertrophy
  - Diabetes
  - Dyslipidemia

- **Novel and Uremia-Related Risk Factors**:
  - Inflammation
  - Oxidative stress
  - Endothelial dysfunction
  - Anemia
  - Vascular calcification
  - Uremic bone disease
  - Sympathetic activation
  - Subclinical hypothyroidism
  - Protein-energy wasting
  - Insulin resistance
  - Uremic toxins
  - Fat mass: adipokine imbalance
  - Genetics
  - Adipose tissue
  - Coagulation disorders
  - Atherosclerotic plaque

**References**:
Volume Overload

Fluid overload is a major cause of morbidity and mortality in ESRD population.

Volume has been largely ignored, because solute clearance has been the major issue in dialysis adequacy goals.
How do we remove all that volume?

- **Inadequate** response to decreased intravascular volume, when ultrafiltration rate exceeds plasma refilling rate.

- There is an **association** between rapid ultrafiltration and increased mortality.

- The **safety and tolerability** of the dialysis procedure is related to the ultrafiltration rate, which is determined by the **interdialytic weight gain** and **length** of each session.

Dialysis **duration** and **ultrafiltration rate** are **tightly related**.
"Volume First Initiative" materializes the next best chance to improve patients’ outcomes.

Extending treatment time or frequency is an effective way to address volume control and tolerance of dialysis sessions, with less dialysis-related morbidity and mortality.

John W M AGAR. Hemodialysis International 2015
Kt/v B2 clearance middle molecules
Kt/v Urea Clearance Small Molecules
Phosphate Serum Normal levels

Surrogate parameters of middle molecules clearance
Dialysis Adequacy

- Phosphate Serum Normal levels
- Kt/v B2 Clearance Middle Molecules
- Kt/v Urea Clearance Small Molecules
- Extracellular volume Blood Pressure Normal Values
- Fluid Removal UF rate < 10–7 ml/kg/h

Surrogate parameters of volume control
Leading cause of death in patients on maintenance dialysis, mainly related to volume shifts and electrolyte disorders.

Long Interdialytic interval is an important risk factor for sudden Cardiac Death

Has not been addressed with Conventional HD prescription

1. USRDS Annual Data Report 2017
**Sudden Cardiac Death**

**Modifiable risk factors** for Sudden Cardiac Death in **dialysis patients**, related to **dialysis procedure**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dietary counseling for potassium and fluid gain</td>
<td>Bleyer et al.(^{10})</td>
</tr>
<tr>
<td>2. Individualize and adjust potassium bath at least monthly for each patient, consider point-of-care devices to measure potassium on a more regular basis</td>
<td></td>
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<tr>
<td>3. Do not use dialysate potassium concentration &lt; 2 mEq/L, particularly if predialysis potassium &lt; 5 mEq/L; if patients present with high serum potassium levels, consider extending the dialysis time, but do not lower dialysate potassium concentration to &lt; 2 mEq/L</td>
<td>Kamik et al.,(^{15}) Pun et al.,(^{14}) Kovesdy et al.,(^{13}) Jadoul et al.(^{12})</td>
</tr>
<tr>
<td>4. Consider the use of dialysate potassium profiling (i.e., start with dialysate concentration of 4 mEq/L and gradually reduce it during the treatment to 2 mEq/L) when predialysis potassium level is ≤ 6.5 mEq/L</td>
<td>Redaelli et al.(^{23})</td>
</tr>
<tr>
<td>5. Adjust dialysate bicarbonate concentration to achieve a target predialysis bicarbonate of 20-22 mEq/L and reduce the risk of severe intradialytic alkalosis</td>
<td>Heguilen et al.(^{22})</td>
</tr>
<tr>
<td>6. Reduce the risk of high ultrafiltration rate (&gt; 10 mL/kg/h) by sustaining dialysis time &gt; 4 h</td>
<td>Flythe et al.,(^{32}) McIntyre et al.,(^{30}) Burton et al.(^{31})</td>
</tr>
<tr>
<td>7. Measure magnesium monthly and supplement magnesium if needed</td>
<td>Sakaguchi et al.(^{28})</td>
</tr>
<tr>
<td>8. Do not use dialysate calcium concentration &lt; 2.25 mEq/L (and preferably maintain at 2.5 mEq/L), particularly in combination with a low potassium bath in patients at high risk of arrhythmias</td>
<td>Genovesi et al.,(^{10}) Pun et al.(^{29})</td>
</tr>
<tr>
<td>9. Avoid the use of digoxin for heart failure or control of atrial fibrillation in hemodialysis patients, and if unavoidable, consider using a higher potassium bath</td>
<td>Chan.(^{33})</td>
</tr>
<tr>
<td>10. Be aware of medications that prolong QTc interval, which may be prolonged further by rapid shift in potassium, calcium, and magnesium concentrations</td>
<td>Data from the general population(^{34-36})</td>
</tr>
</tbody>
</table>

*Hung A et al. Am J Kidney Dis. 2015*
Modifiable risk factors for Sudden Cardiac Death in dialysis patients, related to dialysis procedure.

**Summary of Procedures and Techniques to Reduce Risk of Sudden Cardiac Death in the Hemodialysis Population**

1. Dietary counseling
2. Individualize and use point-of-care device
3. Do not use dialysis with potassium < 3.5 mmol/L; consider external concentration
4. Consider the use of 4 mEq/L antecedent predialysis potassium
5. Adjust dialysate potassium to 20-22 mEq/L
6. Reduce the risk of arrhythmia
7. Measure magnitude
8. Do not use dialysis with potassium at 2.5 mEq/L or higher risk of arrhythmia
9. Avoid the use of beta-blockers in patients, and
10. Be aware of medications that prolong QTc interval, which may be prolonged further by rapid shift in potassium, calcium, and magnesium concentrations.

**Avoid rapid electrolyte and volume shifts during dialysis sessions**

1. **Adjust** dialysate composition
2. **Adjust** ultrafiltration rate
Dialysate composition is a **critical aspect** of the **dialysis prescription**, if we want to **avoid rapid electrolyte shifts**.¹

Often, the concentrations of **key components** may be determined by default, based on **dialysate manufacturer specifications** or hemodialysis **facility practices**.²

Dialysate should be considered “as a drug to be adjusted” to the individual **patient’s needs**.

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The electrolyte composition of dialysate is important for fluid management, hemodynamic tolerance and prevention of arrhythmias.

**One-size-fits-all approach is not appropriate!**

1. Avoid **positive sodium** balance
2. Avoid **positive calcium** balance
3. Avoid **high potassium** gradient
4. Avoid **low concentration**:  
   - Magnesium < 1 mEq/L  
   - Calcium < 2 mEq/L  
   - Potassium < 2 mEq/L
5. Normalized **pre-HD bicarbonate serum** levels in range of > 22 < 26 mmol/l
6. Adjust **Potassium, Calcium and Phosphate concentration** in nocturnal regimens

**Electrolyte** composition of **dialysate** is important for fluid management, hemodynamic tolerance and prevention of arrhythmias.}

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Importance</th>
<th>Recomendation</th>
</tr>
</thead>
</table>
| Dialysate sodium concentration       | Related with:  
• Management of volume control  
• Hemodinamic tolerance | Prescribed in the range of 134-138 mEq/L, with deviations based on individual patient circumstances. Avoid positive sodium balance. |
| Dialysate potassium concentration    | Arrhythmias and cardiac death                   | Individualize concentration to avoid high K gradient. Minimum concentration 2-3 mEq/L. Maximum concentration < 2 mEq/L. Potassium concentration < 2 mEq/L. Dialysis should be 3 mEq/L. |
| Dialysate bicarbonate concentration  | Related with:  
• Management of volume control  
• Hemodinamic tolerance | Normalized pre-HD bicarbonate serum levels in range of 22 to 26 mmol/l. Adjust concentration. Avoid positive calcium balance. Minimum concentration 2,5 -3 mEq/L. Maximum concentration < 2 mEq/L. Calcium concentration < 2 mEq/L. Dialysis should be 3 mEq/L. |
| Dialysate calcium concentration      | Related with:  
• Intradialytic hypotension  
• Vascular calcification | Avoid calcium balance. Minimum concentration < 2 mEq/L. Calcium concentration < 1 mEq/L. Nocturnal dialysis should be 3 mEq/L. |
| Dialysate magnesium concentration   | Arrhythmias and cardiac death                   | Avoid low concentration: Magnesium < 1 mEq/L. Calcium < 2 mEq/L. Potassium < 2 mEq/L. |

Dialysis Adequacy

- Phosphate Serum Normal levels
- Kt/v B2 Clearance Middle Molecules
- Kt/v Urea Clearance Small Molecules
- Extracellular volume Blood Pressure Normal Values
- Fluid Removal UF rate < 10 ml/kg/h
- Individualize Dialysate Composition

Surrogate parameter of electrolyte balance
Preservation of RRF has been considered an important aspect of peritoneal dialysis adequacy, and should be considered in hemodialysis practice too.

Sustaining RRF is important for the dialysis patient because:
- Increases clearances of middle molecule and protein bound toxins
- Reduces inter-dialytic weight gains
- Increases blood pressure control
- Reduces inflammatory markers
- Is associated with better nutrition status
- Is associated with better quality of life

• Novel markers of renal function may provide alternative methods of estimating RRF, which may simplify its measurement

We cannot underestimate the maintenance of residual renal function in HD patients

We must try to preserve it!
We should measure it!

Beneficial effects extend to very low levels

RRF is strongly associated with improvement in survival

Shafi et al. Kidney Int. 2017
Davenport A. Hemodialysis International 2017
Tangvoraphonkchai et al. Seminars in Dialysis 2017
Dialysis Adequacy

Surrogate parameters
- small and middle molecules clearance

Determinant factor helps achieving adequacy goals

Broader Concept of Dialysis Adequacy

KDIGO
Dialysis Adequacy

Dialysis adequacy cannot be a concept of clearance of small solutes alone, but a concept that concerns other factors related to patient survival.

Broader concept of Dialysis Adequacy

Surrogate parameters:
- Volume control
- Electrolyte shift

Determinant factor helps achieving adequacy goals

Surrogate parameters:
- Small and middle molecules clearance

Phosphate Serum Normal levels

Kt/v Urea Clearance Small Molecules

Extracellular volume Blood Pressure Normal Values

Persistance Residual Renal Function

Individualize Dialyisate Composition

K/DOQI
How do we achieve this broader concept of adequacy?

“We must change, not only what we are going to measure related to dialysis parameters, but also the way we are going to prescribe dialysis.”

“Adequate dialysis schedule”
How do **we achieve this broader concept** of adequacy?

**Short**

3 session/week

Conventional HD prescription

Is not **adequate**!!

This prescription **is the minimum treatment necessary to maintain life**, but it is **inadequate** in preventing **dialysis-related complications** and in **improving outcomes** ¹

¹ Y Watanabe et al. Ther Apher Dial, 2015
Short, thrice-weekly hemodialysis is inadequate regardless of small molecule clearance.

Z.J. Twaradowski
Division of Nephrology, Department of Medicine, University of Wisconsin

This way of thinking is not new!

Advantages of long dialysis

From the above discussion, the advantages of long dialysis to the patients are obvious: better tolerance of dialysis, better control of blood pressure, better removal of middle molecules, better rehabilitation, and longer survival.
The **goal of dialysis** is to **restore the body’s intracelluar and extracelluar fluid environment toward** that of **healthy individuals** with functioning kidneys to the **greatest extent possible**.¹

Conventional HD is far from **fluid and solute removal** performed by **healthy kidneys**

---

1. Brenner and Rector’s The Kidney, 2011
2. www.AdvancingDialysis.org
PD provides similar dialysis dose (standardized weekly Kt/V) to that of thrice-weekly HD prescription, despite less efficient small-solute clearance

Because it is a continuous and frequent treatment, (compared with conventional HD), PD provides:

- More physiological clearance of solutes and water, with less fluid and electrolyte shifts
- Less interdialytic oscillations
- More clearance of middle molecules
- Better preservation of residual renal function

PD could offer a number of advantages over conventional HD, at least during the first 2-3 years when patients maintain residual renal function

The goal of dialysis is to restore the body’s intracellular and extracellular fluid environment toward that of healthy individuals with functioning kidneys to the greatest extent possible.1

Do we think that it is enough to replace only 10-15% of healthy kidney function?

2. www.AdvancingDialysis.org
What else should we do, if we want to increase dialysis dose?
1. More **solute removal**

We still don’t know which solutes we SHOULD remove,

As well as

we still don’t know, which solutes we SHOULD NOT remove!!
More Solute Removal

Convective therapies provide:
- Better middle molecule clearance
- Increase removal of inflammatory mediators
- More hemodynamic stability
- Possibly better cardiovascular outcome with high substitution volume (> 20 L per session)

Effect of Hemodiafiltration or Hemofiltration Compared With Hemodialysis on Mortality and Cardiovascular Disease in Chronic Kidney Failure: A Systematic Review and Meta-analysis of Randomized Trials

Authors’ conclusions

Convective dialysis may reduce cardiovascular but not all-cause mortality and effects on nonfatal cardiovascular events and hospitalisation are inconclusive. However, any treatment benefits of convective dialysis on all patient outcomes including cardiovascular death are unreliable due to limitations in study methods and reporting. Future studies which assess treatment effects of convection dose on patient outcomes including mortality and cardiovascular events would be informative.
In this analysis, data from participants in seven European countries (Belgium, France, Germany, Italy, Spain, Sweden and the UK) in DOPPS Phase 4 (2009–11) and Phase 5 (2012–15) were used.

Conclusions. Our results do not support the notion that HDF provides superior patient survival. Further trials designed to test the effect of high-volume HDF (versus lower volume HDF versus HD) on clinical outcomes are needed to adequately inform clinical practices.
What should we do?

1. More **solute removal**
   - More frequent and/or longer sessions

2. More **volume control**
   - More Weekly Treatment Time!

More frequent and/or longer sessions
Longer sessions

Survival as an index of adequacy

Bernard Charra, Edouard Calemard, Martial Reif, Jean-Claude Terrat, Thierry Vanel, and...

Centre de rein artificiel Tassin, France

Tassin's artificial kidney center's experience

This group reported one of the best dialysis survival estimates of any program or registry

This evidence is not new!

Eight hours of dialysis three times/week (24 hours/week) (Kt/V of 1.67)

Blood Pressure Control

Effects of Intensive HD vs conventional HD on predialysis systolic blood pressure in FHN Daily Trial, FHN Nocturnal Trial, and Canadian Nocturnal Trial.

Effects of **Intensive HD vs conventional HD** on **regression of left ventricular mass** in FHN Daily Trial, FHN Nocturnal Trial, and Canadian Nocturnal Trial.
Intradianlytic Hypotension

Incidences of levels I, II, and III intradialytic hypotension for Intensive HD versus conventional HD in the FHN Daily Trial and the FHN Nocturnal Trial.

2. www.AdvancingDialysis.org
Effects of **Intensive HD vs conventional HD** on **serum phosphate levels** in FHN Daily Trial, FHN Nocturnal Trial, and Canadian Nocturnal Trial.

2. AdvancingDialysis.org
Effects of **Intensive HD vs conventional HD on the physical and mental health composite score** in FHN Daily Trial, FHN Nocturnal Trial, and Canadian Nocturnal Trial.
Intensive HD

Using data from two regional Nocturnal HD programmes from Canada and the USRDS from 1994 to 2006, performed a matched cohort study comparing survival between NHD and deceased and living donor kidney transplantation.

Survival by treatment modality

IHHD was defined as ≥ 4 dialysis/week or ≥20 hours per week

Pauly r et al. NephrolDial Transplant. 2009
Nishio Lucar et al. ASN Kidney Week. New Orleans 2017
Survival and Hospitalization for Intensive Home Hemodialysis Compared with Kidney Transplantation

Canadian patients receiving intensive home hemodialysis (IHHD; ≥16 hours per week) vs kidney transplant

**Time-to-death or treatment failure** comparing IHHD patients and kidney transplant recipient subtypes

**Time to first hospitalization** comparing IHHD patients and kidney transplant recipient subtypes

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Number of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHHD</td>
<td>43</td>
</tr>
<tr>
<td>LD</td>
<td>97</td>
</tr>
<tr>
<td>SCD</td>
<td>105</td>
</tr>
<tr>
<td>ECD</td>
<td>40</td>
</tr>
</tbody>
</table>

More frequent and longer dialysis prescription is the dialysis option that more closely mimics the kidney's function.
Why do we continue prescribing Short 3 sessions/week for the majority of our patients?
This is not the result of demonstrated clinical superiority of the prescription but it is the result of increasing financial and logistical pressures.  

Policy makers must work with the renal professional, to ensure that financing approaches to control costs, do not adversely impact the quality of care.

Why do we continue prescribing Short 3 sessions/week for the majority of our patients? This is not the result of demonstrated clinical superiority of the prescription but it is the result of increasing financial and logistical pressures.

Policy makers must work with the renal professional, to ensure that financing approaches to control costs, do not adversely impact the quality of care.


Is it time to change?
Relevant studies that have changed dialysis adequacy over years.

First serious approach to quantifying dialysis
Wolf et al

1951

Hypothesis “Square meter hour”
Babb et al

1971

Equilibrated Kt/v
Daugirdas

1990s

URR by Lowrie

1996

CANUSA Study

1999

HEMO Study

2002

NECOSAD Study

2003

ADEMEX trial

2002

Hong Kong Study
(Lo et al)

2003

Alberta Nocturnal Trial

2007

FHN Trials

2010-2011

ESHOL Turkish HDF

2013

Last Guidelines

2015

2018

First HD in North America
Performed by Murray

1949

NCDS Study

1983

Kt/v urea as the only adequacy parameter
Is not enough!!

Conventional HD Short thrice-weekly
Is not enough!!

KDIGO
Dialysis Adequacy

Relevant studies that have changed dialysis adequacy over years:

- **First serious approach to quantifying dialysis**
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- **1996**
  - HEMO Study

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  - NECOSAD Study

- **2003**
  - ADEMEX trial
  - Hong Kong Study (Lo et al)

- **2007**
  - Alberta Nocturnal Trial

- **2008**
  - MPO Study

- **2010-2011**
  - FHN Trials

- **2012**
  - CONTRAST

- **2013**
  - ESHOL
  - Turkish HDF

- **2015**
  - Last Guidelines

- **2018**
  - If we really want to change our patient’s outcomes

**TIME TO MOVE FORWARD**

- **KDIGO**

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**TIME TO MOVE FORWARD**

If we really want to change our patient’s outcomes
1. After 3 decades of focusing on adequacy prescription defined by Kt/V urea, we must change our approach.

2. The unmet clinical needs derived from conventional hemodialysis have prompted questions about the validity of the current adequacy goal, and have generated interest in other clinical parameters for patient's outcomes that may be more important than solute removal.

3. Weekly treatment time is the one factor with the potentially highest impact on dialysis dose, that can help achieve more solute clearance as well as more volume control.
4. We need to think whether, instead of prescribing conventional HD for the majority of patients, we can turn to alternative dialysis prescriptions probably starting with patients who have a longer life expectancy, and with those that can specifically benefit from alternative dialysis schedules.

5. Home dialysis is an attractive and cost-effective modality to increase time and frequency due to favorable logistics; and also offers more freedom and quality of life.

6. When home dialysis is not possible, we need to think of different possibilities to increase time and frequency, but in an in-center setting, such as:
   - More nocturnal dialysis
   - 4 times/week sessions
   - Alternate-day sessions

7. Further studies are required to compared different dialysis prescriptions
In the near future, we can have a different picture of RRT worldwide, with an improvement of patient’s outcomes, because of a change in Nephrologists’ way of thinking!!

The FUTURE is in our HANDS!!

Conclusions