VOLUME MANAGEMENT IN
PERITONEAL DIALYSIS

Lucy Todd, MSN, ACNP, CNN
Senior Principal Medical Liaison
Worldwide Medical
Baxter Healthcare
<table>
<thead>
<tr>
<th>Presentation Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Volume Status in PD</strong></td>
</tr>
<tr>
<td><strong>Physiology of Ultrafiltration</strong></td>
</tr>
<tr>
<td><strong>Volume Management: Prescription Design</strong></td>
</tr>
<tr>
<td>• Short Dwell</td>
</tr>
<tr>
<td>• Long Dwell</td>
</tr>
<tr>
<td><strong>Volume Management: Beyond Glucose</strong></td>
</tr>
<tr>
<td><strong>Volume Overload</strong></td>
</tr>
<tr>
<td>• Diagnosis</td>
</tr>
<tr>
<td>• Management</td>
</tr>
</tbody>
</table>
Volume Status in PD Patients

**Cohort**
- 135 Study centers
- 28 Countries
- 1054 Incident PD patients
- 3-5 years follow up
- Bioimpedance spectroscopy Baseline and Q3mo

**Volume status at baseline (pre-PD)**
- 36% Euvolemic
- 33% Moderate volume overload
- 24% Severe volume overload

**Change in volume overload over time**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume overload</td>
<td>1.9 L +/- 2.3L</td>
<td>1.2 L +/- 1.8L</td>
<td>1.4 L +/- 1.8L</td>
<td>1.4 L +/- 1.7L</td>
</tr>
</tbody>
</table>

**Competing risk model on time to death, HR (95% CI)**

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Diabetes</th>
<th>CV disease</th>
<th>Volume overload</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>1.06</td>
<td>1.49</td>
<td>1.86</td>
<td>1.59</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.04-1.07</td>
<td>1.04-2.15</td>
<td>1.29-2.69</td>
<td>1.08-2.33</td>
</tr>
</tbody>
</table>

**Conclusions** In this cohort of incident patients on PD, we found substantial volume overload at start of dialysis. Volume overload improved over time, and associated with survival.


Visual Abstract by Michelle Rheault, MD

Survival and Fluid Removal: Anuric Patients

Proportion Surviving

Months in Study

> 750 mL UF

< 750 mL UF

N = 177
P = 0.005

Volume Status in PD

Physiology of Ultrafiltration

Volume Management: Prescription Design
- Short Dwell
- Long Dwell

Volume Management: Beyond Glucose

Volume Overload
- Diagnosis
- Management
Peritoneal System
TWO TRANSPORT PATHWAYS

Peritoneal Membrane: Three layers\(^1\)
- Mesothelium
- Interstitium
- Endothelial cell/capillary wall

Lymphatic System\(^1, 2\)
- 1.0-1.5 mL/min;
- 1.5 - 2.1 L/day\(^1\)

Three Pore Model

- **Large Pore**: Intercellular cleft
  - Transports water & larger solutes, irrespective of dialysate type
- **Small Pore**: Intercellular cleft
  - Transports water & smaller solutes, irrespective of dialysate type
- **AQP**: Transcellular free water channel (AQP1)
  - Activated by dextrose

Protein Loss ~0.1mL/min (approximately 5 gm/day)

**Figure adapted from Guedes AM. Perit Dial Int. 2019; 39:201-209.**

**Rippe B and Stelin G. Kidney Int. 1989; 35:1234-1244.**
Volume Management: ISPD Recommendations 2020

01 Initial PET 6-12 weeks post training; repeat as clinically indicated.  
   Routine monitoring: PET, volume status, BP & clinical exam

02 Icodextrin to improve UF independent of transport type
   “Compared to glucose, use of icodextrin can translate into improved fluid status and fewer episodes of fluid overload”

03 Dietary counseling of appropriate salt / water intake

04 Protection of RRF; Loop diuretics if RRF present
   Furosemide 160-480 mg/day (split-2 doses)
   Metolazone 5-10 mg/day

05 Preservation of peritoneal membrane function
   Avoid peritonitis & hypertonic glucose solutions

References:
Fast transport rate is associated with lower survival; APD and icodextrin may mitigate this mortality risk (grade 1A evidence).\(^2\)

Clinical Practice Guidelines: ISPD recommendations for the evaluation of peritoneal membrane dysfunction in adults: Classification, measurement, interpretation and rationale for intervention

Guideline 2b: *Clinical implications and mitigation of fast solute transfer*: A faster peritoneal solute transport rate (PSTR) is associated with lower survival on PD. (GRADE 1A) This risk is in part due to the lower ultrafiltration (UF) and increased net fluid reabsorption that occurs when the PSTR is above the average value. The resulting lower net UF can be avoided by shortening glucose-based exchanges, using a polyglucose solution (icodextrin), and/or prescribing higher glucose concentrations. (GRADE 1A)

Compared to glucose, use of icodextrin can translate into improved fluid status and fewer episodes of fluid overload. (GRADE 1A)

Use of automated PD and icodextrin may mitigate the mortality risk associated with fast PSTR. (practice point)

Volume Management

MECHANISMS OF ULTRAFILTRATION

• In Hemodialysis – **hydraulic** trans-membrane pressure

• In Peritoneal Dialysis - **dialysate dependent**
  • Crystalloid (dextrose) – **osmotic** pressure
    UF : AQP ~50% (free water), small/large pores~50%
  • Colloid (icodextrin)– **oncotic** pressure
    UF : all small/large pores~100%

• Results of Ultrafiltration:
  – Fluid removal
  – Convective removal of solutes (key for LMW solutes)
## Composition of PD Fluids

<table>
<thead>
<tr>
<th></th>
<th>Crystalloid PD Solution&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Colloid PD Solution&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextrose (g/dL)</td>
<td>1.5, 2.5, 4.25</td>
<td>—</td>
</tr>
<tr>
<td>Icodextrin (g/dL)</td>
<td>—</td>
<td>7.5</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>132</td>
<td>132</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>Calcium (mEq/L)</td>
<td>3.5/2.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Magnesium (mEq/L)</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Lactate (mEq/L)</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Osmolarity (mOsm/L)</td>
<td>346-485</td>
<td>282</td>
</tr>
<tr>
<td>pH</td>
<td>4.0-6.5</td>
<td>5.0-6.0</td>
</tr>
</tbody>
</table>

1. Data on File
2. Data on File
Glucose Concentration: PD Fluids

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Glucose Concentration</th>
<th>Osmolality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5%</td>
<td>1360 mg/dl</td>
<td>347 mOsm/L¹</td>
</tr>
<tr>
<td>2.5%</td>
<td>2260 mg/dl</td>
<td>397 mOsm/L¹</td>
</tr>
<tr>
<td>4.25%</td>
<td>3860 mg/dl</td>
<td>485 mOsm/L¹</td>
</tr>
<tr>
<td>Icodextrin-7.5%</td>
<td>0 mg/dl</td>
<td>282 mOsm/L²</td>
</tr>
<tr>
<td>Blood</td>
<td>65-99³</td>
<td>280-295 mOsm/L</td>
</tr>
</tbody>
</table>

Prescription Considerations:

- **Glucose Load:** Always use lowest concentration needed to achieve UF targets⁴
- **ISPD:** “Icodextrin can translate into improved fluid status and fewer episodes of fluid overload.”⁶
- **ISPD recommends icodextrin to improve UF independent of transport type**⁵
- **Diabetics:** Keep blood sugar well controlled⁴

---

1. Data on File
2. Data on File
Colloidal Peritoneal Dialysis Solution (icodextrin)

• Starch-derived polymer: **weight**-average molecular weight 13,000-19,000 daltons (structurally similar to glycogen)

• Induces ultrafiltration via colloid osmosis
  – Water transport across small intercellular pores of peritoneal capillary endothelium
  – Maintains colloid osmotic pressure gradient for the duration of the long dwell due to slow rate of absorption via the lymphatics

Please see important safety information at the end of this presentation.
Icodextrin Mechanism of Action: Colloidal Osmosis

HIGH REFLECTION COEFFICIENT (SIZE) OF ICODEXTRIN UNDERLIES COLLOID EFFECTS AND SUSTAINS UF DURING LONG DWELLS
Icodextrin is a glucose-free osmotic agent. Metabolism of icodextrin to glucose occurs predominantly after absorption from the peritoneal cavity via lymphatic pathways.

**Reduced Membrane Glucose Exposure**

- Peritoneal cavity
  - Icodextrin

- Intravascular Compartment
  - Icodextrin
  - Oligosaccharides (maltose) → amylase → Maltose
  - Maltase → Glucose

- Intracellular Compartment
  - Maltose
  - Maltase → Glucose
Effects of icodextrin: Glucose / Insulin

Metabolic and Laboratory Effects of Icodextrin

Serum Sodium
- Predominantly due to dilutional effect of icodextrin metabolites (osmotic effect)
- Similar to hyponatremia related to hyperglycemia or mannitol-like solutes in blood

Amylase Assay
- Serum amylase may be low due to interference of icodextrin metabolites with the enzymatic-based amylase assay
- Serum lipase does not appear affected by icodextrin; may be adequate method to diagnose pancreatitis

Alk Phosphatase
- Increases observed in clinical studies
- Increased levels not associated with increases in liver function tests
- No evidence of progressive increase in serum levels seen over 12-month study period
- Levels returned to normal about two weeks after icodextrin was discontinued

1. Data on File
Prescription Elements: Transport Type

DETERMINED BY THE PET

High (H) /High Average (HA)  
(0.65 to 1.03)

- Higher D/P creatinine
- Greater vascular surface area
- Equilibrate rapidly
- Rapid absorption of glucose $\rightarrow$ results in diminished UF
- Need shorter dwells to minimize reabsorption and maximize UF

Low (L) /Low Average (LA)  
(0.34 to 0.64)

- Lower D/P creatinine
- Less vascular surface area
- Equilibrate slowly
- Slow absorption of glucose $\rightarrow$ results in optimal UF
- Need longer dwells to enhance solute clearance

Prescription Elements: Dwell Time

SHORT DWELL VS. LONG DWELL FUNCTION

**SHORT DWELL**

- Provides UF and diffusive clearance of small solutes
- CAPD-day time exchanges
  - 4 - 6 hours based on lifestyle
- APD-night time exchanges
  - 1.5 - 3 hours based on transport type
- Potential clinical problem: sodium sieving (short dwell too short; APD)

**LONG DWELL**

- Provides convective clearance of larger solutes
- Optimizes sodium removal
- Potential clinical problem: reabsorption of fluid, especially for H & HA (when using dextrose)
- APD-day time dwell management
  - exchanges dependent upon transport status and fluid selection
  - Required in anuric pts per KDOQI

Dwell time and number of exchanges should be determined by transport type and clearance goal.

Ultrafiltration in PD: Dwell Time Matters

ULTRAFILTRATION PROFILE DURING DEXTROSE EXCHANGE

Ultrafiltrate Generation

Ultrafiltration

Peak Ultrafiltration

Ultrafiltrate Reabsorption

Osmotic Equilibrium

Dwell Time

Negative Ultrafiltration

Image courtesy of S. Guest MD
Peak UF with Different Strengths of Dextrose
High Average Transporter

THE SHORT DWELL: SODIUM SIEVING
Sodium Removal: When is Sodium Removed?

- High rates of UF (water via AQP1) in the early dwell period
- Ultrafiltrate is virtually DEVOID of Sodium
- Solutes (i.e. Na+) diffuse more slowly, across the small pores

When is Sodium Removed?

MINIMAL SODIUM SIEVING WITH 1.36% DEXTROSE AND IN HIGH TRANSPORTERS

Sodium Sieving & Icodextrin

LACK OF NA SIEVING WITH ICODEXTRIN IMPLIES UF THROUGH NA PERMEABLE “PORE”, NOT AQUAPORIN PORE

THE LONG DWELL: REABSORPTION
Long-dwell UF Potential: 2.5% Dextrose

![Graph showing net UF (mL) over time (hr) with different UF rates: Low, Low-Avg, High-Avg, and High. The graph indicates the net UF for CAPD (night) and APD (day).](#)

Long-dwell UF Potential: 4.25% Dextrose

Compared to glucose, use of icodextrin can translate into improved fluid status and fewer episodes of fluid overload.

Volume Management: ISPD Recommendations 2020

01. Initial PET 6-12 weeks post training; repeat as clinically indicated. Routine monitoring: PET, volume status, BP & clinical exam

02. Icodextrin to improve UF independent of transport type. “Compared to glucose, use of icodextrin can translate into improved fluid status and fewer episodes of fluid overload.”

03. Dietary counseling of appropriate salt / water intake

04. Protection of RRF; Loop diuretics if RRF present
   - Furosemide 160-480 mg/day (split-2 doses)
   - Metolazone 5-10 mg/day

05. Preservation of peritoneal membrane function
   - Avoid peritonitis & hypertonic glucose solutions

References:
Icodextrin Functions Irrespective of Transport Type

“Compared to glucose, use of icodextrin can translate into improved fluid status and fewer episodes of fluid overload”²

Icodextrin: Clinical Outcomes

RCT 59 HA/H TRANSPORTERS ALL DM ON CAPD OVER 12 MONTHS RANDOMIZED TO ALL GLUCOSE OR ICODEXTRIN FOR LONG DWELL

Mean UF difference icodextrin vs glucose was 197 mL/day (p<0.006)
Decreased glucose exposure in icodextrin group (p<0.01)

### Management of Day Dwell in APD

#### COMPUTER MODELING CLEARANCE STUDY: DAYTIME PRESCRIPTIONS IN H, HA & LA ANURIC PTS

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>UF</th>
<th>Na⁺ Removal</th>
<th>Kt/V</th>
<th>B2M Clearance mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Std</td>
<td>-230</td>
<td>-26</td>
<td>0.30</td>
<td>0.33</td>
</tr>
<tr>
<td>1</td>
<td>183</td>
<td>18</td>
<td>0.34</td>
<td>0.18</td>
</tr>
<tr>
<td>2</td>
<td>210</td>
<td>22</td>
<td>0.70</td>
<td>0.57</td>
</tr>
<tr>
<td>3</td>
<td>476</td>
<td>71</td>
<td>0.42</td>
<td>0.51</td>
</tr>
<tr>
<td>4</td>
<td>574</td>
<td>77</td>
<td>0.74</td>
<td>0.56</td>
</tr>
</tbody>
</table>

**Diagram:**

- **Standard:** 14 hr, 2.27% G
- **Therapy 1:** $T_{OPT}$, 2.27% G, DRY
- **Therapy 2:** 7 hr, 2.27% G, 7 hr, 2.27% G
- **Therapy 3:** 14 hr, 7.5% Icodextrin
- **Therapy 4:** $T_{OPT}$, 2.27% G, Rest of the day, 7.5% Icodextrin

(T$_{OPT}$ = dwell time optimized for transport type)

### PDOPPS: Current Practice Patterns

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>A/NZ 324</th>
<th>Japan 532</th>
<th>Canada 376</th>
<th>UK 221</th>
<th>US 2657</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Kt/V urea</td>
<td>2.13 (0.82)</td>
<td>1.89 (0.71)</td>
<td>1.89 (0.93)</td>
<td>2.26 (0.66)</td>
<td>2.30 (0.63)</td>
</tr>
<tr>
<td>Residual Kt/V urea</td>
<td>0.87 (0.79)</td>
<td>0.78 (0.76)</td>
<td>0.67 (0.69)</td>
<td>1.04 (0.73)</td>
<td>0.77 (0.80)</td>
</tr>
<tr>
<td>Peritoneal Kt/V urea</td>
<td>1.25 (0.52)</td>
<td>1.14 (0.46)</td>
<td>1.21 (0.58)</td>
<td>1.22 (0.54)</td>
<td>1.54 (0.51)</td>
</tr>
<tr>
<td>24-hour urine volume, L</td>
<td>0.87 (0.69)</td>
<td>0.80 (0.63)</td>
<td>0.85 (0.65)</td>
<td>1.19 (0.79)</td>
<td>0.75 (0.75)</td>
</tr>
<tr>
<td>24-hour urine volume per BSA, L/1.73 m^2</td>
<td>0.79 (0.64)</td>
<td>0.86 (0.65)</td>
<td>0.78 (0.60)</td>
<td>1.01 (0.69)</td>
<td>0.67 (0.66)</td>
</tr>
<tr>
<td>Anuric^a</td>
<td>9%/19%</td>
<td>7%/37%</td>
<td>15%/25%</td>
<td>6%/30%</td>
<td>23%/24%</td>
</tr>
<tr>
<td>PD solution type^b</td>
<td>Icodextrin</td>
<td>47%</td>
<td>43%</td>
<td>58%</td>
<td>58%</td>
</tr>
<tr>
<td>PD solution glucose concentration^b</td>
<td>Without any 2.5% or 4.25% use</td>
<td>17%</td>
<td>68%</td>
<td>22%</td>
<td>52%</td>
</tr>
<tr>
<td>Use of 2.5% but not 4.25%</td>
<td>77%</td>
<td>32%</td>
<td>66%</td>
<td>47%</td>
<td>51%</td>
</tr>
<tr>
<td>Use of any 4.25%^c</td>
<td>6%</td>
<td>0%</td>
<td>12%</td>
<td>1%</td>
<td>45%</td>
</tr>
</tbody>
</table>

^a. The first number assumes the anuric status of patients missing urine volume data is unknown and excludes these patients from the anuric % / Second number assumes patients missing urine volume data are anuric in order to account for the potential practice in some countries/facilities whereby urine volume is not reported for patients known to be anuric.

^b. PD solution type only provided by non-LDOs in the US.

^c. Abbreviations: BSA, body surface area; Kt/V, urea clearance; PD, peritoneal dialysis; UK, United Kingdom; US, United States

The US is hyper focused on solute clearance at the expense of optimal volume management

Presentation Plan

Volume Status in PD

Physiology of Ultrafiltration

Volume Management: Prescription Design
- Short Dwell
- Long Dwell

Volume Management: Beyond Glucose

Volume Overload
- Diagnosis
- Management
Minimizing Glucose Exposure

**Techniques to Minimize Glucose Exposure**

- Incremental start
  - Dry periods with compensating RRF
- Diuretic use UO >100 mL/day
- 2 gm Na+ diet
- Fluid restriction
- Icodextrin use
  - glucose free solution

Incremental Start: Initiation with Full Dose PD Often not Required

- RKF CONTRIBUTES TO TOTAL $Kt/V$
- WHAT GFR GIVES A $Kt/V$ OF $1.7$ WITHOUT DIALYSIS?

9.7 mL/min/1.73 m²

(computer modeled from 1200 patients)¹

GFR at dialysis initiation²

<table>
<thead>
<tr>
<th>GFR</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;15</td>
<td>10.6%</td>
</tr>
<tr>
<td>10-14</td>
<td>27.3%</td>
</tr>
<tr>
<td>5-9</td>
<td>47.9%</td>
</tr>
<tr>
<td>&lt;5</td>
<td>14.2%</td>
</tr>
</tbody>
</table>

As RKF declines the dose of dialysis must increase.

2. USRDS 2019 Vol 2 fig 1.19
Volume Management: ISPD Recommendations 2020

01 Initial PET 6-12 weeks post training; repeat as clinically indicated. 1,2
Routine monitoring: PET, volume status, BP & clinical exam3

02 Icodextrin to improve UF independent of transport type4
“Compared to glucose, use of icodextrin can translate into improved fluid status and fewer episodes of fluid overload”2

03 Dietary counseling of appropriate salt / water intake1

04 Protection of RRF5; Loop diuretics if RRF present1
Furosemide 160-480 mg/day (split-2 doses)6
Metolazone 5-10 mg/day6

05 Preservation of peritoneal membrane function1
Avoid peritonitis & hypertonic glucose solutions

Volume Management

CANADIAN SOCIETY OF NEPHROLOGY GUIDELINES 2011

• Treatment of hypervolemia
  - 3.2.1 Sodium intake should be restricted to 65 mmol (1500 mg) or less daily in pts with hypervolemia
  - 3.2.2 In patients with RRF, high-dose diuretics (furosemide 250 mg with or without metolazone 5 mg po QD) increase sodium excretion and urine volume
  - 3.2.3 Hypertonic 4.25% dextrose solution may be required to achieve euvolemia: however, sustained use of such solution is not desirable
  - 3.2.4 Icodextrin solution is preferred over glucose-based dialysate for long-duration (>8 hour) dwells
Fluid Management in PD

47 hypertensive CAPD patients

- Na⁺ Restriction
  - 20 normotensive
  - Na⁺ Restriction and ↑UF
    - 17 normotensive*
    - 7 hypertensive
      - 3 hypertensive

- 27 hypertensive

- 3 normotensive with enalapril
- 4 normotensive with enalapril

*37 (79%) patients normotensive by volume control alone

Strict Volume Control Normalizes BP

- Aggressive dietary approach, followed by UF approach, lowered the body wt 2.8 kg in 47 hypertensive PD pts
- BP 158/96 dropped to 120/78
- In 19 pts with RRF, daily urine volume dropped to 28% of pre-treatment
- Kt/V dropped from 2.06 to 1.85 with loss of RRF

ISPD 2020:
High-quality PD should achieve and maintain clinical euvoolemia while accounting for RKF and its preservation. Avoid RKF compromise by considering both peritoneal UF and UO in patient management.

Does Attainment of Euvolemic Necessarily Affect RKF Adversely?

- Multicenter, double blind, RCT of icodextrin vs. 2.5% dextrose for long dwell
- N=50, high transporters with UO <750 mL/day
- Icodextrin group lost weight, total body water and salt, dextrose group gained all three (p<0.05)
- BP control not different
- Urine volume better maintained in icodextrin group
  - Difference: 89 mL/d (p<0.04)

**Volume Management: ISPD Recommendations 2020**

1. **Initial PET 6-12 weeks post training; repeat as clinically indicated.**¹,²
   - Routine monitoring: PET, volume status, BP & clinical exam³  

2. **Icodextrin to improve UF independent of transport type**⁴
   - “Compared to glucose, use of icodextrin can translate into improved fluid status and fewer episodes of fluid overload”²

3. **Dietary counseling of appropriate salt / water intake**¹

4. **Protection of RRF; Loop diuretics if RRF present**¹
   - Furosemide 160-480 mg/day (split-2 doses)⁶
   - Metolazone 5-10 mg/day⁶

5. **Preservation of peritoneal membrane function**¹
   - Avoid peritonitis & hypertonic glucose solutions

---

## CANUSA Study: Effect of Residual Renal Function and Urine Volume on Mortality

### Table 2: Cox model of relative risk of death with time-dependent CCr divided into peritoneal clearance and GFR and entered as time-dependent covariates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Risk</th>
<th>95% Confidence Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.02</td>
<td>1.005-1.044</td>
</tr>
<tr>
<td>CVD</td>
<td>2.42</td>
<td>1.499-3.904</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.25</td>
<td>0.769-2.036</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>0.96</td>
<td>0.912-1.000</td>
</tr>
<tr>
<td>LA transport</td>
<td>1.66</td>
<td>0.379-7.218</td>
</tr>
<tr>
<td>HA transport</td>
<td>2.33</td>
<td>0.554-9.801</td>
</tr>
<tr>
<td>H transport</td>
<td>2.01</td>
<td>0.430-9.357</td>
</tr>
<tr>
<td>SGA</td>
<td>0.74</td>
<td>0.647-0.842</td>
</tr>
<tr>
<td>Ccrp (5 L/wk per 1.73m² greater)</td>
<td>1.00</td>
<td>0.898-1.105</td>
</tr>
<tr>
<td>GFR (5 L/wk per 1.73m² greater)</td>
<td><strong>0.88</strong></td>
<td>0.829-0.943</td>
</tr>
</tbody>
</table>

### Table 3: Cox model of relative risk for death with urine volume forced in as a time-dependent covariate

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Risk</th>
<th>95% Confidence Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (1 yr older)</td>
<td>1.02</td>
<td>1.002-1.041</td>
</tr>
<tr>
<td>CVD</td>
<td>2.37</td>
<td>1.465-3.821</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.31</td>
<td>0.807-2.134</td>
</tr>
<tr>
<td>Serum albumin (1 g/L increase)</td>
<td>0.96</td>
<td>0.914-1.003</td>
</tr>
<tr>
<td>LA transport</td>
<td>1.84</td>
<td>0.418-8.075</td>
</tr>
<tr>
<td>HA transport</td>
<td>2.71</td>
<td>0.631-11.623</td>
</tr>
<tr>
<td>H transport</td>
<td>2.46</td>
<td>0.523-11.590</td>
</tr>
<tr>
<td>SGA (1 unit greater)</td>
<td>0.78</td>
<td>0.672-0.876</td>
</tr>
<tr>
<td>Ccrp (5 L/wk per 1.73m² greater)</td>
<td>0.93</td>
<td>0.795-1.079</td>
</tr>
<tr>
<td>GFR (5 L/wk per 1.73m² greater)</td>
<td>0.99</td>
<td>0.943-1.044</td>
</tr>
<tr>
<td>Urine vol (250 ml daily greater)</td>
<td><strong>0.64</strong></td>
<td>0.508-0.800</td>
</tr>
</tbody>
</table>
Higher residual urine volume was significantly associated with a lower risk of death and exhibited a stronger association with mortality than GFR calculated using 24-hour urine collection and eGFR-urea, creatinine.

Monitoring residual urine volume may be beneficial to predict survival of dialysis pts.
Icodextrin: Urine Output

MULTI-CENTER PROSPECTIVE RCT: N=100 CAPD; UO ≥ 750CC/DAY RANDOMIZED TO ICODEXTRIN VS. 1.5% / 2.5% DEXTROSE-BIOCOMPATIBLE SOLUTIONS.

No difference in GFR; better preservation of urine output

1.2 USE OF DIURETICS TO PRESERVE RRF

Recommendations:

- 1.2.3 Strong consideration should be given to the use of high-dose oral furosemide (up to 250 mg daily) and oral metolazone (up to 5 mg daily) in all PD patients with significant (>100 mL daily) urine output, provided that this is not associated with signs and symptoms of postural hypotension or volume depletion (grade B).
Why such high diuretic doses?

FUROSEMIDE 160-480 MG/DAY (SPLIT-2 DOSES) & METOLAZONE 5-10 MG/DAY

Per Dr George Arnoff’s book: Drug Prescribing in Renal Failure:

- Furosemide, bumetanide, & ethacrynic acid are organic acids which must reach the tubular lumen to be active.

- “In patients with impaired renal function, endogenous organic acids accumulate and compete with diuretics for secretion into the tubular lumen.”

- “Consequently, as renal function decreases, larger doses of diuretics are required.”

• 61 CAPD patients new to dialysis randomized to furosemide 250 mg/day or control
• Change in urine volume: +6.47 vs. -23.3 mL/mo (P = 0.047)
• No effect on rate of decline of urinary solute clearances
Triple Diuretic Treatment: CAPD

TWO PHASE PROSPECTIVE, DOUBLE BLIND RCT (6 MONTH)

SINGLE DRUG ARM
Furosemide:
1,000 mg/day

TRIPLE DRUG ARM
- Furosemide:
  1,000 mg/day
- HCTZ:
  100mg/day
- Spironolactone:
  50 mg/day

Triple diuretic therapy blocks Na+ through whole nephron

There was no serious adverse event in this study.

Table 2. Overhydration measured by BIS in the single diuretic group and the triple diuretic group at baseline, 3rd month, and 6th month of study

<table>
<thead>
<tr>
<th>OH (L)</th>
<th>Single diuretic</th>
<th>Triple diuretics</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.27 ± 2.35</td>
<td>2.94 ± 2.08</td>
<td>0.34</td>
</tr>
<tr>
<td>3rd month</td>
<td>2.03 ± 1.80</td>
<td>1.03 ± 0.68</td>
<td>0.01</td>
</tr>
<tr>
<td>6th month</td>
<td>2.78 ± 2.42</td>
<td>1.39 ± 1.64</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Table 4. Adverse event profiles

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Single diuretic</th>
<th>Triple diuretics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia$^a$</td>
<td>4 (14.8)</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>Hypokalemia$^b$</td>
<td>7 (25.9)</td>
<td>6 (25.0)</td>
</tr>
<tr>
<td>Hyperkalemia$^c$</td>
<td>1 (3.7)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (3.7)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1 (3.7)</td>
<td>1 (4.2)</td>
</tr>
</tbody>
</table>

Data are presented as number (%).

$^a$Serum sodium < 135 mmol/L, $^b$serum potassium (K) < 3.5 mmol/L, $^c$K > 5.5 mmol/L.

“There was no serious adverse event in this study.”
Long Term Diuretics in HD Patients

N=13 HD patients studied over 1 year
(10 completed full year)

Furosemide doses:
3 = 250 mg/d
3 = 500 mg/d (in 2 doses)
1 = 750 mg/d (in 2 doses)
6 = 1000 mg/d (in 2 doses)

*Furosemide levels < 40 ug/ml (ototoxic level 85 ug/ml)*
• Audiometry at baseline and Q 3 months – no change in normal hearing range
• Bullous Dermatitis – in 2 of 10 (sunlight induced)

<table>
<thead>
<tr>
<th>URINE</th>
<th>MONTHS</th>
<th>MEDIAN</th>
<th>RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume ml/day</td>
<td>0</td>
<td>750</td>
<td>120-1.290</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.250*</td>
<td>200-1.840</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>960*</td>
<td>180-1.580</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>625</td>
<td>140-1.580</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>710</td>
<td>180-1.820</td>
</tr>
<tr>
<td>Na+ mmol/day</td>
<td>0</td>
<td>37</td>
<td>6-68</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>75*</td>
<td>16-115</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>54*</td>
<td>12-142</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>40</td>
<td>9-155</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>41</td>
<td>9-153</td>
</tr>
<tr>
<td>Cl- mmol/day</td>
<td>0</td>
<td>14</td>
<td>2-49</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>69*</td>
<td>16-103</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>52*</td>
<td>12-118</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>40**</td>
<td>9-135</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>42**</td>
<td>10-144</td>
</tr>
<tr>
<td>K+ mmol/day</td>
<td>0</td>
<td>21</td>
<td>1-45</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>28*</td>
<td>2-55</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>27**</td>
<td>3-49</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>16</td>
<td>2-56</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>28**</td>
<td>9-50</td>
</tr>
<tr>
<td>Ca2+</td>
<td>0</td>
<td>0.40</td>
<td>0.12-1.35</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.04**</td>
<td>0.35-2.30</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>1.05**</td>
<td>0.26-2.36</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>0.62</td>
<td>0.21-2.18</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>0.69</td>
<td>0.19-2.19</td>
</tr>
<tr>
<td>Osmolality mosm/kg</td>
<td>0</td>
<td>296</td>
<td>212-445</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>287</td>
<td>223-323</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>275</td>
<td>207-328</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>284</td>
<td>182-332</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>280</td>
<td>229-359</td>
</tr>
<tr>
<td>F, mg/day (Furosemide excretion)</td>
<td>0</td>
<td>11.9</td>
<td>2.1-33.4</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>8.9**</td>
<td>1.9-26.8</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>7.9*</td>
<td>1.4-26.6</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>7.5*</td>
<td>1.1-27.2</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>7.5*</td>
<td>1.1-27.2</td>
</tr>
<tr>
<td>ECC ml/min/1.73 m² (Endogenous Creatinine Clearance)</td>
<td>0</td>
<td>5.6</td>
<td>0.7-6.8</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>4.5**</td>
<td>0.6-6.4</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>4.3**</td>
<td>0.6-6.3</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>3.2**</td>
<td>0.5-6.0</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>1.9**</td>
<td>0.5-5.9</td>
</tr>
</tbody>
</table>

*p<0.005  **p<0.02

1.2.2 Angiotensin converting-enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) should be strongly considered, unless contraindicated, in all PD patients with significant (>100 mL daily) urine output.

1.2.3 Strong consideration should be given to the use of high-dose oral furosemide (up to 250 mg daily) and oral metolazone (up to 5 mg daily) in all PD patients with significant (>100 mL daily) urine output, provided that this is not associated with signs and symptoms of postural hypotension or volume depletion.
Effect of ACE-I & ARB on RRF in PD: 2 RCTs


**Multivariate analysis, Ramipril 5 mg/day vs. placebo:**
- RKF loss at 12 mo:
  - 2.07 ml/min Ramipril
  - 3.00 ml/min control (p=0.03)

**Valsartan 40-80 mg/day vs. placebo.** p<0.01 increased residual CrCl by 2-3 ml, residual diuresis by 200-300 ml/day and weekly total clearance
Risk Factors for Loss of RKF

- Radiocontrast dye
- Aminoglycoside antibiotics
- NSAIDS, including cox-2 inhibitors
- ECF volume depletion
- Urinary tract obstruction
- Hypercalcemia
- Withdrawal of immunosuppressive therapy from transplanted kidney
Volume Management: ISPD Recommendations 2020

01 Initial PET 6-12 weeks post training; repeat as clinically indicated. 1,2
   Routine monitoring: PET, volume status, BP & clinical exam3

02 Icodextrin to improve UF independent of transport type4
   “Compared to glucose, use of icodextrin can translate into improved fluid status and fewer episodes of fluid overload”2

03 Dietary counseling of appropriate salt / water intake1

04 Protection of RRF5; Loop diuretics if RRF present1
   Furosemide 160-480 mg/day (split-2 doses)6
   Metolazone 5-10 mg/day6

05 Preservation of peritoneal membrane function1
   Avoid peritonitis & hypertonic glucose solutions

Longitudinal Relationship Between Solute Transport and Ultrafiltration Capacity in Peritoneal Dialysis Patients

- Single center retrospective observational study
- Cohort: All patients from 1990-2003
- 574 new patients available for study with annual PET data
Long-term Functional Effects on the Peritoneal Membrane

MEMBRANE AT PD INITIATION


MEMBRANE OVER TIME ON PD:
↑ FIBROSIS AND ANGIOGENESIS
Low Glucose Therapy
May Stabilize Peritoneal Membrane Function

UK Renal Association: Minimizing Glucose Exposure

Avoid use of 4.25% & 2.5% as much as possible due to systemic effects:¹

- Poor DM control and Hyperinsulinemia
- Weight gain

Minimize hypertonic solution use:

- Diuretics to maximize residual diuresis
  - furosemide 250mg QD
- Substitute icodextrin for glucose during long dwell

ISPD: Both loop diuretics and icodextrin help maintain fluid balance in PD patients²

Possible Membrane Preservation

MESOTHELIAL RAAS SYSTEM

Ang II → TGFβ1

Ang I → ACE

Angiotensinogen → Renin

Glucose

Effect of Valsartan vs. Lisinopril on Peritoneal Sclerosis in Rats

A. Normal-Sham Rats

B. PD Solution (3.86%) only

C. 3.86% + Valsartan
   (10-15 mg/day)

D. 3.86% + Lisinopril
   (2-2.5 mg/day)

ACEI Effect on Peritoneal Membrane Function PD Patients

## Presentation Plan

<table>
<thead>
<tr>
<th>Volume Status in PD</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Physiology of Ultrafiltration</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Volume Management: Prescription Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Short Dwell</td>
</tr>
<tr>
<td>• Long Dwell</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Volume Management: Beyond Glucose</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Volume Overload</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diagnosis</td>
</tr>
<tr>
<td>• Management</td>
</tr>
</tbody>
</table>
Fluid Overload vs. UF Insufficiency

Fluid overload is a clinical syndrome with multiple components and etiologies.

Ultrafiltration insufficiency is a pathophysiologic characterization of one of the causes of the clinical syndrome.

Distinction between syndrome and causation determines further intervention.

Volume overload is not always UF insufficiency!
### Essential Clinical Evaluation of Volume Overload

#### Work-up

1. History & physical exam
2. Observe a 2-liter rapid in and out exchange to assess flow mechanics
3. Perform a 2-liter 4.25% dextrose PET

---

**Residual Renal Function**

<table>
<thead>
<tr>
<th>Residual Renal Function</th>
<th>Reversible Issues</th>
<th>Membrane Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate Prescription</td>
<td>Dietary Indiscr...</td>
<td>Mechanical Issues</td>
</tr>
<tr>
<td>Dwell time</td>
<td>Deficient educat...</td>
<td>Malposition</td>
</tr>
<tr>
<td>Dialysate tonicity</td>
<td>Complex regimen</td>
<td>Obstructions</td>
</tr>
<tr>
<td></td>
<td>Burn-out</td>
<td>Leaks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Entrapment</td>
</tr>
</tbody>
</table>

**Membrane Evaluation**

- Modified PET

---

Evaluation of UF Insufficiency

MODIFIED PET: RULE OF FOURS

- 2 L of 4.25% dextrose (rather than 2.5%)
- Do an additional measure of dialysate sodium at 60 min
- Abnormal findings indicating possible UF Insufficiency
  - Ultrafiltration < 400 mL
  - Dialysate sodium dip ≤ 5 meq/L at 60 min indicates UF insufficiency

Membrane Evaluation

**Low UF capacity identified**

Net UF at 4 hours <400 ml using 4.25%

- 2 patients with 300 ml UF at 4 hours
  - Pt 1
    - Dialysate Na+ 125 mEq/L at 60 min
  - Pt 2
    - Dialysate Na+ 129 mEq/L at 60 min

Rule out mechanical problems/leaks

**Fast Peritoneal Solute Transfer Rate**

Local inflammation
-(interstitial thickening & peritoneal membrane capillary proliferation)
- Inherent fast transfer rate
  - variability present at baseline
- Acquired membrane injury
  - Long-term PD/Peritonitis

**Low osmotic conductance to glucose**

Reduced free water transport
-(decreased AQP1 function)
- Intrinsic low UF
  - variability present at baseline
- Acquired membrane injury
  - Progressive fibrosis/vasculopathy
  - At risk for Encapsulating Peritoneal Sclerosis

Summary

**VOLUME MANAGEMENT: ISPD RECOMMENDATIONS 2020**

01. Routine monitoring: PET¹, volume status, BP & clinical exam²

02. Icodextrin to improve UF independent of transport type³

03. Dietary counseling of appropriate salt / water intake¹

04. Protection of RRF⁴; Loop diuretics if RRF present¹
   - Furosemide 160-480 mg/day (split-2 doses)⁵
   - Metolazone 5-10 mg/day⁵

05. Preservation of peritoneal membrane function¹
   - Avoid peritonitis & hypertonic glucose solutions

---

QUESTIONS?

Lucy_Todd@Baxter.com

LBTodd170@gmail.com
SUPPLEMENTAL SLIDES
Management of Fluid Overload in APD

Dietary salt and fluid restriction

Initiate or increase diuretics if residual kidney function present (>100 mL day)

Optimize peritoneal sodium and water removal

Eliminate or shorten exchanges with net fluid reabsorption

† to two daytime dextrose exchanges or one icodextrin exchange (minimum dwell time of 10 hours)

One 10-hour icodextrin exchange and one glucose exchange

Increase dextrose (DEX) concentration

Nine hour APD therapy should be ≤ 4 cycles in low or low average transporters and ≤ 5 cycles in high or high average transporters

Acutely and intermittently

Figure 1. A stepwise approach in managing a patient on PD with volume overload. APD, automated peritoneal dialysis; ICO, icodextrin; PD, peritoneal dialysis.
Membrane Dysfunction Classifications

### Fast Peritoneal Solute Transfer Rate

*Local inflammation*

- Inherent fast transfer rate
  - *variability present at baseline*
- Acquired membrane injury
  - *Long-term PD/Peritonitis*

### Low osmotic conductance to glucose

*Reduced free water transport*

- Intrinsic low UF
  - *variability present at baseline*
- Acquired membrane injury
  - *Progressive fibrosis/vasculopathy*
  - *most serious outcome is EPS*

---

**Definition**
- D/P creatinine ratio above the population mean value at the end of a 4-hr PET using either 2.27/2.5% or 3.86/4.25% glucose/dextrose-based solutions. While most studies report that PSTR is normally distributed, with a typical average value of 0.65, multicenter studies show a significant center effect.
- Can be present at the start of PD and/or develop or resolve over time

**Pathophysiology**
- Membrane inflammation causing a large effective vascular surface area
- Neovascularization
- Both the above may potentially be, in part, genetically determined

**Definition**
- Sodium dip at 60 min ≤5 mmol/l or sodium sieving ratio <0.07 with a 3.86% glucose/4.25% dextrose PET

**Pathophysiology 1**
- Explanations largely not understood
- Potential influence of genetic determinants (e.g. aquaporin expression)
- Note: a low ∆D$_{Na}$ 0-60 min can also be observed in patients with very fast PSTR due to early dissipation of the osmotic gradient

**Pathophysiology 2**
- Structural alterations in the peritoneal interstitium in keeping with progressive fibrosis
- Usually associated with fast PSTR

---