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.

Goals of Fluid Management in PD

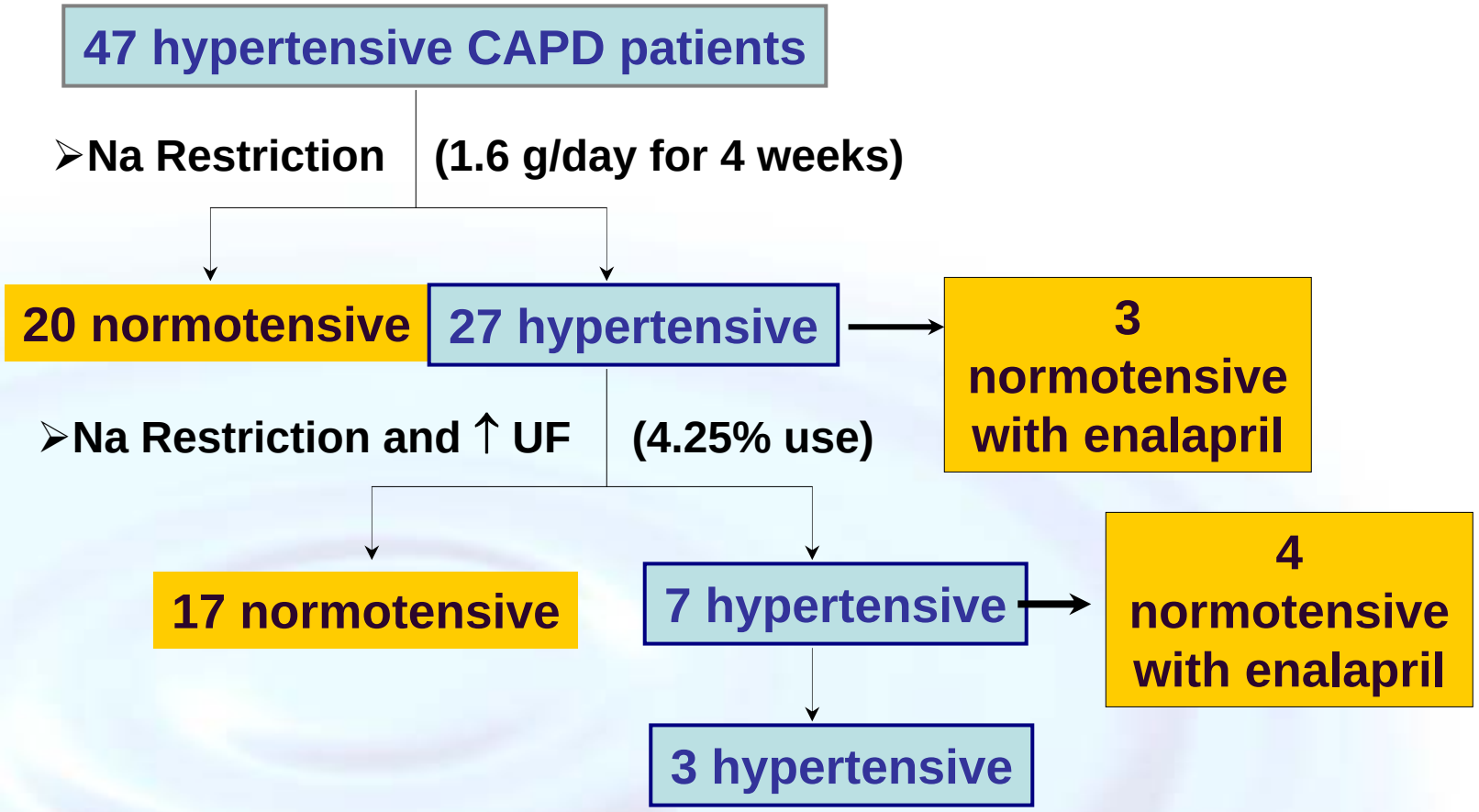
- Reduction in Symptomatic Fluid Retention.
- Blood pressure control:
  - Preservation of Residual Renal Function.
  - Prevention or mitigation of Cardiovascular Disease (IHD, LVH, CHF, CVA, PVD).
  - Reducing accelerated atherosclerosis process.
  - Prevention of symptoms simulating uremia.
- Reduction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

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.

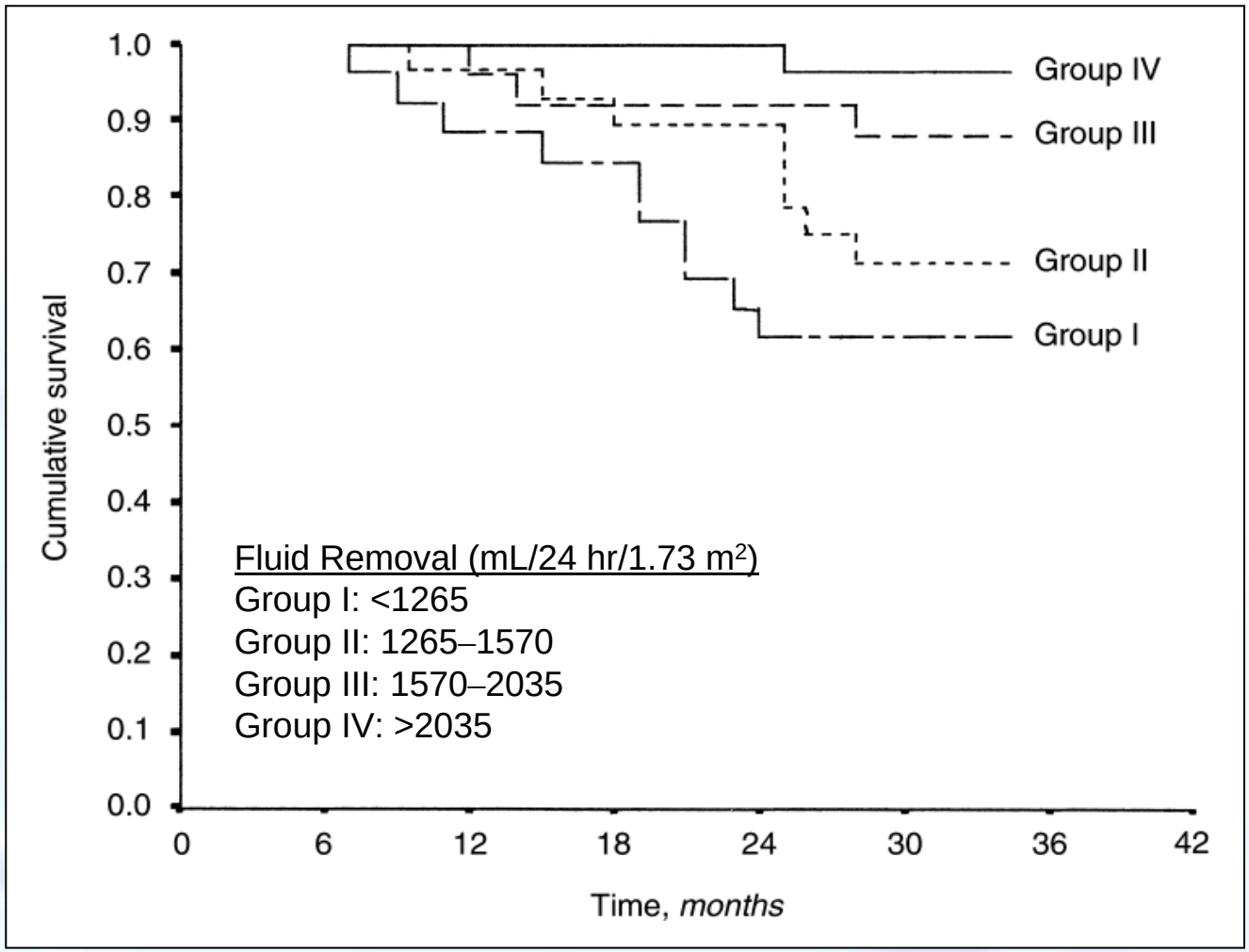
Tzamaloukas et al, *JASN* (6): 198-206, 1995

Fluid Removal and Na Restriction: Impact on Blood Pressure Control



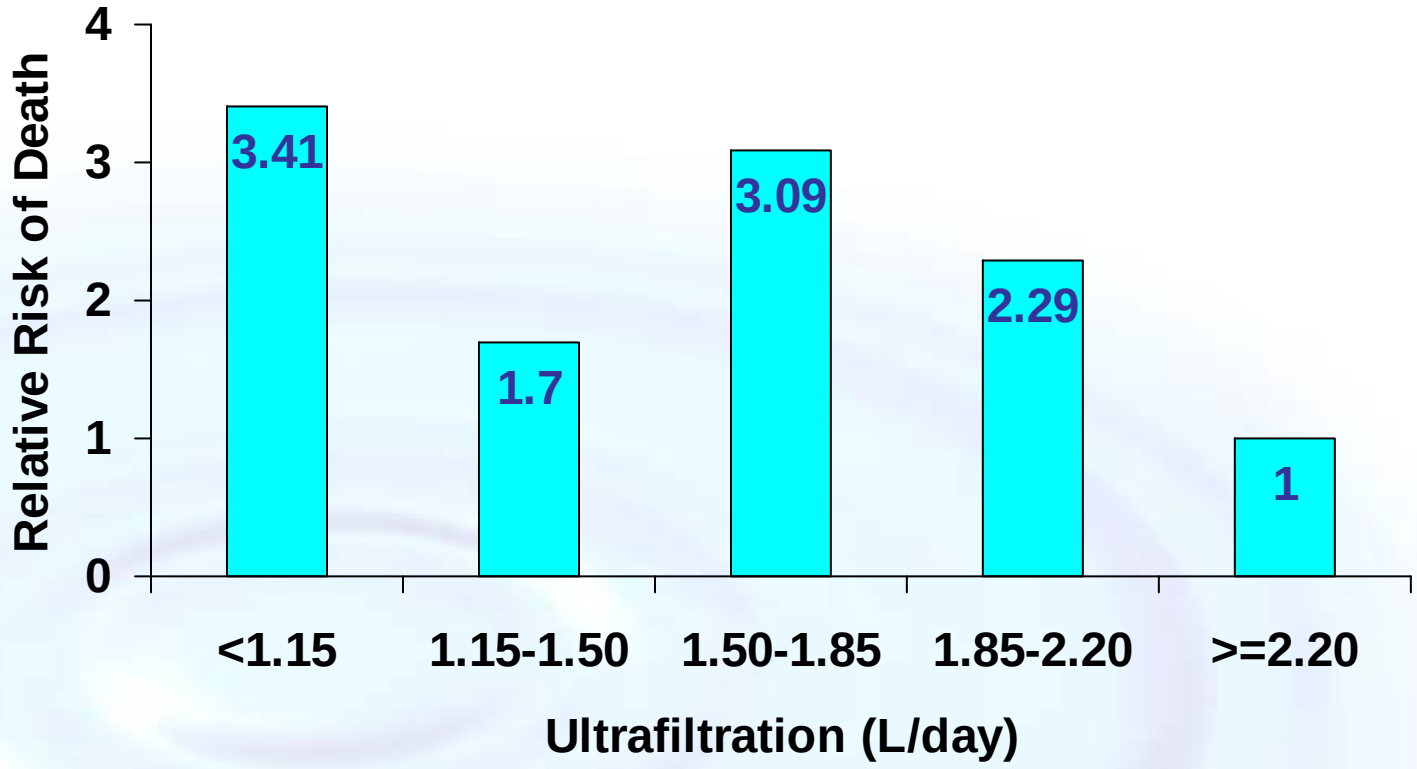
Gunal et al, *AJKD* (37): 588-193, 2001

Fluid Removal in PD: Impact on Survival



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

Fluid Removal in PD: Ultrafiltration Volume and Survival



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

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.

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.

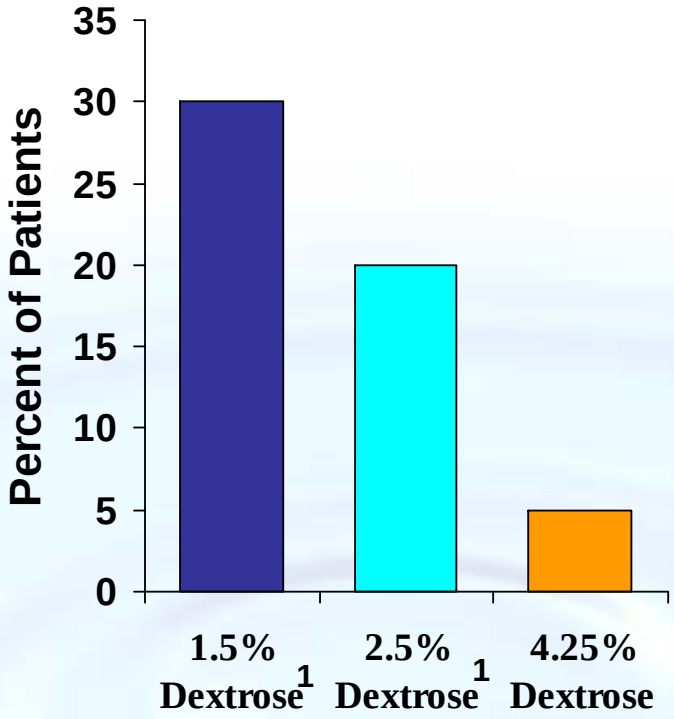
Fluid Management in PD: Role of Diuretics

- 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.

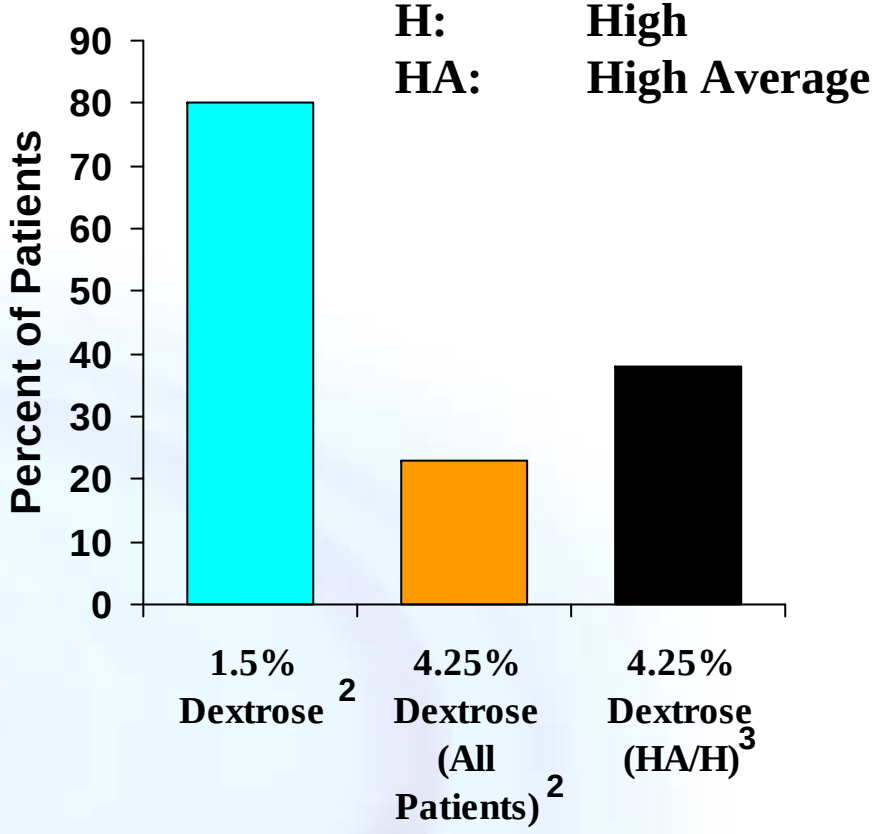
	Urine Volume (mL/24 hr)		
	Baseline	**Month 6**	**Month 12**
Furosemide 250 mg/day (n = 31)	**1020**	**1196**	**1070**
Control (n = 30)	**1040**	**840**	**733**

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

Fluid Management in PD: Negative UF with Lower Glucose Solutions



CAPD



APD

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

Fluid Management in PD: Long Dwell Limitations of Glucose

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

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.

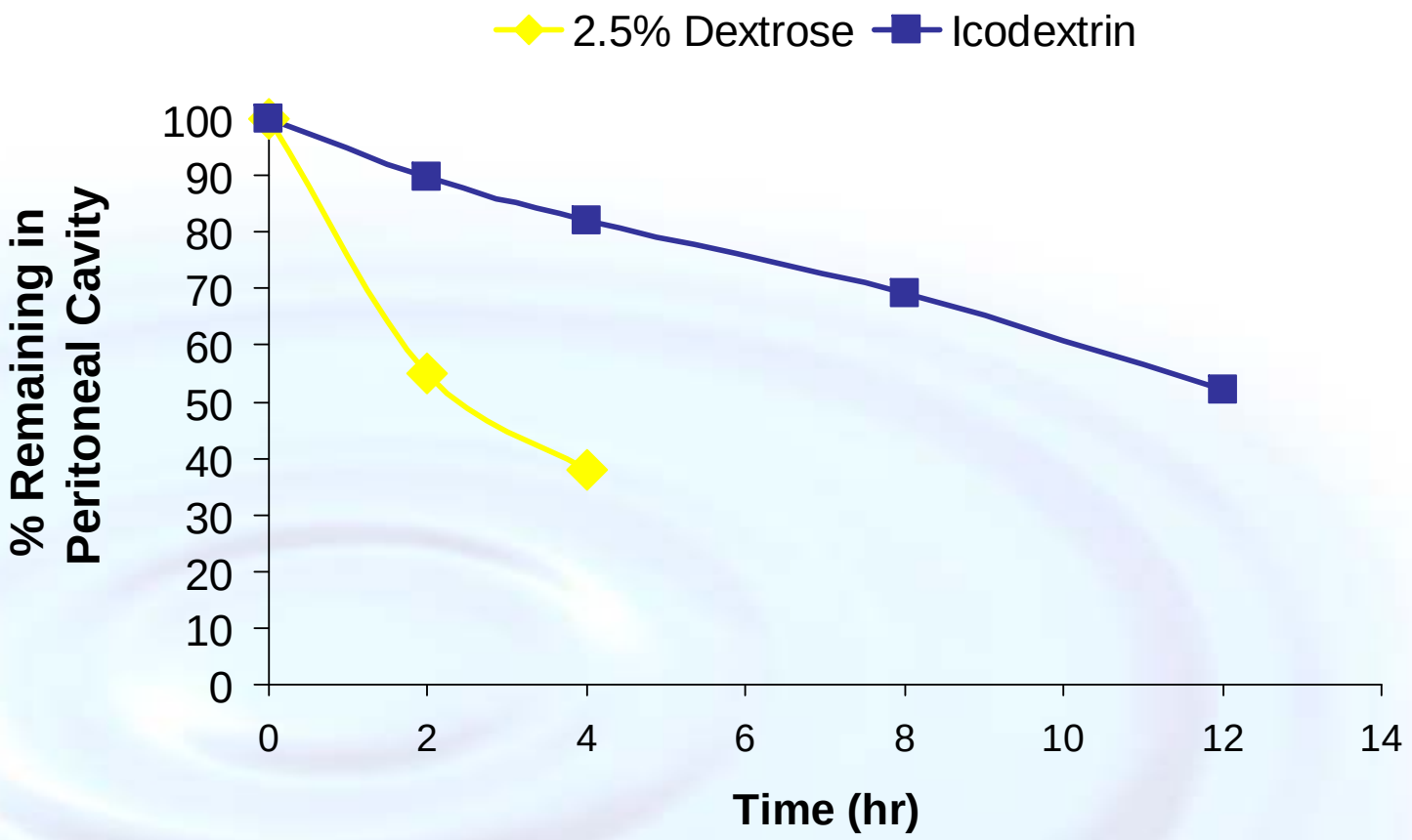
Fluid Management in PD: Colloid Osmosis

- 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.

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

Fluid Management in PD: Absorption Profiles of Icodextrin versus Glucose

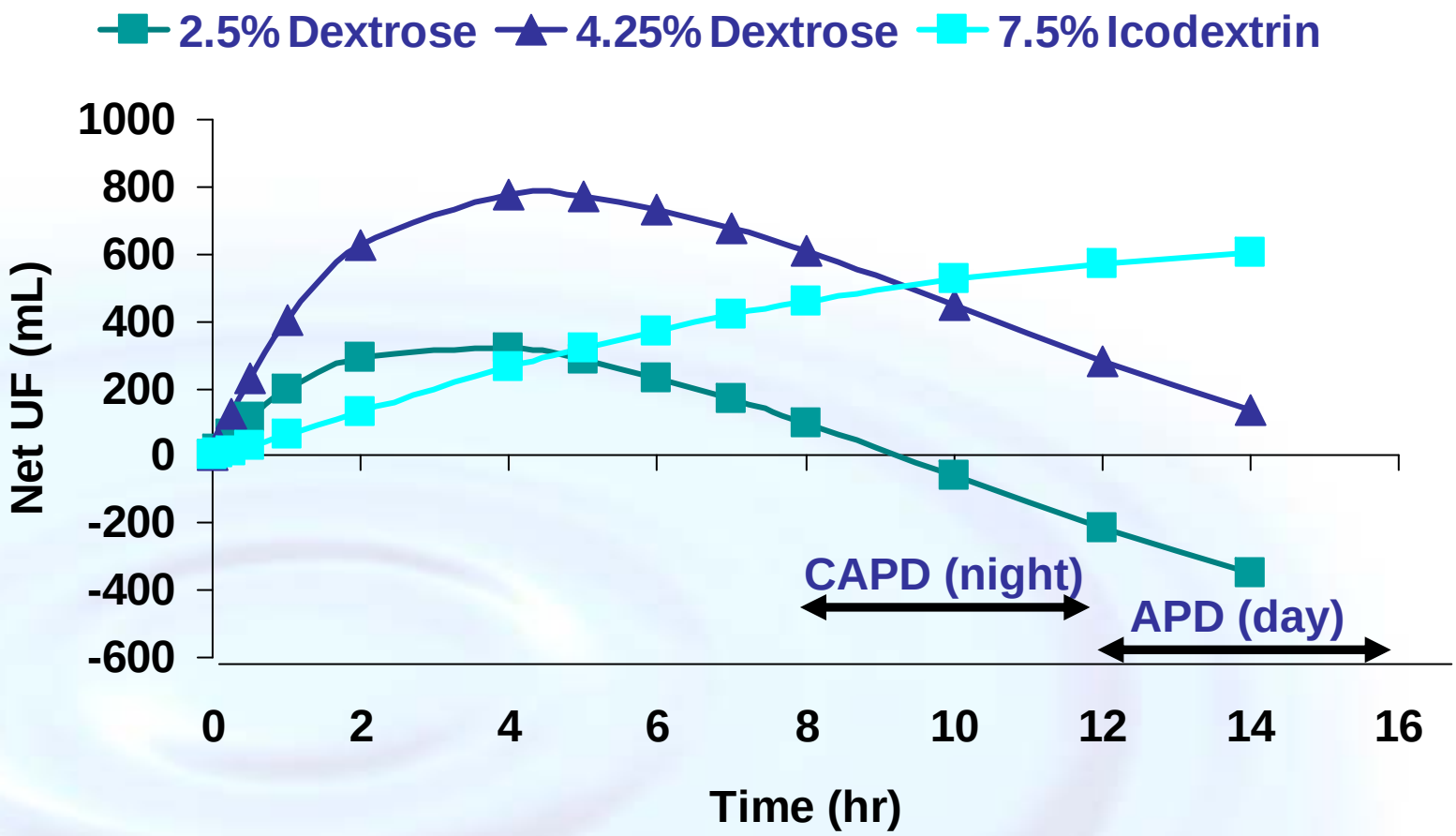


Adapted from Moberly, et al. *Kidney Int.* 2002;62(suppl 81):S23-S33.

Fluid Management in PD: Icodextrin Solution Composition

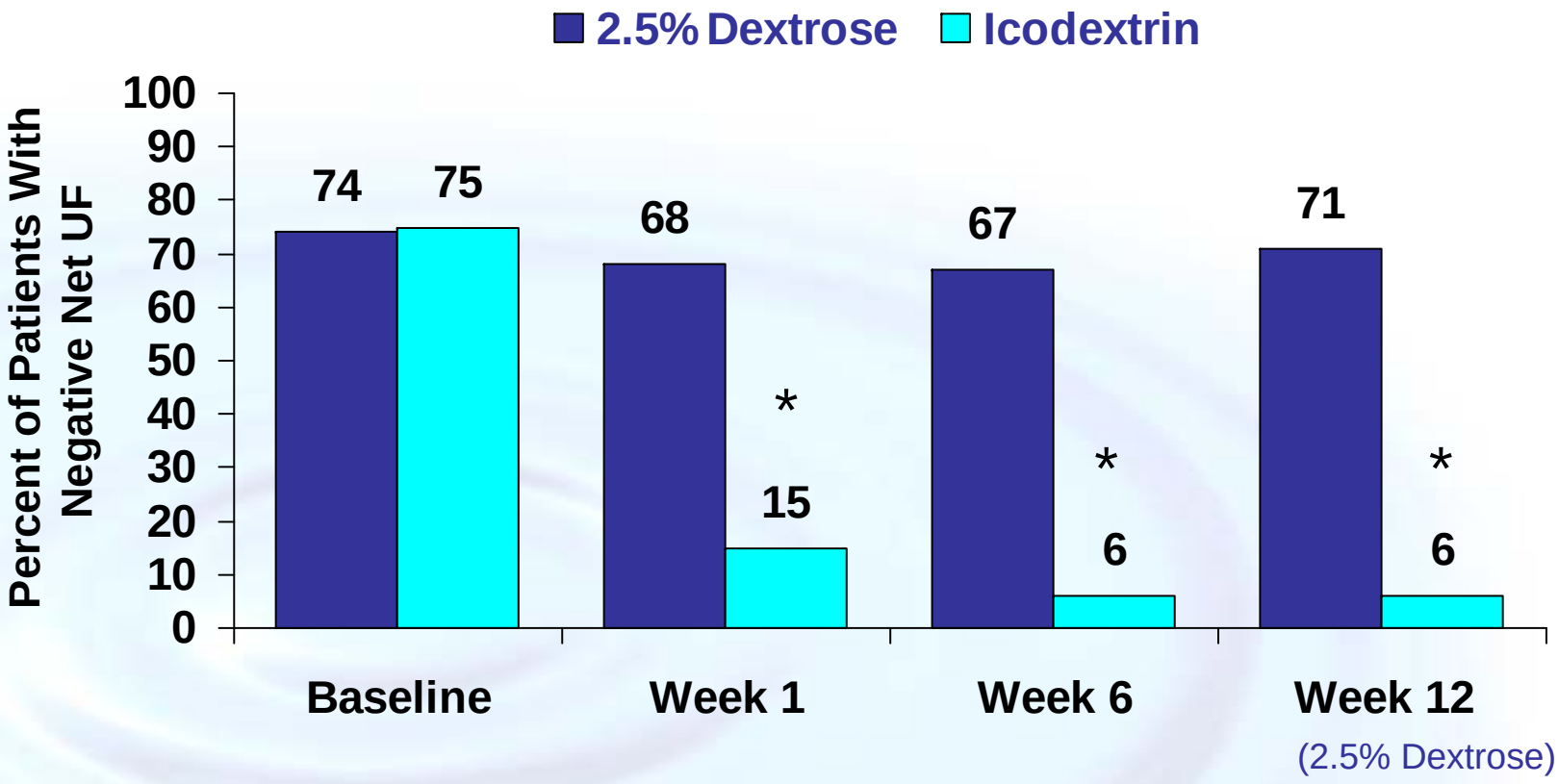
	Icodextrin-based Solution	Typical Glucose-based Solutions
Dextrose (g/dL)	—	1.5, 2.5, 4.25
Icodextrin (g/dL)	7.5	—
Sodium (mEq/L)	132	132
Chloride (mEq/L)	96	96
Calcium (mEq/L)	3.5	2.5
Magnesium (mEq/L)	0.5	0.5
Lactate (mEq/L)	40	40
Osmolarity (mOs/L)	282–286	344, 395, 483
pH	5.2	5.2

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

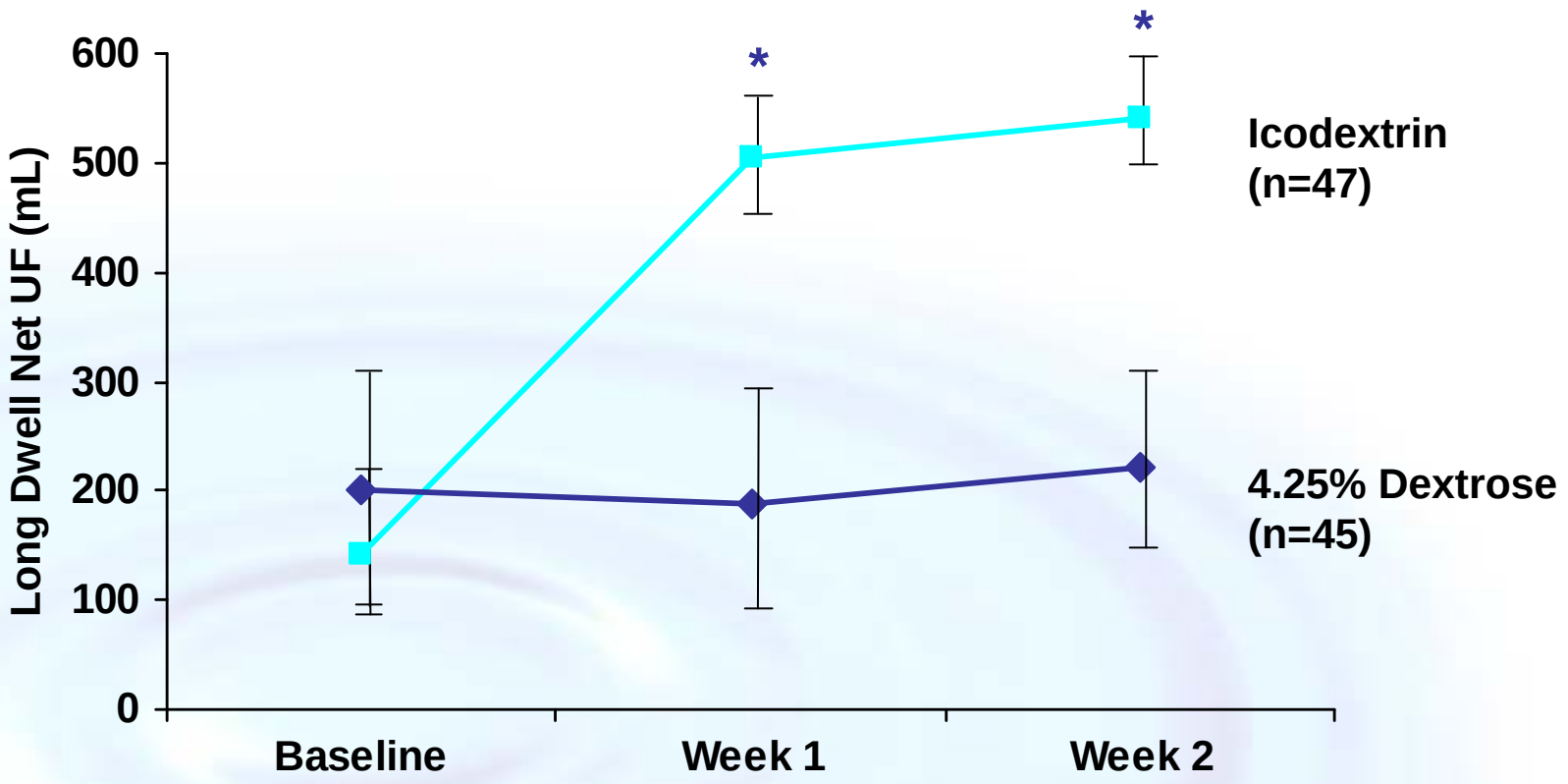
Long Dwell in APD: 7.5% Icodextrin vs 2.5% Dextrose



***P <0.001 vs 2.5% dextrose**

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

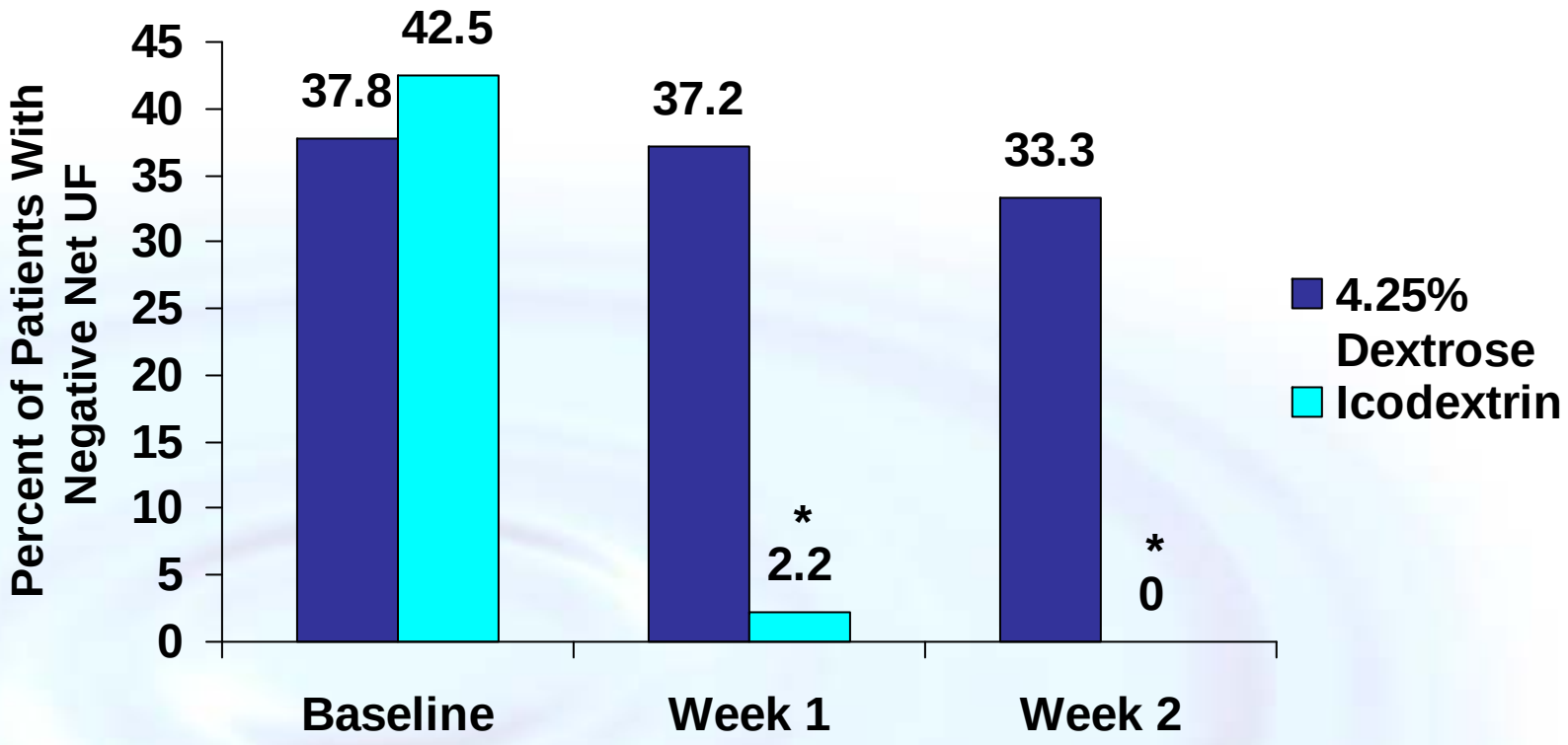
Long Dwell in APD: High Transport 7.5% Icodextrin vs 4.25% Dextrose



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

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

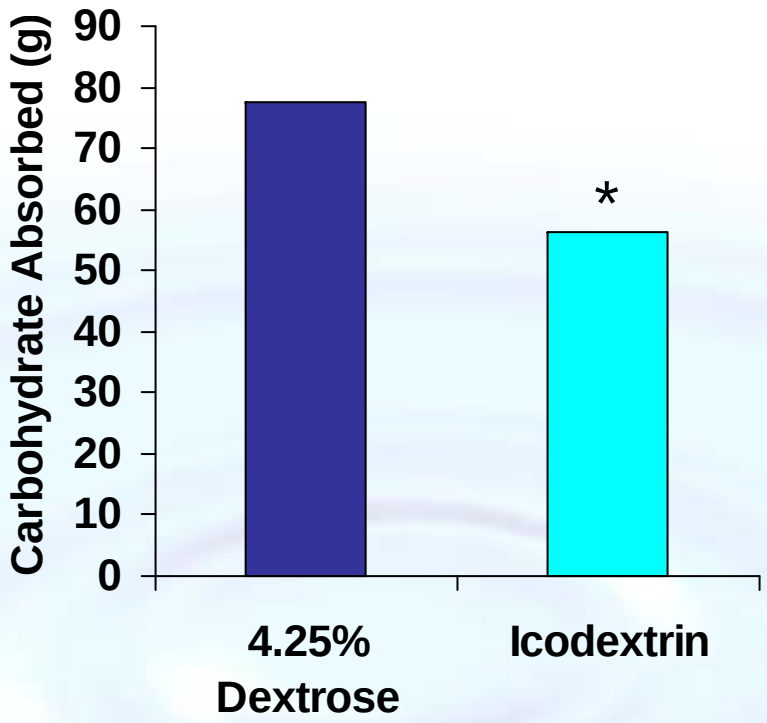
Long Dwell in APD: High Transport 7.5% Icodextrin vs 4.25% Dextrose

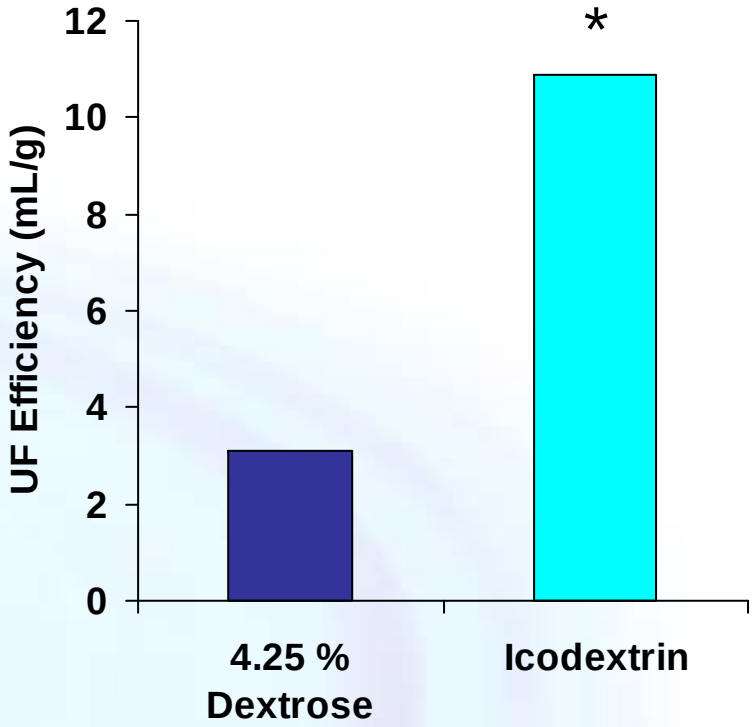


*$P < 0.0001$ vs 4.25% dextrose

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

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





****P*<0.001 vs 4.25% dextrose.**

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

7.5% Icodextrin versus Dextrose: Lack of Effect on RRF

Study or Subgroup	Icodextrin Mean	SD	Total	Glucose Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year	Mean Difference IV, Fixed, 95% CI
Posthuma 2000	2.5	3.12	12	1.7	2.52	13	27.7%	0.80 [-1.43, 3.03]	2000	
Wolfson(52w) 2002	2.91	3.74	175	4.6	10.66	112	32.9%	-1.69 [-3.74, 0.36]	2002	
Plum 2002	2.9	3.58	20	1.7	2.62	19	35.9%	1.20 [-0.76, 3.16]	2002	
Konings 2003	3.4	13.08	19	4.1	4.3	13	3.5%	-0.70 [-7.03, 5.63]	2003	
Total (95% CI)			226			157	100.0%	0.07 [-1.10, 1.25]		

Heterogeneity: Chi² = 4.57, df = 3 (P = 0.21); I² = 34%

Test for overall effect: Z = 0.12 (P = 0.90)

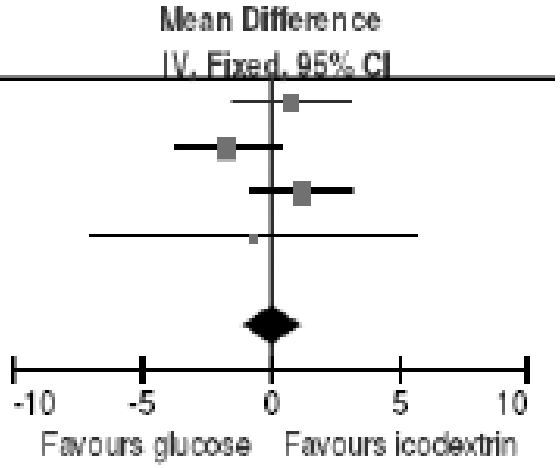
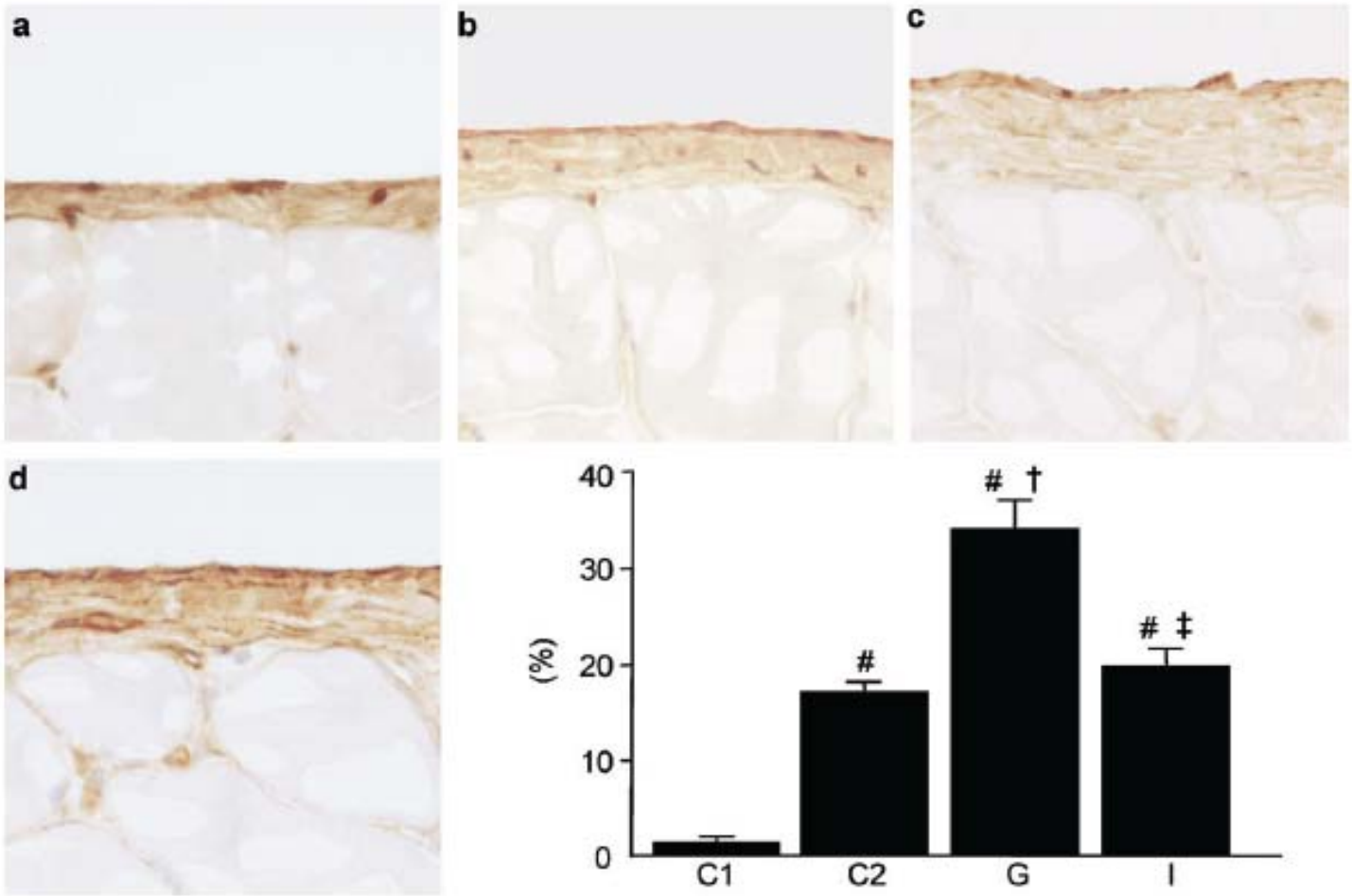


Figure 5 — Comparison of the effects of icodextrin and glucose on residual renal function. IV = inverse variance statistical method.

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

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



Groups	
C1	a
C2	b
G	c
I	d

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 ($n = 8$). $^{\#}P < 0.05$ versus C1, $^{\dagger}P < 0.05$ versus C2, $^{\ddagger}P < 0.05$ versus G.

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

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**

EXTRANEAL (Icodextrin) Prescribing Information, Baxter Healthcare Corporation.

Optimal Fluid Management: ISPD Guidelines

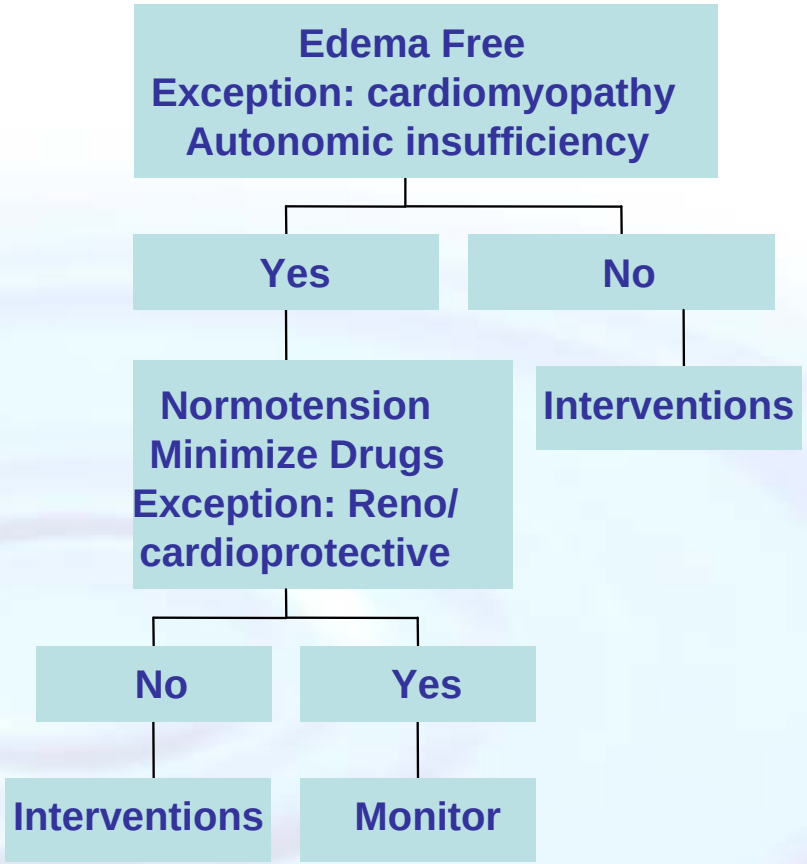
- Routine standardized monitoring and awareness of PET status
- Dietary counseling of appropriate salt and water intake.
- Protection of Residual Renal Function (RRF).
- Loop diuretics if RRF present.
- Patient education for enhanced compliance.
- Minimizing use of hypertonic glucose and monitoring for 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

Optimal Fluid Management: Rational for Therapeutic Approach

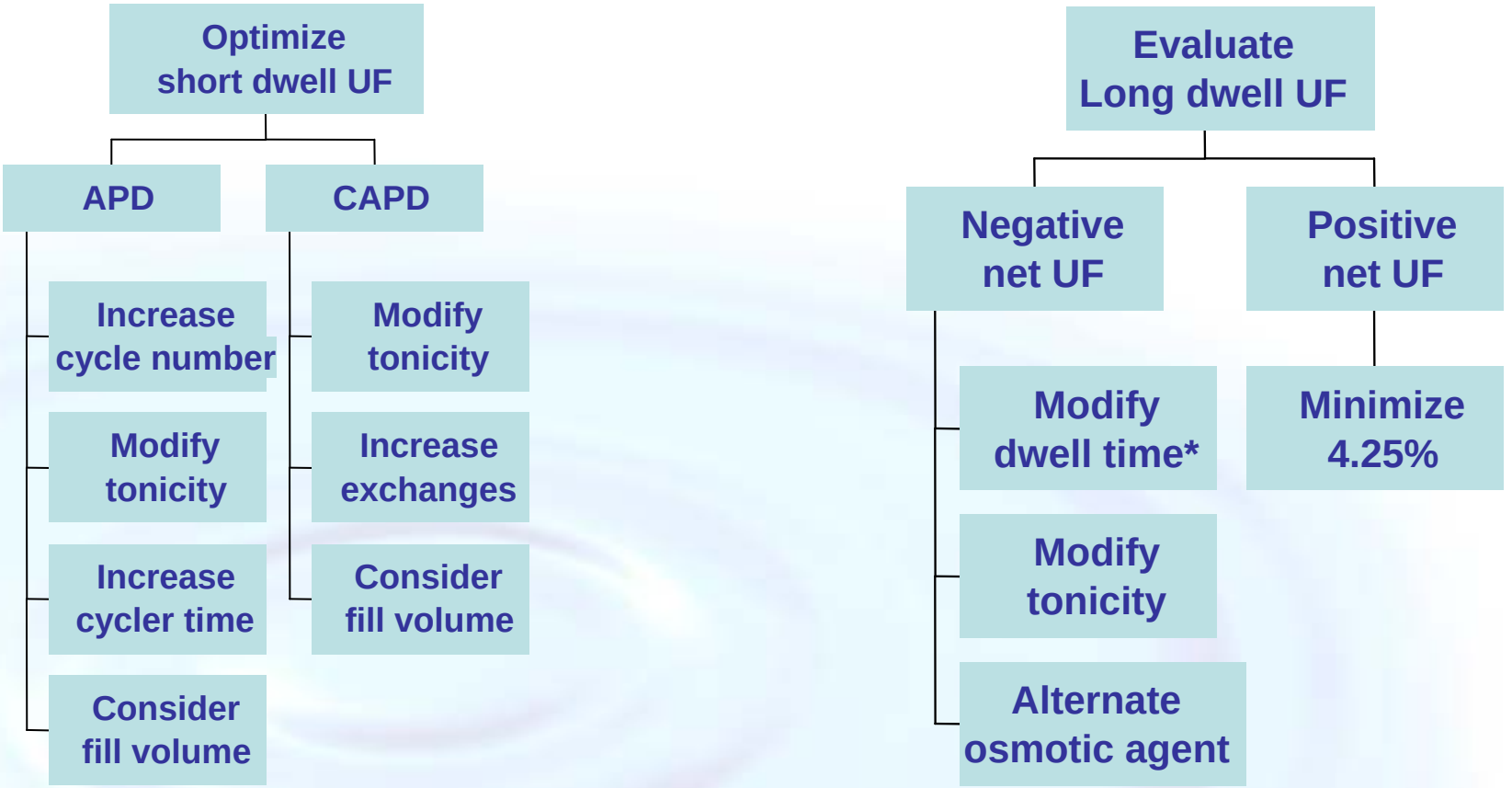
- Hypertension in ESRD is predominantly volume-dependent (salt sensitive).
- Correction of volume expansion in most ESRD patients leads to normalization of BP with limited anti-hypertensive medications.
- An edema-free state is a minimal requirement for normovolemia, but does not ensure presence of normovolemia.

Optimal Fluid Management: Algorithm



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

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)

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.

Questions

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.