How to Preserve Residual Kidney Function in Dialysis Patients

CME for Physicians
14th Congress of the ISPD

Joanne Bargman MD FRCP C
Professor of Medicine, University of Toronto
Director, the Home Peritoneal Dialysis Program
University Health Network
Toronto
Outline

- The recognition of the importance of residual renal function
- *Why* is preserved residual renal function associated with improved survival?
- How to preserve residual renal function in dialysis patients
Outline

- The recognition of the importance of residual renal function
- *Why is preserved residual renal function associated with improved survival?*
- How to preserve residual renal function in dialysis patients
Residual Renal Function in Dialysis Patients

- the presence or measurement of residual renal function was not important for most nephrologists, especially those looking after hemodialysis patients
- bilateral nephrectomies were sometimes performed to help improve blood pressure control, or pre-transplantation
Maiorca et al: residual renal function different at baseline between patients who survived and those who died over a 3 year follow-up

Residual Renal Function and Outcome: One of the First Observations

Nephrol Dial Transplant 1995
The Association of Residual Renal Function, but Not Dose of PD, with Survival

Table 5. Association of Weekly Peritoneal ($K_{p_{cr}}$) and Residual Renal ($K_{r_{cr}}$) Creatinine Clearance With Odds of Death: Three Logistic Models

<table>
<thead>
<tr>
<th>Variable</th>
<th>$K_{p_{cr}}$ Only (N = 673)</th>
<th>$K_{r_{cr}}$ Only (N = 559)</th>
<th>$K_{p_{cr}}$ Only (N = 443)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\chi^2$</td>
<td>$P$</td>
<td>OR</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>30.2</td>
<td>&lt;0.001</td>
<td>1.046</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>1.7</td>
<td>NS</td>
<td>0.750</td>
</tr>
<tr>
<td>Race (nonwhite)</td>
<td>2.5</td>
<td>NS</td>
<td>1.512</td>
</tr>
<tr>
<td>Diabetes (no)</td>
<td>11</td>
<td>&lt;0.001</td>
<td>2.023</td>
</tr>
<tr>
<td>$K_{p_{cr}}$ (L/wk)</td>
<td>1</td>
<td>NS</td>
<td>1.009</td>
</tr>
<tr>
<td>$K_{r_{cr}}$ (mL/min)</td>
<td>1</td>
<td>NS</td>
<td>1.009</td>
</tr>
</tbody>
</table>

The Importance of Residual Renal Function

- The Canadian-USA study of adequacy of PD showed that total (renal + peritoneal) Kt/V urea was associated with outcome
- Re-analysis of the CANUSA study, separating renal and peritoneal clearance:
  - Outcome is predicted by renal clearance, and not peritoneal clearance
Mortality in The CANUSA Study: Renal vs Peritoneal Contribution

- CANUSA study, separating renal & peritoneal clearance

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.02*</td>
</tr>
<tr>
<td>CVD</td>
<td>2.42*</td>
</tr>
<tr>
<td>SGA</td>
<td>0.74*</td>
</tr>
<tr>
<td>peritoneal CrCl (5L/wk)</td>
<td>1.00</td>
</tr>
<tr>
<td>renal GFR (5L/wk)</td>
<td>0.88*</td>
</tr>
</tbody>
</table>

Bargman J Am Soc Nephrol 2001
The CANUSA Study: Renal vs Peritoneal Contribution to Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Mortality Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peritoneal CrCl</td>
<td>1.00</td>
</tr>
<tr>
<td>Renal GFR (per 5L/wk)</td>
<td>0.88</td>
</tr>
<tr>
<td>Urine volume (per 250 ml)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Bargman J Am Soc Nephrol 2001
Residual Renal Function vs Peritoneal Small Solute Clearance

Similar results found in

- large prevalent PD patient surveys (Rocco)
- prospective observational study in Hong Kong (Szeto)
- The NECOSAD Study

Peritoneal small solute clearance does not predict outcome when there is residual kidney function
Urine Output and Outcome in HD Patients: The CHOICE Study

- 734 incident hemodialysis patients
- self-reported urine output > 1 cup/day
  - 84% had urine output at baseline
  - 28% had urine output at 1 year

Shafi et al Am J Kidney Dis 2010
Urine Output and Outcome in HD Patients: The CHOICE Study

- Urine output at baseline associated with better quality of life
- Urine output at 1 year independently associated with less all-cause mortality (HR 0.7, CI 0.52-0.93, p=0.02)
- Urine output at 1 year associated with reduction in Epo of 12,000U/week (p=0.001)

Shafi et al Am J Kidney Dis 2010
Urine Output at Baseline or at 1 Yr and All-Cause Mortality

All-Cause Mortality by Baseline Urine Output

All-Cause Mortality by Urine Output at 1 year

Shafi et al Am J Kidney Dis 2010
Importance of Residual Renal Function

- all the new guidelines now emphasize the association of residual renal function with improved survival
- preservation of residual renal function is an important part of these guidelines

Table 15. Efforts To Protect RKF

| Avoidance of nephrotoxic agents, especially aminoglycosides, nonsteroidal anti-inflammatory drugs, COX-2 inhibitors and radiocontrast media |
| Avoidance of excessive ultrafiltration and hypotension during treatment |
| Routine use of biocompatible dialyzer membranes |
| Routine use of bicarbonate-based dialysate |
| Aggressive treatment of severe hypertension |
| Use of ACE inhibitors and/or ARBs |
| Use of ultrapure dialysate |

COX-2: Cyclooxygenase-2
Outline

- The recognition of the importance of residual renal function

- Why is preserved residual renal function associated with improved survival?

- How to preserve residual renal function in dialysis patients
Why is Residual Renal Function So Important to Outcome?

1. maybe it is just associated with being a healthier patient
2. better clearance of middle molecular weight uremic toxins
3. maintenance of euvolemia (via salt & water excretion)
4. intrinsic anti-inflammatory effect
The Association of Preserved RRF and Mortality

Healthier, less-inflamed patient

Better preserved RRF

? Improved survival
## Establishing a Causal Relationship Between Residual Renal Function And Survival

<table>
<thead>
<tr>
<th>Condition</th>
<th>Question for RRF</th>
<th>Criteria Met</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporality</td>
<td>Does decrease in RRF precede adverse outcomes?</td>
<td>yes</td>
</tr>
<tr>
<td>Strength</td>
<td>Is there a strong association?</td>
<td>yes</td>
</tr>
<tr>
<td>Dose-response</td>
<td>Is survival benefit proportional to RRF?</td>
<td>yes</td>
</tr>
<tr>
<td>Consistency</td>
<td>Consistent among studies, modalities</td>
<td>yes</td>
</tr>
<tr>
<td>Biological sense</td>
<td>Is there a biologic framework?</td>
<td>yes</td>
</tr>
<tr>
<td>Experiment</td>
<td>Are there studies to maintain RRF resulting in improved survival?</td>
<td>no</td>
</tr>
</tbody>
</table>

Perl and Bargman Am J Kidney Dis 2009
Residual Renal Function: Clearance of Uremic Toxins

Contribution of RRF to Clearance of Small vs Large Solutes

Bammens et al, 2003
## Risk factors for hypertension in PD patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Hypertension</td>
<td>2.58-2.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RRF (CrCl)</td>
<td>3.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RRF (GFR)</td>
<td>4.13</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Menon Neph Dial Transpl 2001
Residual Renal Function and Left Ventricular Mass Index

LVMI vs peritoneal clearance and RRF

Wang et al Kidney Int 2002
RRF is Associated with Better Endothelial Function

- 72 prevalent PD patients
- Flow-mediated dilatation measured as index of endothelial function
- RRF strong predictor independent of duration of dialysis

Han Perit Dial Int 2010
Current concepts suggest that decline in renal function is accompanied by an increase in cardiovascular mortality.
Worsening RRF

Increasing CV mortality

Whatever the cause of this association, it may also apply to decline in residual renal function in patients on dialysis.
Outline

- The recognition of the importance of residual renal function
- Why is preserved residual renal function associated with improved survival?
- How to preserve residual renal function in dialysis patients
How to Preserve Residual Renal Function in Dialysis Patients

- put patients on PD
  - and
- put patients onto PD without putting them on HD first
Decline in Residual Renal Function: PD vs HD

Loss of Residual Renal Function: PD vs HD

- PD pts had a 65% lower risk of losing RRF compared to HD pts
- at each time interval studied, HD pts were 3X more likely to have lost RRF

Effect of One Month of HD on Residual Renal Function on PD Patients

Kim et al, Perit Dial Int 2000
Does the Type of PD Solution Make a Difference?

- initial studies found increase in urine volume and GFR with “biocompatible” solutions
- results complicated by increased D/P creatinine and reduced ultrafiltration
- relative volume excess may have driven the increased urine volume and GFR
  - *Williams et al Kidney Int 2004*
  - *Haag Weber Neph Dial Transpl 2010*
- other studies have not found preservation of RRF with “biocompatible” solutions
  - *Szeto et al Neph Dial Transpl 2007*
  - *Fan et al Kidney Int 2008*
  - *Johnson et al J Am Soc Nephrol 2012*
Does the Type of PD Solution Make a Difference?

What about Icodextrin?

- When patients had normal volume status and were given icodextrin, urine output fell
  - Konings et al Kidney Int 2003
  - Rodriguez-Carmona et al Perit Dial Int 2007

- When patients had increased volume status and were given icodextrin, no change in urine output

Changes to residual renal function may simply reflect the changes to volume status
Preservation of Residual Renal Function

- Avoid volume depletion
  - studies of vigorous Na+ restriction and the use of hypertonic dialysate show marked fall-off in RRF
  - patients often note diminished urine volume if they use hypertonic dialysate
**Effect of Hypotension and Volume Depletion on Residual Renal Function**

<table>
<thead>
<tr>
<th>HD: Hypotensive Episodes</th>
<th>P value</th>
<th>PD: underhydration</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted for baseline GFR</td>
<td>.003</td>
<td>Adjusted for baseline GFR</td>
<td>.003</td>
</tr>
<tr>
<td>+ age, sex, PKD, co-morbidity</td>
<td>.004</td>
<td>+ age, sex, PDK, co-morbidity</td>
<td>.003</td>
</tr>
<tr>
<td>+ dialysis Kt/V at 3 months</td>
<td>0.02</td>
<td>+ dialysis Kt/V at 3 months</td>
<td>.004</td>
</tr>
</tbody>
</table>

*Jansen et al Kidney Int 2002*
Preservation of Residual Renal Function

- **Avoid nephrotoxic drugs**
  - NSAID’s and especially COX-2 inhibitors
    - most aches and pains are non-inflammatory anyway, and can be managed by acetaminophen
  - prolonged courses of aminoglycosides
  - avoid fibrates if possible (*my opinion*)
Avoid intravenous dye studies
- consider necessity of the study
- can alternative to dye be used?
  - Dobutamine stress echo
- use iso-osmolar, nonionic dye, keep patient hydrated
- use N-Acetyl Cystine
- minimize volume of dye
  - eg don’t image the left ventricle
Preservation of Residual Renal Function (RRF)

- Consider conventional causes of renal failure
  - pre-renal
  - post-renal
Preservation of Residual Renal Function

- ACE inhibitors and angiotensin receptor blockers (ARB’s) can slow down deterioration of renal function
ACE-Inhibitors, Angiotensin Receptor Blockers and GFR
ACE-Inhibitors, Angiotensin Receptor Blockers and GFR

![Graph showing the relationship between GFR and time with the effect of ACE/ARB medications.]
ACE-Inhibitors, Angiotensin Receptor Blockers and GFR
Preservation of Residual Kidney Function with Angiotensin Receptor Blockers

Preservation of Residual Kidney Function with ACE Inhibition

Li et al, Ann Int Med 2003
Preservation of Residual Kidney Function by ACE Inhibitors and Angiotensin Receptor Blockers

- **preservation of 1 ml/min – so what?**

- most studies show that each ml/min of residual GFR associated with 15 – 25% reduction in annual mortality

- this is theoretically as life-prolonging as results seen in the ACE-I, statin or spironolactone trials for heart disease
Preservation of Residual Kidney Function: What About Diuretics?

- diuretics increase renal salt and water excretion
- they do not acutely change GFR
- no evidence over longer term that they either improve or worsen GFR
- after 1 year: preservation of urine volume
- main use is for management of volume status
Effect of Daily Furosemide on Urine Volume: Results After 1 Year

Urine Volume (ml/day)

Control

250mg furosemide

baseline

12 months

Medcalf Kidney Int 2001
Other Ways to Preserve RRF

- Continue immunosuppression in “failed” renal transplants
  - Davies Perit Dial Int 2001

- N-acetyl cysteine
  - Feldman et al Perit Dial Int 2010
there is a strong association between preserved residual renal function and survival benefit in dialysis patients
this is a biologically sensible association
better preservation of RRF may be a major benefit of PD compared to HD
preserving renal function is the major focus of the new generation of adequacy guidelines for both HD and PD