

# **Importance of UF and Clinical Management in PD**

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## **DISCLOSURES**

Dr Abu-Alfa has served as a Consultant for Baxter Healthcare, and has received research grants and honoraria for speaking engagements and/or organization of PD educational conferences from Baxter Healthcare.

Dr Abu-Alfa is the immediate past co-President for the North American Chapter of the International Society for Peritoneal Dialysis.

## Educational Objectives

- Discuss fluid balance in PD with focus on clinical needs, goals and effect on outcomes.
- Identify areas of interventions for optimization of fluid removal.
- Identify patients at risk for fluid retention.
- Review role of alternative osmotic agents: Icodextrin.
- Review ISPD guidelines and clinical algorithms for fluid management in PD.

## Rationale for Fluid Management in PD

- Maintaining a clinically-guided adequate fluid balance is an important function of renal replacement therapy.
- Achieving optimal fluid balance should be considered a component of overall PD adequacy as therapy.
- Optimal fluid management plays an important role in patient outcomes.

4

Optimal fluid management in PD is highly desired for many reasons. Fluid management is not the same as UF management, although the latter is a very important component in achieving fluid balance.

## Goals of Fluid Management in PD

- Reduction in Symptomatic Fluid Retention.
- Blood pressure control:
  - Preservation of Residual Renal Function.
  - Prevention or mitigation of Cardiovascular Disease (IHD, LVH, CHF, CVA, PVD).
  - Reducing accelerated atherosclerosis process.
  - Prevention of symptoms simulating uremia.
- Reduction in mortality.

5

One should differentiate between symptomatic fluid retention and hypertension, which is still a manifestation of excess fluid

## Symptomatic Fluid Retention in PD

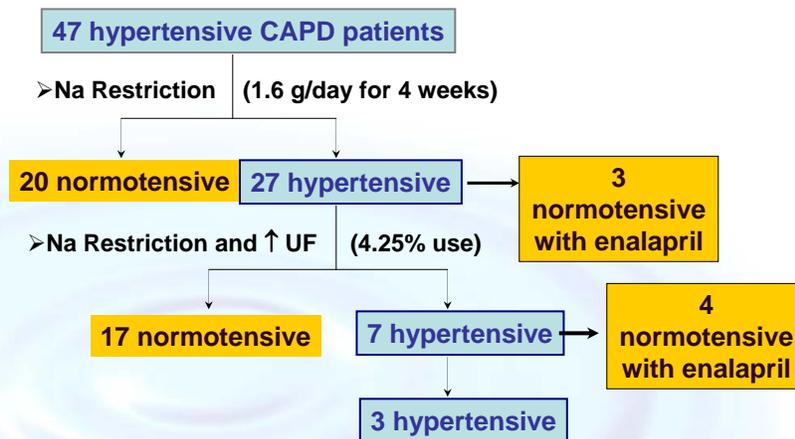
- 71 Episodes of SFR were identified in 66 PD patients.
- High rates of non-compliance with dietary salt and fluid restrictions as well as PD prescription were noted in the SFR group when compared to a control group (149 pts).
- Edema (100%), pulmonary congestion (80%) and hypertension (83%) were the most common manifestations of SFR.

Tzamaloukas et al, *JASN* (6): 198-206, 1995

6

In a important study, it was noted that many PD patients had SFR in an earlier era, but HTN remains the more common problem today.

## Fluid Removal and Na Restriction: Impact on Blood Pressure Control



Gunal et al, *AJKD* (37): 588-193, 2001

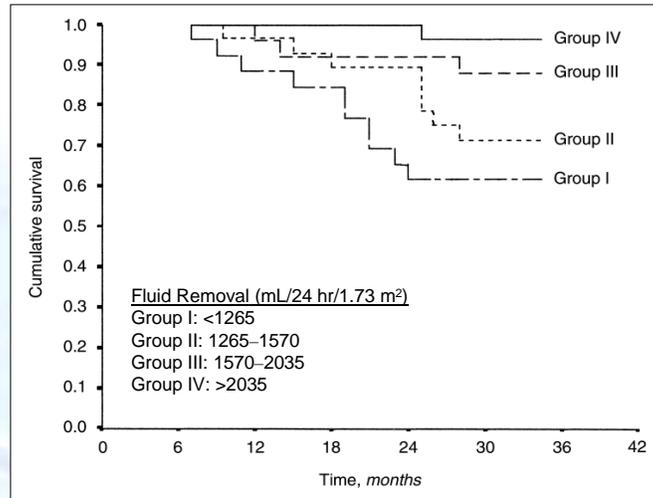
7

Hypertension could be controlled with strict dietary Na restriction (about 1.6 g per day) in about 43% of patients in this study from Turkey.

Addition of one hypertonic 4.25% exchange pre day resulted in most of the remaining patients having better BP control.

Few needed an ACEi for BP control.

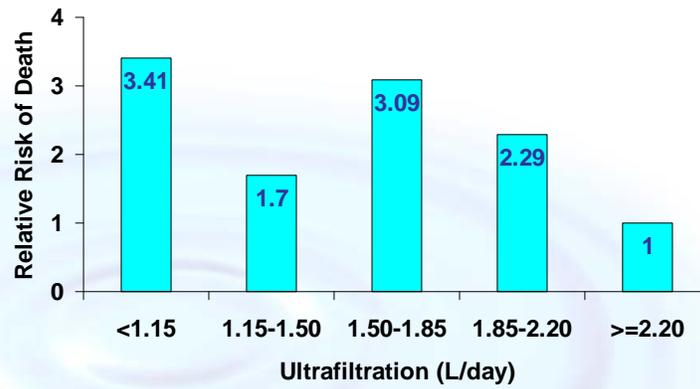
## Fluid Removal in PD: Impact on Survival



Ates et al. *Kidney Int.* 2001, (60):767-776.

8

## Fluid Removal in PD: Ultrafiltration Volume and Survival



Jansen, et al. *Kidney Int.* 2005;68:1199-1205.

9

There is vague relationship between net UF volume and RR of death from a European experience.

## Fluid Removal in PD: Urine Volume Effect on Survival

- Re-analysis of data from CANUSA study:
  - Effects of peritoneal and renal clearances on survival in 601 patients
  - Addition of 24-hour urine volume as a time-dependent covariate showed a marked association with the relative risk (RR) of death.
  - Each 250-mL increase in daily urine volume associated with a 36% decrease in the RR of death (RR, 0.64; 95% CI, 0.51 to 0.80).

Bargman, et al. *J Am Soc Nephrol.* 2001;12:2158-2162.

10

The CANUSA study was reanalyzed. UO was the most important determinant of survival with each 250 cc imparting a significant risk reduction for death. This highlights the importance of preserving residual renal function.

## **Fluid Management in PD: Areas of Potential Intervention**

- Dietary Evaluation.
- Residual renal function:
  - Use of diuretics.
  - Use of ACEI and ARB to preserve RRF.
- Compliance: Quality of life issues.
- Characterization of edema :
  - Leaks and hernias.
- Catheter function and outflow obstruction.
- Peritoneal UF profile:
  - Optimizing Prescription.

Mujais, et al. *Perit. Dial Int.* 2000;20(suppl 4):S5-S21.

11

Optimal fluid management in PD requires many interventions.

## Fluid Management in PD: Role of Diuretics

- 61 CAPD patients new to dialysis randomized to receive furosemide 250 mg/day or serve as controls.
- Change in urine volume: +6.47 vs -23.3 mL/month ( $P = 0.047$ ).
- No effect on rate of decline of urinary solute clearances.

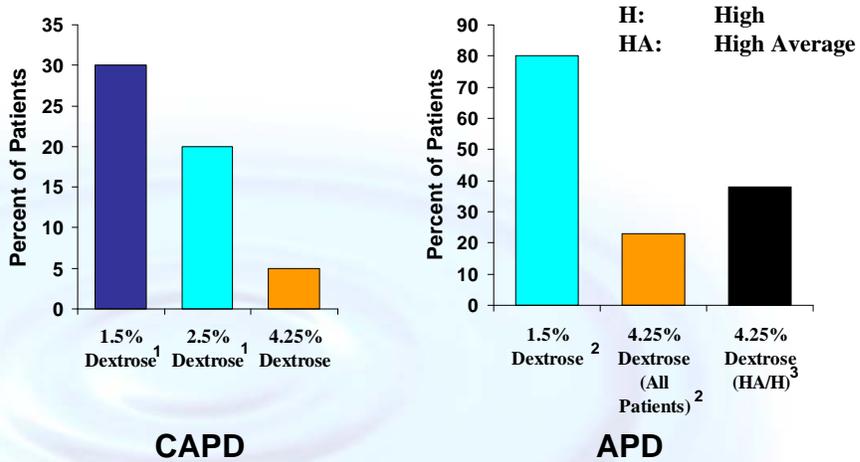
	Urine Volume (mL/24 hr)		
	Baseline	Month 6	Month 12
<b>Furosemide 250 mg/day (n = 31)</b>	<b>1020</b>	<b>1196</b>	<b>1070</b>
<b>Control (n = 30)</b>	<b>1040</b>	<b>840</b>	<b>733</b>

Medcalf J et al. *Kidney Int.* 2001;59:1128-1133.

12

Diuretics should be used early in PD, as highlighted in this study. The use of diuretics help reduce the need for hypertonic glucose early on in PD as desired. The use of diuretics do not affect clearance in this cohort as would be expected.

## Fluid Management in PD: Negative UF with Lower Glucose Solutions



<sup>1</sup> Wolfson, et al. *Kidney Int.* 2002;62(suppl 81):S46-S52  
<sup>2</sup> Woodrow, et al. *Nephrol Dial Transplant.* 1999;14:1530-1535  
<sup>3</sup> Finkelstein, et al. *J Am Soc Nephrol.* 2005;16:546-554.

The lower the glucose concentration used, the higher the chance that a long dwell will result in negative UF, or retention.

This is particularly true for patients with High, or High average as shown in the right panel, with 40% of those patients having a negative UF even when using 4.25% dextrose solutions.

## Fluid Management in PD: Long Dwell Limitations of Glucose

- Increased risk of fluid absorption and diminished or negative ultrafiltration<sup>1-2</sup>
- Reduced small solute clearance in high and high-average transporters<sup>1-2</sup>
- Possible adverse systemic metabolic effects from increased glucose absorption<sup>1,3</sup>
- Possible impact on peritoneal membrane function of hypertonic glucose exposure<sup>3</sup>

1. Twardowski ZJ. *Clinical Dialysis*. 3rd ed. Appleton & Lange; 1995:322-342.
2. Mujais S, et al. *Perit Dial Int*. 2000;20:S5-S21.
3. Mistry CD, Gokal R. *Perit Dial Int*. 1996;16:S104-S108.

14

There are also other limitations to using dextrose solutions in high/high average solutions.

## **Fluid Management in PD: Colloid Osmosis**

- Macromolecules with high reflection coefficients.
- Isotonic with plasma.
- Induces water transport across small intercellular pores.
- Enhances UF with increased vascular surface area.
- Maintains colloid osmotic pressure gradient for the duration of the long dwell due to slow rate of absorption via the lymphatic system.
- Avoids sodium sieving.
- Physiologic example: albumin.
- Availability for use in PD solutions: Icodextrin.

15

The use of a macromolecule such as icodextrin allows colloid osmosis to be the basis for fluid removal.

## Colloid Osmosis

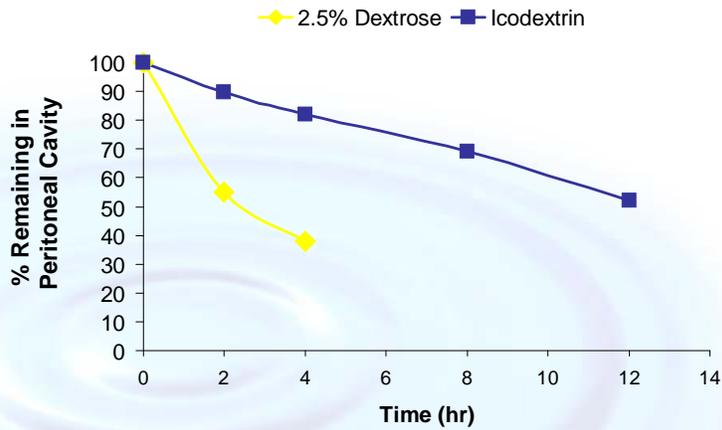
### Pharmacokinetics of Icodextrin

- Absorption:
  - Convective transport via lymphatic pathways
  - 40% (60 g) absorbed during 12-hour dwell
- Metabolism:
  - Metabolized by amylase to maltose
  - Maltose is metabolized by intracellular maltase to glucose
  - Predominantly in plasma; minimal peritoneal
  - Excreted via renal and dialytic clearances
- Plasma levels:
  - Reach steady-state within 1 week of initiation
  - Are stable during long-term therapy
  - Return to baseline within 7 days of discontinuation

16

This slide summarizes for metabolism of icodextrin. It is important the icodextrin does get absorbed but at a much slower rate and a less extent than Dextrose. Plasma levels of its metabolites (shorter molecules, of variable MW) stabilize by about 7 days when it is used for one exchange per 24 hours.

## Fluid Management in PD: Absorption Profiles of Icodextrin versus Glucose



Adapted from Moberly, et al. *Kidney Int.* 2002;62(suppl 81):S23-S33.

17

Comparative curves of glucose and icodextrin absorption over a typical 4 hrs dwell and 12 dwell respectively.

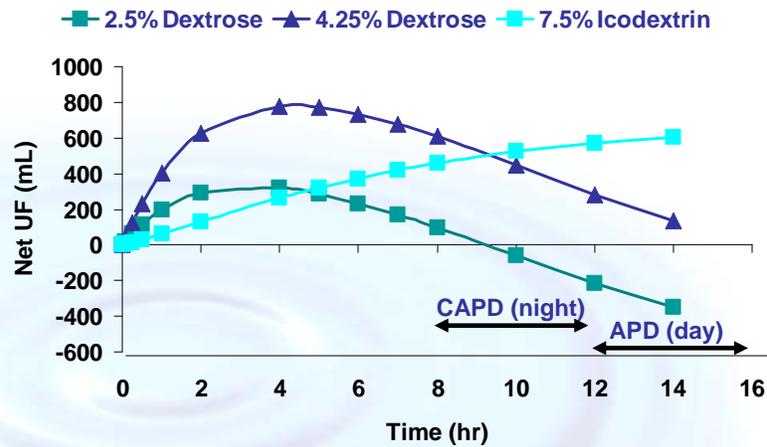
## Fluid Management in PD: Icodextrin Solution Composition

	Icodextrin-based Solution	Typical Glucose-based Solutions
Dextrose (g/dL)	—	1.5, 2.5, 4.25
Icodextrin (g/dL)	7.5	—
Sodium (mEq/L)	132	132
Chloride (mEq/L)	96	96
Calcium (mEq/L)	3.5	2.5
Magnesium (mEq/L)	0.5	0.5
Lactate (mEq/L)	40	40
Osmolarity (mOs/L)	282–286	344, 395, 483
pH	5.2	5.2

18

This table provides comparison between icodextrin (Extraneal, Baxter Healthcare) and typical commercial dextrose solutions (Dianeal, Baxter Healthcare). It is iso-osmolar to slightly hypo-osmolar relative to uremic plasma.

## Fluid Management in PD: Icodextrin Comparison with 2.5% and 4.25%



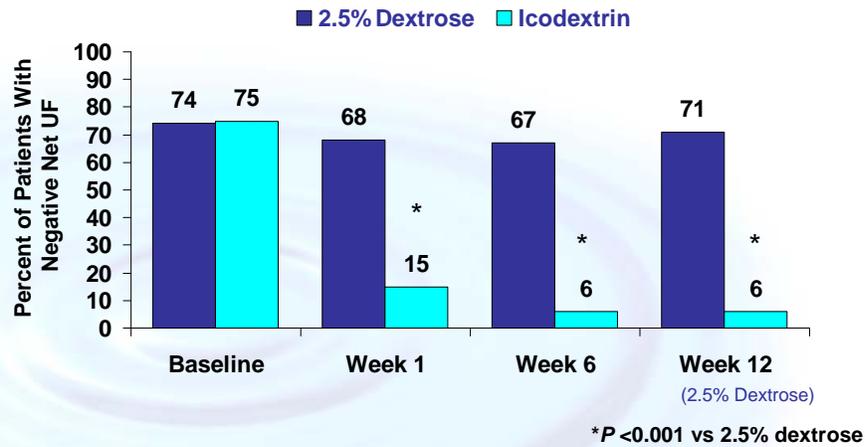
Adapted from Mujais S, Vonesh E. *Kidney Int.* 2002;62(suppl 81):S17-S22

19

The temporal profile of UF with icodextrin is distinct from that of glucose-induced UF. There is a slower but constant rise in net UF during a long dwell, as compared to hyperbolic curve for glucose.

Hypertonic glucose remains the Rx for choice for immediate UF as in pulmonary edema using 45 mins successive dwells, as icodextrin will not be effective in this situation and should not be used for that immediate purpose.

## Long Dwell in APD: 7.5% Icodextrin vs 2.5% Dextrose

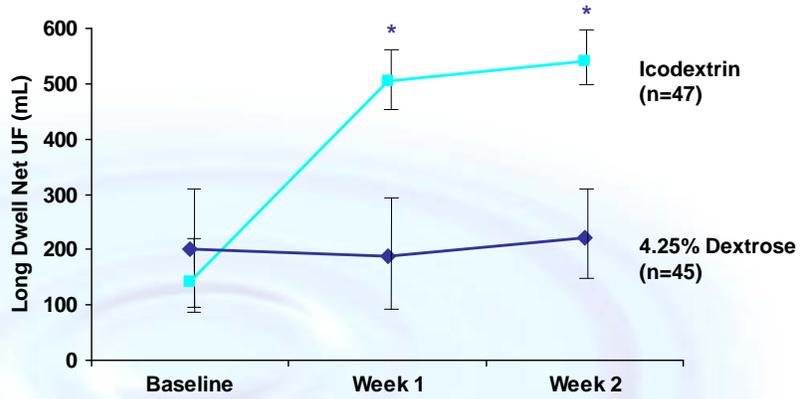


Wolfson, et al. *Kidney Int.* 2002;62(suppl 81):S46-S52

20

This study showed that the use of Icodextrin resulted in a significant decrease in % of patients having a negative UF during the long dwell of APD, when Icodextrin was compared to 2.5% Dextrose. The patient population included all transport types.

## Long Dwell in APD: High Transport 7.5% Icodextrin vs 4.25% Dextrose



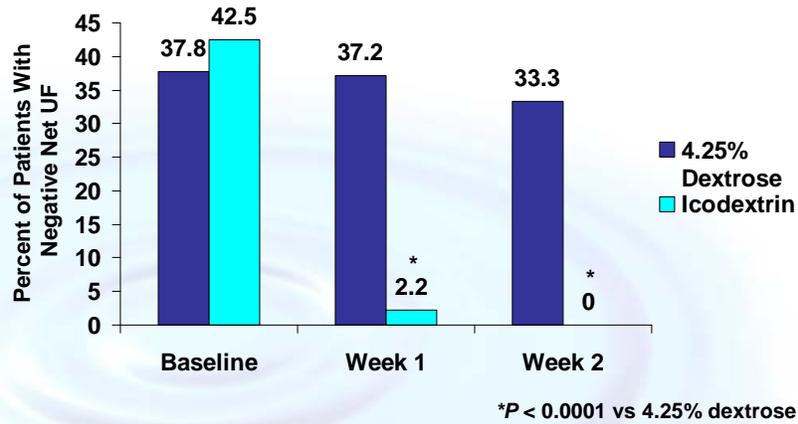
\* $P < 0.001$  vs 4.25% dextrose (adjusted for baseline values).

Finkelstein, Abu-Alfa et al. *J Am Soc Nephrol* 2005;16:546-554

21

In an RCT limited to patients with high transport membrane profile, the use of icodextrin resulted in a significantly larger UF volume when used for the long dwell as compared to 4.25% dextrose solution.

## Long Dwell in APD: High Transport 7.5% Icodextrin vs 4.25% Dextrose

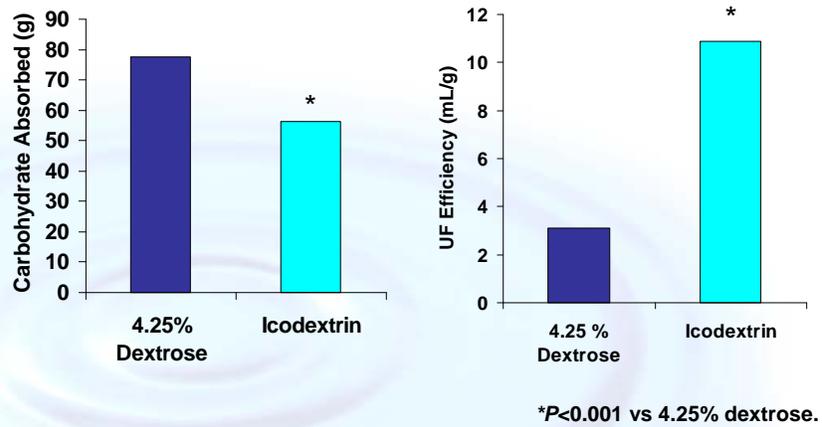


Finkelstein, Abu-Alfa et al. *J Am Soc Nephrol* 2005;16:546-554

22

When analyzed in terms of % of patients with negative UF, no patients had a negative UF with Icodextrin as compared to about 33% of those using 4.25% dextrose.

## Long Dwell in APD: High Transport 7.5% Icodextrin vs 4.25% Dextrose



Mujais and Lin. *Perit Dial Int.* 2006;26(suppl 1):S4.

23

The use of Icodextrin in the same RCT was associated with lower CHO absorption as compared to 4.25%. When effect was expressed as ml UF/ gram of CHO absorbed, the UF efficiency index was almost 4 folds higher for Icodextrin as compared to 4.25% in this group of patients with High transport profile.

## 7.5% Icodextrin versus Dextrose: Lack of Effect on RRF

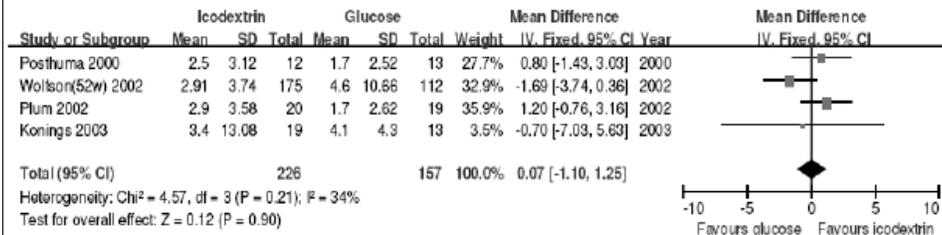


Figure 5 — Comparison of the effects of icodextrin and glucose on residual renal function. IV = inverse variance statistical method.

Qi H et al; Peritoneal Dialysis International 2011; Epub Nov 30, 2010

24

Icodextrin use has not resulted in any negative effect on residual renal function, in this small meta-analysis of available data.

## 7.5% Icodextrin versus 4.25%: Membrane Changes in Rat Model

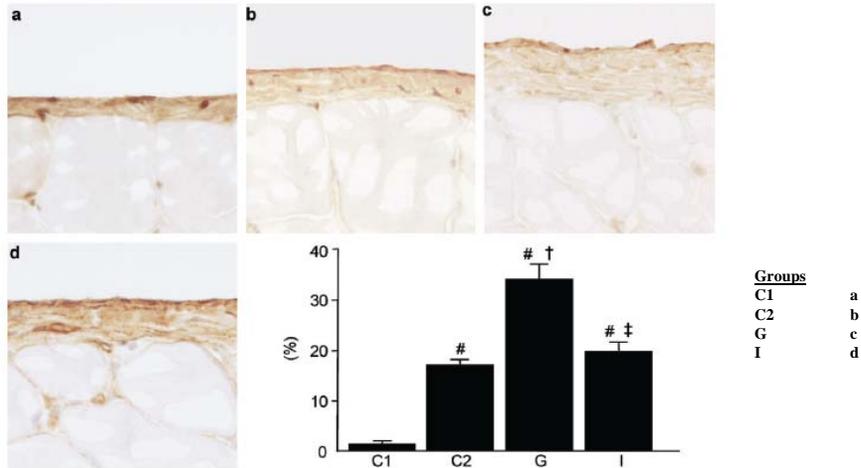


Fig. 5. Fibrosis was evaluated with fibronectin immunostaining of the peritoneum for the (a) control group, (b) diabetic rats with 5/6 kidney ablation, (c) diabetic rats with 5/6 kidney ablation injected standard 4.25% glucose-based peritoneal dialysis fluid (PDF) for 8 weeks ( $n = 8$ ), (d) diabetic rats with 5/6 kidney ablation injected 7.5% icodextrin -based PDF for 8 weeks ( $n = 8$ ). <sup>#</sup> $P < 0.05$  versus C1, <sup>†</sup> $P < 0.05$  versus C2, <sup>‡</sup> $P < 0.05$  versus G.

Nakao A et al: *Nephro Dial Transplant* 2010; 25: 1479-1488

25

The use of Icodextrin was associated with lower degrees of peritoneal fibrosis as compared to 4.25% glucose solution, and at a comparable to unexposed diabetic rates with 5/6 nephrectomy. This again demonstrates the effect of uremia on the peritoneal membrane per se, and the accentuation of this effect with the use of hypertonic glucose.

## Icodextrin-based PD Solution: Important Risk Information

- Only use glucose-specific monitors and test strips to measure blood glucose levels in patients using icodextrin-based PD Solution.
- Blood glucose monitoring devices using glucose dehydrogenase pyrroloquinolinequinone (GDH PQQ) or glucose-dye-oxidoreductase (GDO)-based methods must not be used.
- Use of GDH PQQ or GDO based glucose monitors and test strips has resulted in falsely elevated glucose readings due to presence of maltose and has led patients or health care providers to withhold treatment of hypoglycemia or to administer insulin inappropriately.
- Information regarding glucose monitor and test strip methodology can be obtained from their manufacturers. For a list of toll free numbers for glucose monitor and test strip manufacturers, please contact the Baxter Renal Clinical Helpline 1-888-RENAL-HELP or visit [www.glucosesafety.com](http://www.glucosesafety.com)

EXTRANEAL (Icodextrin) Prescribing Information, Baxter Healthcare Corporation.

26

The use of Icodextrin requires careful attention to the type of glucometer strips being used by the patient, in the clinic, hospital and ER.

Interference of icodextrin metabolites is limited to the use of strips with GDH-PQQ or GDO based methods, with no interference with assays using glucose oxidase, hexokinase, including clinical laboratory methods.

A global website is available to verify the compatibility of glucometer strips from different manufacturers.

## Optimal Fluid Management: ISPD Guidelines

- Routine standardized monitoring and awareness of PET status
- Dietary counseling of appropriate salt and water intake.
- Protection of Residual Renal Function (RRF).
- Loop diuretics if RRF present.
- Patient education for enhanced compliance.
- Minimizing use of hypertonic glucose and monitoring for suboptimal UF response as a warning sign for possible ultra-filtration failure.
- Preservation of peritoneal membrane function.
- Hyperglycemia control.

Mujais, et al. *Perit Dial Int.* 2000;20(suppl 4):S5-S21  
Lo Wai-Kei et al: *Perit Dial Int.* 2006; 26: 520-522

27

ISPD guidelines for fluid management are summarized in this slide.

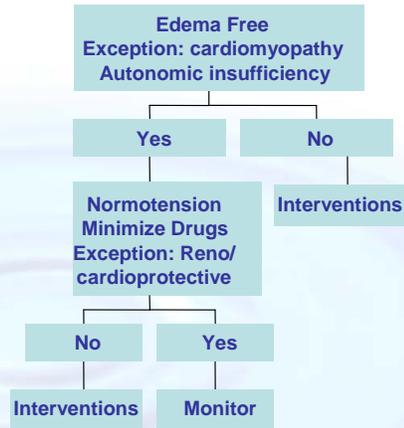
## **Optimal Fluid Management: Rational for Therapeutic Approach**

- Hypertension in ESRD is predominantly volume-dependent (salt sensitive).
- Correction of volume expansion in most ESRD patients leads to normalization of BP with limited anti-hypertensive medications.
- An edema-free state is a minimal requirement for normovolemia, but does not ensure presence of normovolemia.

28

A rationale for a proposed therapeutic algorithm is summarized in this slide. It is important to note that HTN remains the main manifestation of fluid excess in PD patients today, as compared to edema, symptomatic fluid retention.

## Optimal Fluid Management: Algorithm

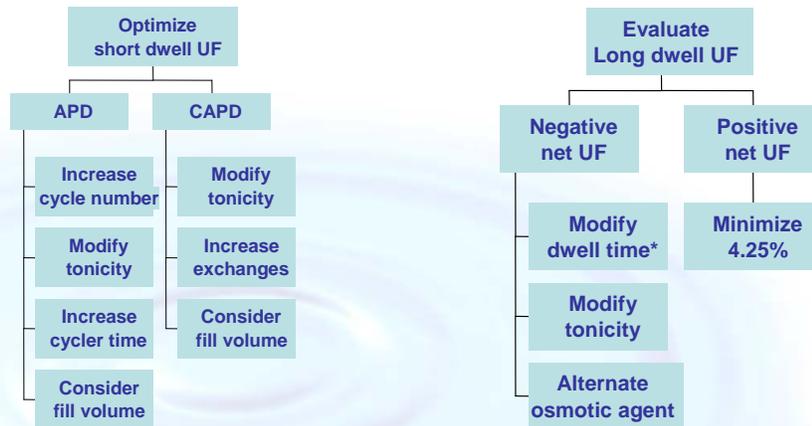


Abu-Alfa et al, *Kidney Int* (62), Suppl 81 (2002)

29

The proposed algorithms in this and following slides, are based on separating the shorts from the long dwells for both APD and CAPD, in terms of approach to optimizing UF.

## Optimal Fluid Management: Algorithms for Short and Long Dwells



\*Options include having a dry day, a mid-period drain or a full exchange.

Modified from Abu-Alfa et al, *Kidney Int* (62), Suppl 81 (2002)

30

## **Fluid Management in PD Summary**

- Monitoring and managing fluid balance is important in PD patients.
- Attaining an edema-free state and normotension should be the main therapeutic goals while minimizing need for hypertonic solutions.
- Use of icodextrin helps enhance fluid removal while reducing the need for hypertonic glucose solutions.
- Individualizing and separating the short and long dwells dialysis prescriptions will enhance ultra-filtration and overall fluid management.

31

Summary slide

## Questions



32

## Question 1

The use of diuretics in PD patients will result in faster loss of residual renal function while reducing the need for hypertonic dextrose solutions, complicating such use.

Is this statement:

- TRUE
- or
- FALSE

## Answer 1

The use of diuretics in PD patients will result in faster loss of residual renal function while reducing the need for hypertonic dextrose solutions, complicating such use.

The Answer is FALSE.

Use of diuretics can potentially result in significant volume depletion and loss of residual GFR. However, careful use of diuretics, in combination with appropriate dextrose concentrations while watching the patient closely is recommended in order to reduce the need for hypertonic dextrose solutions and potential changes to the membrane.

## Question 2

The use of icodextrin on daily basis will result in progressive accumulation of its metabolites. It is thus recommended to alternate its use with dextrose for the long dwells.

Is this statement:

- TRUE
- or
- FALSE

## Answer 2

The use of icodextrin on daily basis will result in progressive accumulation of its metabolites. It is thus recommended to alternate its use with dextrose for the long dwells.

The Answer is FALSE.

Use of icodextrin was evaluated following protocols using one daily bag for the long dwell of CAPD or APD. There was no progressive accumulation of metabolites in the plasma as levels stabilized after 1 week of use, and declined to background 1 week after discontinuation. Metabolites are metabolized to glucose, but some are cleared back through the peritoneal membrane into the dialysate during non-icodextrin dwells and through renal excretion.

36