ULTRAFILTRATION FAILURE

WESTERN CANADA PD DAYS

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OUTLINE/OBJECTIVES

- **Definition and causes of ultrafiltration failure (UFF)**
  - Risks associated with inadequate ultrafiltration and persistent volume overload
  - Early versus late ultrafiltration failure
  - How to maintain normal volume status in the face of UFF
NOT TO GET TOO PHILOSOPHICAL, BUT…
HOW DO YOU DEFINE ULTRAFILTRATION FAILURE?

- fluid removal doesn’t keep up with fluid intake?
- so is “fluid overload” the same thing as ultrafiltration failure?
- some people assume that ultrafiltration failure means peritoneal membrane failure
  - not the same thing
  - peritoneal membrane failure is just one cause of ultrafiltration failure
  - example: someone ultrafilters 1000 ml/day, but takes a high salt diet and copious fluids, and is edematous
    - is this ultrafiltration “failure”?
DEFINITION: ULTRAFILTRATION FAILURE

“Ultrafiltration Failure”

Fluid overload (from any cause)

Peritoneal membrane failure
CAUSES OF FLUID OVERLOAD

- congestive heart failure
- excessive salt and water intake
- decline of residual kidney salt and water excretion
- reluctance to use more hypertonic dialysis fluid or icodextrin
- mechanical problems with the dialysis
- **true peritoneal membrane failure**
Dynamics of Fluid Balance in the Dialysis Patient

intake → The patient → output

ultrafiltration
urine volume
Dynamics of Fluid Balance in the Dialysis Patient

intake

The patient

ultrafiltration
output
urine volume
VOLUME OVERLOAD - INTAKE

- excessive salt and water consumption
  - PD has often been “advertised” as allowing a more liberal dietary intake
  - patients with high salt intake are protected from volume overload while they have residual renal function (RRF)
    - once urine volume diminishes, patient may develop fluid overload
Dynamics of Fluid Balance in the Dialysis Patient

The patient

- intake
- ultrafiltration
- output
- urine volume
The Association of Residual Renal Function, but Not Dose of PD, with Survival

Table 5. Association of Weekly Peritoneal ($K_{\text{wp}}$) and Residual Renal ($K_{\text{r}}$) Creatinine Clearance With Odds of Death: Three Logistic Models

<table>
<thead>
<tr>
<th>Variable</th>
<th>$K_{\text{wp}}$ Only (N = 673)</th>
<th>$K_{\text{r}}$ Only (N = 559)</th>
<th>$K_{\text{pr}}$ (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>$K_{\text{wp}}$ (L/wk)</td>
<td>1</td>
<td>NS</td>
<td>1.009</td>
</tr>
<tr>
<td>$K_{\text{r}}$ (mL/min)</td>
<td>12.7</td>
<td>&lt;0.001</td>
<td>0.876</td>
</tr>
</tbody>
</table>

The CANUSA Study: Renal vs Peritoneal Contribution to Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Mortality Risk</th>
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<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
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 (my opinion)
- minimize volume of dye
  - eg don’t image the left ventricle
ACE inhibitors and angiotensin receptor blockers (ARB’s) can slow down deterioration of renal function
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 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
- But this is important 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 RESIDUAL KIDNEY FUNCTION

- Continue immunosuppression in “failed” renal transplants
  - Davies Perit Dial Int 2001
Dynamics of Fluid Balance in the Dialysis Patient

intake → The patient → output

ultrafiltration

urine volume
“ULTRAFILTRATION FAILURE”

Use of the wrong type of PD fluid

- usually this means failure to account for the long dwell
- reluctance to use hypertonic fluid because of perception that it will hurt the peritoneal membrane
Temporal Profiles of APD and CAPD

- APD: Nighttime (9 hrs) and Daytime (15 hrs)
- CAPD: Nighttime (9 hrs) and Daytime (15 hrs)
Ultrafiltration Profiles of Dextrose-Based Solutions

ULTRAFILTRATION FAILURE – OTHER CAUSES

- failure of the peritoneal membrane to respond to UF conditions (true membrane failure)
- mechanical failure of dialysis procedure
FAILURE OF THE PERITONEAL MEMBRANE

**Definition:** Inability to maintain volume homeostasis despite the use of hypertonic dialysate solutions (3 or more daily)

or

- Failure to ultrafilter > 400 ml using a 4.25% bag for 4 hours (the Rule of 4’s)
TRUE PERITONEAL MEMBRANE FAILURE

- on PET test, D/P creatinine is high
- these high transporters have rapid absorption of glucose across peritoneal membrane
- rapid dissipation of osmotic gradient
- poor ultrafiltration
MECHANICAL FAILURE OF THE DIALYSIS PROCEDURE

- diminished effluent return because the dialysis fluid is leaving the peritoneal cavity
- PET test is unchanged
MECHANICAL FAILURE OF THE DIALYSIS PROCEDURE
Definition and causes of ultrafiltration failure (UFF)

Risks associated with inadequate ultrafiltration and persistent volume overload

- Early versus late ultrafiltration failure
- How to maintain normal volume status in the face of UFF
PD ULTRAFILTRATION AND SURVIVAL

group I, <1265 mL/24 h/1.73 m²;

group II, 1265 to 1570 mL/24 h/1.73 m²;

group III, 1570 to 2035 mL/24 h/1.73 m²;

and

group IV, > 2035 mL/24 h/1.73 m²

PD NA+ REMOVAL AND SURVIVAL


group I, <130 mmol/24 h/1.73 m²;
group II, 130 to 181 mmol/24 h/1.73 m²;
group III, 181 to 232 mmol/24 h/1.73 m²; and

group IV, > 232 mmol/24 h/1.73 m².
THE IMPORTANCE OF ULTRAFILTRATION: THE EAPOS STUDY

- multi-centre study in Europe examining predictors of outcome in anuric APD patients
- small solute clearance parameters did not predict survival
- baseline ultrafiltration volume significantly predicted survival
- time-dependent ultrafiltration volume was also of borderline statistical significance
FLUID REMOVAL AND SURVIVAL IN EAPOS

PREDICTORS OF SURVIVAL IN ANURIC PD PATIENTS

- recent study of anuric PD patients in Shanghai
- similar to EAPOS, ultrafiltration volume was an important predictor of survival

Lin et al Neph Dial Transpl 2010

Table 4. Multivariate Cox regression analysis showing independent predictors of mortality in 86 anuric PD patients followed up for a median of 25.3 months (range, 6 to 54 months)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>RR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (1 year)</td>
<td>1.064</td>
<td>1.019–1.111</td>
<td>0.005</td>
</tr>
<tr>
<td>Serum albumin (1 g/L)</td>
<td>0.850</td>
<td>0.744–0.973</td>
<td>0.018</td>
</tr>
<tr>
<td>UF(t) (100 ml/24 h)</td>
<td>0.800</td>
<td>0.709–0.901</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Log rank test
P < 0.001

UF > 1 L
UF < 1 L
THE IMPORTANCE OF SODIUM AND WATER REMOVAL

- evidence suggests that ultrafiltration volume and euvolemia are important for survival
- this makes sense physiologically, given risks of chronic volume overload
  - LVH
  - increased sympathetic tone
  - congestive heart failure
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Early vs Late Ultrafiltration (Membrane) Failure

- some patients have problems with ultrafiltration at the start of PD
- other patients develop it over the course of PD

Figure 1 — Frequency distribution of the number of patients with (black boxes) and without (open boxes) ultrafiltration failure and the duration of peritoneal dialysis (PD; months).

Smit et al. Perit Dial Int 2004
EARLY VS LATE ULTRAFLTRATION FAILURE

- early UF failure is probably a marker of inflammation
- these patients are rapid transporters from the beginning
- late UF failure a marker of a change in the structure of the peritoneal membrane
WHAT HAPPENS TO THE PERITONEAL MEMBRANE OVER TIME?

- new blood vessel formation
  - this makes the patient a more rapid transporter
- submesothelial fibrosis
  - this leads to diminished osmotic conductance

Slides courtesy of Peter Margetts
LONG-TERM CHANGES IN THE PERITONEAL MEMBRANE

Fibrosis

New blood vessel formation

Devuyst O et al. JASN 2010;21:1077-1085
LONG-TERM CHANGES IN THE PERITONEAL MEMBRANE: RESULTS

- acquisition of rapid transport status
  - reduction in ultrafiltration
- diminished osmotic conductance
  - reduced ultrafiltration for any given osmotic gradient
WHAT IS OSMOTIC CONDUCTANCE?

Osmotic gradient

Blood

Dialysate
WHAT IS OSMOTIC CONDUCTANCE?

Osmotic gradient

Blood

Dialysate

water

water
LOW OSMOTIC CONDUCTANCE: FOR A GIVEN OSMOTIC GRADIENT, LESS WATER MOVEMENT
Transport Status and Ultrafiltration

Expected relation between D/P creatinine and UF

Long-Term PD Patients: Transport Status and Ultrafiltration

LATE ULTRAFILTRATION FAILURE: THE DOUBLE WHAMMY!

- there is a tendency for some patients to become more rapid transporters over time
- in addition, for whatever osmotic gradient there is, less ultrafiltration occurs
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MANAGEMENT OF RAPID TRANSPORTERS (I)

- reinforce salt and water restriction
- use more hypertonic dialysate
- icodextrin can be quite helpful here (*as effective in high transporters as other transport types*)
HYPERTONIC DEXTROSE-BASED SOLUTIONS

- Hypertonic dialysate will result in more UF and convective removal of solute
■ there is a metabolic “cost” to this:
  ■ to the patient (calories, lipids, etc)
  ■ *maybe* to the peritoneal membrane
ICODEXTRIN: A DIFFERENT APPROACH TO ULTRAFILTRATION

- macromolecules that are absorbed more slowly from the peritoneal cavity
- induces water transport across small intercellular pores
- works more efficiently in rapid transporters: enhances UF with increased vascular surface area (more pores)
REMEMBER THE HARE AND THE TORTOISE?

- the hare ran quickly but soon grew tired
- the tortoise, slow and steady, won the race
REMEMBER THE HARE AND THE TORTOISE?

- the hare ran quickly but soon grew tired
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- dextrose
- icodextrin
SUSTAINED ULTRAFILTRATION: ICODEXTRIN VS DEXTROSE

ICODEXTRIN WORKS WELL IN ALL TRANSPORT TYPES

ULTRAFILTRATION EFFICIENCY RATIO: THE “METABOLIC COST” OF UF

- Icodextrin leads to more ultrafiltration per gram of carbohydrate absorbed
  (expressed as mls ultrafiltered / g carbohydrate absorbed)

Finkelstein et al J Am Soc Nephrol 2005
BUT ICODEXTRIN HAS A CALORIC LOAD TOO

- amount of calories absorbed from icodextrin ~ number of calories absorbed from a 2.5% dextrose solution
BUT ICODEXTRIN HAS A CALORIC LOAD TOO

- amount of calories absorbed from icodextrin ~ number of calories absorbed from a 2.5% dextrose solution
USE OF ICODEXTRIN TO ACHIEVE EUVOLEMIA

- more costly (but cheaper than changing to HD)
- 2 icodextrins/day (off-label!) associated with more UF but higher blood concentrations of metabolites
SHORTENED DWELL TIMES AND/OR SWITCH TO APD

- shortened dwell times allow for less dissipation of the glucose osmotic gradient
- this will lead to increased ultrafiltration and less opportunity for reabsorption
- if dwell times too short, water may be ultrafiltered faster than sodium is removed
- this sodium sieving can impair salt and water removal
- and you still have to deal with the long(er) dwell!
SODIUM REMOVAL IN PATIENTS TRANSFERRED FROM CAPD TO APD

(Rodriguez-Carmona 2002)
SHORTER DWELL TIME AND/OR CONVERSION TO APD

- In CAPD this necessitates more frequent exchanges and risk of burnout
- APD is not a “magic bullet”!
  - Risk of sodium sieving
  - Absorption during the long day dwell
- In anuric patients dry abdomen should be avoided in both CAPD and APD
WHAT ABOUT THE LONG DWELL?

1. use icodextrin or a more hypertonic dialysate (e.g. 2.5%)

2. break up the long dwell
   - day dry (only if there is a lot of RRF)
   - “mid-day” exchange in APD
   - drain out day exchange in APD after a few hours
“push” residual urine output (diuretics)
APD with dry day, or drain out last fill at lunch (if enough RRF)
once anuric, watch closely for volume overload

*consider transfer to hemodialysis if patient is chronically overloaded*
*(start talking about fistula placement with the patient)*
MY OPINION: WHAT WORKS FOR UF

<table>
<thead>
<tr>
<th>CAPD</th>
<th>1.5%</th>
<th>2.5%</th>
<th>1.5%</th>
<th>Icodextrin</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPD</td>
<td>1.5%</td>
<td>2.5%</td>
<td>1.5%</td>
<td>2.5%</td>
</tr>
</tbody>
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### MY OPINION: WHAT WORKS FOR UF

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Icodextrin</th>
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<tbody>
<tr>
<td>CAPD</td>
<td>1.5% 2.5% 1.5%</td>
</tr>
<tr>
<td>CAPD</td>
<td>1.5% 2.5% 1.5% 2.5%</td>
</tr>
<tr>
<td>APD</td>
<td>Icodextrin 2.5% 2.5% 2.5% 2.5%</td>
</tr>
<tr>
<td>NIPD</td>
<td>(dry) 2.5% 1.5% 1.5% 2.5%</td>
</tr>
</tbody>
</table>
### MY OPINION: WHAT WORKS FOR UF

<table>
<thead>
<tr>
<th></th>
<th>1.5%</th>
<th>2.5%</th>
<th>1.5%</th>
<th>Icodextrin</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPD</td>
<td>1.5%</td>
<td>2.5%</td>
<td>1.5%</td>
<td>2.5%</td>
</tr>
<tr>
<td>APD</td>
<td></td>
<td></td>
<td>Icodextrin</td>
<td>2.5% 2.5% 2.5% 2.5%</td>
</tr>
<tr>
<td>NIPD</td>
<td>(dry)</td>
<td></td>
<td></td>
<td>2.5% 1.5% 1.5% 2.5%</td>
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and maybe…

<table>
<thead>
<tr>
<th></th>
<th>Icodextrin</th>
<th>Icodextrin</th>
<th>2.5% 1.5% 2.5%</th>
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<tbody>
<tr>
<td>APD</td>
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SUMMARY

- Attainment of normal volume status is important for the well-being of our dialysis patients
- There is a differential diagnosis in the volume-overloaded PD patient – don’t assume it is membrane failure
- Early versus late ultrafiltration failure have different causes
- Management includes dietary sodium restriction, pushing urine output with diuretics, and changes to the PD prescription
- Consider a transition to hemodialysis if the patient remains chronically volume overloaded despite these interventions