PART FIVE Solutions
Cardiovascular disease is a leading cause of death in patients with end-stage renal disease (ESRD), and hypertension and volume expansion are highly prevalent in long-term peritoneal dialysis (PD) patients. The ADEMEX study made it clear that increased small-solute clearance does not lead to better outcomes. To manage the problem, current clinical practice uses strategies of dietary salt and fluid restriction, diuretics, antihypertensive drugs, icodextrin, extra day dwells, and (as a last resort) PD combined with hemodialysis (HD) or switch to HD. Nevertheless, the prevalence of hypertension remains alarmingly high.

In this article, we briefly discuss the therapeutic measures currently available for treating hypertension and volume overload in PD patients, the limitations of those measures, and the possibility of increasing sodium removal by reducing the dialysate sodium level.

Key words
Hypertension, icodextrin, fluid status, ultrafiltration failure, dialysate sodium

Introduction
Cardiovascular disease is a leading cause of death in patients with end-stage renal disease (ESRD), and interest in understanding the pathophysiology of hypertension and chronic volume expansion in peritoneal dialysis (PD) patients is currently resurgent. The ADEMEX study has clearly shown that increasing small-solute clearance does not lead to better outcomes (1). Hence, it is imperative to look for alternative means to improve long-term survival in PD patients.

Hypertension and volume expansion are both highly prevalent in long-term PD patients. [The prevalence of hypertension is as high as 91%, as reported by Menon et al. (2).] In clinical practice, various strategies are currently used to manage this common clinical problem: dietary salt and fluid restriction; diuretics; antihypertensive drugs; icodextrin; addition of an extra day dwell; and, as a last resort, PD combined with hemodialysis (HD) or switch to HD. Despite the availability and application of all of these treatment measures, the prevalence of hypertension remains alarmingly high, clearly reflecting the failure of currently available methods. That failure demands alternative approaches to the treatment of hypertension and volume overload. In this article, we briefly discuss the therapeutic measures currently available for treating hypertension and volume overload in PD patients, the limitations of those measures, and the possibility of increasing sodium removal by reducing dialysate sodium level.

Discussion
Salt restriction
The strategy of dietary salt restriction is commonly used as an adjunct in the treatment of hypertension and volume expansion in ESRD patients. Because PD is a continuous mode of dialysis, the initial impression was that the removal of salt and water was quite effective. That impression may well be true in the initial period after the start of PD (the so-called honeymoon period); but, as residual renal function (RRF) is eventually lost or declines (usually 2 – 3 years after PD initiation), hypertension re-emerges as a major clinical problem.

Vigorous salt restriction alone can improve hypertension in most PD patients (3), but dietary salt restriction often leads to noncompliance, resulting in a high prevalence of both hypertension and volume overload in PD patients once they become anuric. Reinforcement and education, a strategy commonly applied in clinical practice, is useful only over the short term. Few patients who religiously follow dietary salt restriction have good control of blood pressure (BP),
and the vast majority of PD patients continue to consume more salt than required.

How can we manage this common and often difficult problem seen in everyday clinical practice? If we cannot restrict sodium intake, are there ways to increase sodium removal?

**Diuretics**

Diuretics are useful in enhancing sodium and water removal in patients, particularly those with declining RRF. In a prospective, randomized, controlled trial over a 12-month period, Medcalf and co-workers (4) studied the use of furosemide and showed that long-term administration of that drug in pharmacologic doses increased urine volume. The change in 24-hour sodium excretion was –2.57 ± 1.51 mmol in the control group, as compared with +0.72 ± 0.85 mmol in the diuretic group (\( p = 0.041 \)).

However, the use of diuretics has limitations—for example, the requirement for large doses (with attendant risk of ototoxicity) and ineffectiveness when urine output is less than 100 mL in 24 hours. Moreover, diuretics have no effect on preserving RRF, and their effect on urinary sodium excretion is modest.

Despite their limitations, diuretics are useful in PD patients with RRF. Nevertheless, management of fluid overload in anuric patients or patients with a significantly low urine volume remains difficult.

**Icodextrin**

Evidence suggests that icodextrin may be useful in treating fluid overload and enhancing sodium removal in PD patients. Because of its high molecular weight and reflection coefficient, icodextrin induces ultrafiltration (UF) by colloid osmosis (with water passing through the small pores) in contrast to the crystalloid osmosis of glucose (in which water passes through the ultrasmall transcellular pores). Hence, sodium sieving does not occur with icodextrin.

Table I summarizes the available literature related to use of icodextrin.

Woodrow et al. (7) compared 7.5% icodextrin with 2.27% glucose dialysate for the daytime dwell in 14 patients on automated PD (APD) and noted improved fluid balance and BP control after 1 month. Although the patients’ weight declined by a mean of 0.8 kg, that decline did not reach statistical significance, although other indices such as total body water (TBW) and extracellular water (ECW) decreased significantly. The authors did not measure sodium removal. Of the 14 study patients, 6 developed symptomatic hypotension and required a reduction in antihypertensive drugs. The small number of patients, lack of controls, and short duration were the main limitations of the study. Moreover, discordance between patient weight and other indices of volume measurement indicated that bioimpedance analysis probably overestimated TBW and ECW in the study.

Similarly, Plum et al. (6) compared 7.5% icodextrin with 2.5% glucose in 39 APD patients over a 12-week period and found that sodium removal increased in the icodextrin group to 269 mEq from 226 mEq (\( p < 0.001 \)). That increase was associated with a modest fall in serum sodium. No change in weight or BP occurred despite better UF in the icodextrin group. In the study group, body weight declined after 8 weeks, but returned to pretreatment levels by the end of the study. The authors attributed that result to excessive thirst followed by a compensatory increase in fluid intake by the patients.

In a prospective randomized study, Konings et al. (5) looked at the effect of icodextrin on fluid status, BP, and echocardiographic parameters in 32 PD patients (18 icodextrin, 14 control) over a 4-month period. Use of icodextrin resulted in a significant increase in daily UF volume (716 ± 853 mL vs. 1841 ± 1437 mL, \( p = 0.001 \)) and a reduction in ECW (17.6 ± 5.4 L vs. 15.7 ± 3.9 L, \( p = 0.03 \)) that was related to an increase in UF volume and to the fluid status of the patient, not to peritoneal membrane characteristics. Despite the impressive reduction in ECW, the authors found no improvement in BP control. Another interesting and significant finding was a reduction in left ventricular mass (LVM) in the icodextrin group. The major limitation of the study was the use of 1.5% glucose solution for the long dwell in APD patients. That factor would have confounded the results, favoring the study group patients on icodextrin. Another concern was the significant decline in urine output and RRF in the icodextrin group—a result not seen in earlier studies.

Rodriguez–Carmona et al. (10) carried out a prospective three-stage study of sodium removal in PD patients. In study A, they undertook a cross-sectional survey of sodium removal in 63 patients on continuous ambulatory peritoneal dialysis (CAPD) and 78 patients on APD. In the CAPD group, nocturnal sodium removal was slightly higher in patients using
### Are Low Sodium Dialysis Solutions Needed?

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Patients (n)</th>
<th>Duration (months)</th>
<th>Weight (kg) Pre &amp; Post</th>
<th>BP (mmHg) Pre &amp; Post</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Konings et al. (5)</td>
<td>Randomized</td>
<td>19 Icodextrin</td>
<td>1</td>
<td>142.9±3.8</td>
<td>131.8±3.7</td>
<td>Improvement in UF, ECW, and LVM.</td>
</tr>
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<td>3</td>
<td>138.8±3.2</td>
<td>146.7±3.2</td>
<td>Significant reduction in TBW, ECF, and BP, but no change in weight.</td>
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<td>RCT</td>
<td>28 Icodextrin</td>
<td>6</td>
<td>139.3±5.3</td>
<td>83.8±3.0</td>
<td>Improvement in UF and sodium removal, no change in BP or sodium.</td>
</tr>
</tbody>
</table>

#### Table 1: Summary of published studies related to effect of icodextrin on weight, volume status, and blood pressure control

<table>
<thead>
<tr>
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<th>Study design</th>
<th>Patients (n)</th>
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</tr>
</tbody>
</table>

BP = blood pressure; UF = ultrafiltration; ECW = extracellular water; LVM = left ventricular mass; RRF = residual renal function; APD = automated peritoneal dialysis.

**Weight at 6 months not provided (see text for details).**
icodextrin for the night dwell (74.7 ± 49.5 mmol/L) than in patients not on icodextrin (55.1 ± 48.3 mmol/L). In fact, diurnal sodium removal was higher in patients not on icodextrin (31.7 ± 59.0 mmol/day) than in patients not on icodextrin (3.5 ± 52.7 mmol/day). Surprisingly, UF did not change significantly before or after the addition of icodextrin. It appears that, although sodium removal increased modestly in CAPD patients using icodextrin at night, that increase was offset (counterbalanced) by less sodium removal during the day. On the other hand, in APD patients, sodium removal exhibited a large standard deviation, probably reflecting large variability from patient to patient. In study C, total daily sodium removal increased to 177 mmol/day from 134 mmol/day after the switch to icodextrin, but that change failed to reach statistical significance. The enhanced sodium removal occurred mostly in long dwells and was partly counterbalanced by a reduction in renal sodium excretion. Unfortunately, the authors did not mention the effect of icodextrin on BP in studies A and C.

Davies *et al.* (9) recently published results of a double-blind, randomized, controlled trial [icodextrin (*n* = 28) vs. glucose 2.5% (*n* = 22)] and found improved UF, reduction in TBW and extracellular fluid (ECF) in the icodextrin group. Urine volume was better preserved in the icodextrin group at 6 months (Table II). However, no significant differences were observed in the mean 24-hour BP readings between the study groups. Although the inclusion criteria included BP greater than 140/90 mmHg, the mean BP in the icodextrin group was 139.3 ± 5.3 mmHg (systolic) and 83.8 ± 3 mmHg (diastolic) with antihypertensive drugs. Moreover, no significant reductions in the requirement for antihypertensive drugs were observed.

To summarize, icodextrin seems beneficial in improving fluid status and increasing sodium removal in PD patients. Despite those findings, it is intriguing to note that the effect of icodextrin on BP control is inconsistent. In most studies, the study subjects in the icodextrin group had normal or near-normal BP at the start of the study. That situation makes it difficult to see a change, although a reduction in the use of antihypertensive drugs should at least be seen. It would be interesting to observe the effect of icodextrin on BP control in patients with moderate-to-severe hypertension.

### Table II Changes in urine volume, ultrafiltration, and total sodium loss in study groups at 1, 2, and 6 months

<table>
<thead>
<tr>
<th>Criterion</th>
<th>1 Month</th>
<th>2 Months</th>
<th>6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urine volume</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Icodextrin</td>
<td>–44.3</td>
<td>–34.6</td>
<td>–10.7</td>
</tr>
<tr>
<td>Control</td>
<td>–44.1</td>
<td>–56.6</td>
<td>–126.6</td>
</tr>
<tr>
<td>Difference</td>
<td>–0.2</td>
<td>21.9</td>
<td>115.9 b</td>
</tr>
<tr>
<td><strong>Ultrafiltration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Icodextrin</td>
<td>+166.8</td>
<td>+87.9</td>
<td>+193.4</td>
</tr>
<tr>
<td>Control</td>
<td>–50.1</td>
<td>–311.1</td>
<td>–201.7</td>
</tr>
<tr>
<td>Difference</td>
<td>216.9</td>
<td>399 c</td>
<td>395.1</td>
</tr>
<tr>
<td><strong>Total Na loss</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Icodextrin</td>
<td>+8.3</td>
<td>+4.3</td>
<td>+5.4</td>
</tr>
<tr>
<td>Control</td>
<td>2.4</td>
<td>–53</td>
<td>–19.9</td>
</tr>
<tr>
<td>Difference</td>
<td>5.9</td>
<td>57.3 d</td>
<td>25.2</td>
</tr>
</tbody>
</table>

*Adapted from (9).*

*Significant differences.*

In addition, large variability seems to exist with icodextrin in terms of sodium removal and UF. We observed that the UF achieved with icodextrin declines rapidly when the dwell time exceeds 12 hours, probably because of increased fluid reabsorption (Data not shown). In the study by Davies *et al.* (9), RRF was better preserved in the icodextrin group than in the 2.5% glucose group, but the effect of icodextrin on sodium removal was small (Table II). One advantage of using icodextrin is the avoidance of hypertonic glucose solution, with all of its deleterious consequences. Long-term prospective studies are needed to determine whether the use of icodextrin reduces BP and LVM, and improves cardiovascular mortality in PD patients.

**Role of antihypertensive drugs**

Antihypertensive drugs are commonly used in PD patients to control BP. However, the persistence of a high prevalence of hypertension in PD patients argues strongly against the effectiveness of the approach. In a large multicenter Italian study, Cocchi *et al.* (11) found the prevalence of hypertension to be 88.1% (systolic BP ≥ 140 mmHg, or diastolic BP ≥ 90 mmHg, or both). It is noteworthy that 77.1% of their hypertensive patients were on antihypertensive drugs.

Menon *et al.* (2) studied 207 patients on PD and found that 91.3% were hypertensive at the start of treatment. Interestingly, systolic pressure and mean arterial pressure index (product of the systolic BP and the
number of antihypertensive drugs plus one) improved between 6 months and 1 year, and then steadily and progressively worsened throughout follow-up.

Koc et al. (12) noted an 84% prevalence of hypertension during office visits and an 82% prevalence with ambulatory BP recordings. Hypertension was uncontrolled in 56 of 74 patients despite use of antihypertensive drugs.

It seems likely that antihypertensive drugs are partially effective in controlling hypertension in PD patients. The presence of volume overload and inadequate sodium removal certainly reduces the effectiveness of the drugs.

Supplementary daytime exchange in APD

Rodriguez–Carmona et al. (10) found that, in APD patients, in addition to UF and residual diuresis, the length of each exchange dwell and a supplementary diurnal exchange were independent predictors of sodium removal. (Short exchanges in APD remove less sodium because of sodium sieving.)

Among APD patients, Ortega et al. (13) found similar sodium removal in nightly intermittent PD (NIPD, 72 ± 81 mEq) and continuous cycling PD (CCPD, 103 ± 9 mEq). However, when a daytime exchange was added for CCPD patients, peritoneal sodium removal increased significantly (171 ± 72 mEq vs. 87 ± 86 mEq), as did net UF. Improvement in BP control also occurred with the extra exchange.

In view of the foregoing findings, it may be useful to increase the dwell time in APD patients—that is, use fewer exchanges with longer dwell times—in an effort to increase sodium removal. Adding an extra diurnal exchange is helpful not only in providing additional solute clearance, but also in achieving better sodium removal and BP control.

Overall ineffectiveness of current clinical measures

Currently available therapeutic measures such as salt restriction, diuretics, icodextrin, and modification of the PD prescription have been used in clinical practice for some time, but the prevalence of hypertension has remained unchanged. Although icodextrin has shown a beneficial effect in increasing UF and sodium removal, consistent improvement in BP control has not been shown. Hence, the high prevalence of hypertension in PD patients is unsurprising. We should accept the fact that available methods are inadequate to provide good control of volume expansion and BP and should look for innovative (or novel) techniques to address this common but difficult clinical problem.

Low sodium dialysis solution: A new approach to treat hypertension in PD patients

The concept of using lower-sodium dialysis solution to remove more sodium from the patient is not new. Three decades ago, Ahearn and Nolph (14) used low-sodium dialysis solution to manage hypernatremia in PD patients. They demonstrated that a dialysis solution containing 7% dextrose and 100 – 130 mmol/L sodium removed more sodium per exchange than a standard 7% solution containing 140 mmol/L sodium.

During the subsequent two decades, no studies using low-sodium dialysis solution were published. More recently, in small studies, low-sodium dialysis solution has been shown to increase sodium removal and to improve BP control in PD patients. The current sodium concentration in PD solutions is 132 mmol/L. Further lowering that concentration enhances sodium removal by means of diffusion. Clinical experience with low-sodium solution is limited, but promising.

Recently, we reviewed the published literature related to the use of low-sodium dialysis solution in CAPD and APD patients (15).

LOW SODIUM SOLUTIONS IN APD PATIENTS

Recent evidence suggests that sodium removal is lower in APD patients than in those on CAPD (10). However, the clinical significance of that finding remains unknown. Preservation of RRF, control of BP, and survival rates are comparable between CAPD and APD patients. Theoretically, as compared with CAPD patients, APD patients (particularly anuric ones) should derive more benefit with low-sodium dialysis solution. Unfortunately, only two studies with low-sodium solution have reported results in APD patients.

Freida et al. (16) studied 9 anuric patients in a switchover trial (pre-study period, 1 month; baseline phase, 2 months with dialysis solution sodium 132 mmol/L; then 2 months with dialysis solution sodium 126 mmol/L; and finally a washout period of 1 month). Daily sodium removal increased to 94 mmol/L from 32 mmol/L with the low-sodium solution. Of 8 patients, 4 experienced improvement in BP control and 3 required discontinuation of all antihypertensive drugs. No significant change in net UF or body weight was observed. No effect could be dem-
onstrated on left ventricular dimension. The authors concluded that low-sodium solution was effective in improving BP control in patients with sodium-dependent hypertension. Unfortunately, they did not mention whether icodextrin or extra daytime exchanges were used.

In acute PD patients, Vande Walle et al. (17) used HCO₃-buffered, low-sodium dialysis solution (128 mmol/L) and reported low serum sodium values in their study group.

PLACE OF LOW-SODIUM SOLUTIONS IN CURRENT PD PRACTICE

Figures 1 and 2 illustrate our proposed schemas for using low-sodium dialysis solution to manage hypertension and volume overload in CAPD and APD patients.

Patients on CAPD with substantial RRF should be given a trial of diuretics, preferably in combination with metolazone. If hypertension persists, the next step would be to try icodextrin during the long dwell.

Low-sodium solution (120 mmol/L) should be used during the day dwell if hypertension persists despite earlier measures. Therapy should be tailored according to the needs of the individual patient. We recommend using ultralow sodium solution in patients with persistent hypertension and evidence of volume overload.

Patients on APD can be similarly managed, except that they should be given a trial of enhanced CCPD before low-sodium solution is tried.

Patients in the following categories will probably derive the maximum benefit with low-sodium solutions:

- Overhydrated, anuric CAPD patients with persistent hypertension after failed attempts to lower target weight (such attempts may have included, for example, salt and water restriction, use of hypertonic solutions, and changes in PD prescription such as avoidance of low-glucose solutions.

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**FIGURE 1** Proposed schema for using low-sodium solution to manage hypertension and volume overload in continuous ambulatory peritoneal dialysis (CAPD) patients. *Start 1 exchange with low-sodium solution. Increase the number of exchanges depending on response and tolerability. aGlucose concentration may be higher to achieve an osmolality of 397 mosm/kg. HTN = hypertension; RRF = residual renal function; Glu = glucose.

**FIGURE 2** Proposed schema for using low-sodium solution to manage hypertension and volume overload in automated peritoneal dialysis (APD) patients. *Start low-sodium solution for night exchanges on cycler. Add low-sodium solution for day exchange if response is not optimal. aGlucose concentration may be higher to achieve an osmolality of 397 mosm/kg. HTN = hypertension; RRF = residual renal function; CCPD (E) = continuous cycling peritoneal dialysis (enhanced); Glu = glucose.
for long dwells, use of icodextrin, reduction of the long dwell with a Quantum device) or despite a successful reduction in target weight. Low-sodium solutions have been shown to be helpful in reducing thirst and thereby treating volume expansion in overhydrated PD patients.

- Anuric CAPD patients who appear clinically euvolemic and in whom BP is under control with antihypertensive drugs or remains high despite antihypertensive agents or because of noncompliance (failure to take prescribed drugs).
- Patients on CAPD with substantial or declining RRF requiring antihypertensive drugs despite an intensified diuretic regimen.
- All APD patients requiring antihypertensive drugs, BP controlled or not, for whom conventional strategies have failed.

Patients who are normotensive with the use of antihypertensive drugs may be able to discontinue drugs, given that our aim is to achieve drug-free control of BP.

References


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The development of biocompatible peritoneal dialysis fluids (PDFs) is one of the most significant improvements in the field. The evolution of PDFs can be divided into three phases: (1) identification of the problems; (2) basic laboratory studies and formulation of alternative solutions; and (3) clinical testing of the new alternatives. A summary of representative work for each of these phases, together with insights into future developments, is provided.

Key words
Peritoneal dialysis solutions, biocompatibility

Introduction
Peritoneal dialysis (PD) has changed fundamentally in the 21st century from a therapy based on empiricism to one based on solid scientific foundations. The transformation of PD fluids (PDFs) into biocompatible solutions may constitute the most significant improvement in the field since the development of the permanent PD catheter by Tenckhoff more than three decades ago (1).

Development of biocompatible PDFs requires a good understanding of physical chemistry, peritoneal physiology and pathology, toxicology, and manufacturing practices. The history of progress in the field can be summarized in three phases: (A) recognition and characterization of the problems related to conventional PDFs, (B) laboratory testing and design of potential alternative PDFs, and (C) clinical experience with the new solutions. We are, fortunately, entering this last phase.

Discussion
Recognition and characterization of the problems
The first and primary clinical evidence of membrane dysfunction as a probable manifestation of bioincompatibility was the observation that solute transport increased and ultrafiltration declined as a function of time on PD (2,3). Factors other than solution formulation (for example, peritonitis) were identified as potential offenders, but the principal and ever-present offender seemed to be the PDF.

Undesirable effects from specific PDF components or properties were eventually identified. The most prominent offenders were the low pH of the solutions and the high concentration of glucose (with lactate and other components following on the list).

Perhaps the most important contribution during this phase in the evolution of biocompatible PDFs was the realization of the importance of glucose degradation products (GDPs). The GDPs—rather than glucose per se—are quite toxic to the various elements of the peritoneal membrane; they are critical determinants of advanced glycation end-product (AGE) formation and deposition, and they are active promoters of peritoneal vasodilatation (4,5). Moreover, GDPs have been shown to modulate the levels of surrogate markers of inflammation such as vascular endothelial growth factor (VEGF) and hyaluronan (6).

Laboratory testing and design of potential alternatives
During the past decade, many studies have strongly suggested or shown that the elimination of GDPs and the provision of a PDF with a physiologic pH can improve cell survival and function (7). In addition, the replacement of lactate by bicarbonate can further improve those parameters and contribute to peritoneal vascular stability (5).

Novel manufacturing processes have been developed to solve the problem of caramelization of glucose during heat sterilization. Basically, two solutions are prepared, separated by a septum in a bi-chambered bag. One solution contains glucose and electrolytes at a very low pH (approximately pH 3), and the other solution contains the buffer base at an alkaline pH. Before the solution is used, the septum is broken, and the two solutions are mixed to produce a solution with a neutral pH, minimal GDPs, and physiologic concentrations of electrolytes and buffer base.
The in vitro and ex vivo data showing that such solutions are far more biocompatible than conventional PDFs are both voluminous and convincing (5,8,9). However, the crucial proof of superiority rests on clinical outcome studies.

Clinical experience with new solutions
The first reflection in humans that the new PDFs are more biocompatible was the fact that the concentration of cancer antigen 125 (CA125) in peritoneal effluent increased with the use of those solutions as compared with the use of conventional solutions (10). The concentration of CA125 is a surrogate marker of mesothelial cell mass and has become the standard test to evaluate peritoneal cell viability. In addition to uncontrolled and single-center reports of improvement in CA125 concentrations in peritoneal effluent, a multicenter, multinational, randomized, controlled, crossover study (the Euro Balance Trial) has definitely confirmed such improvement (10). Patients showed an increase in CA125 effluent concentration while on Balance (Fresenius Medical Care, Bad Homburg, Germany) and a decrease upon switching to a conventional PDF. In addition, urine volume increased during the period on Balance, suggesting an improvement in renal function. Further data are required to determine the effect of biocompatible PDFs on renal function, but the results are intriguing.

The Euro Balance Trial did not show a significant difference in the rates of peritonitis between the two solutions despite extensive laboratory data suggesting improved host defense with the use of biocompatible solutions (11). That result is not surprising in view of the low baseline peritonitis rate in the study population, the limited number of patients, and the short observation period. Preliminary results from a single-center experience that compared conventional and pure bicarbonate PDF showed a significant reduction in peritonitis rates (12). Controlled and better-powered studies are needed to confirm the improved host peritoneal defenses suggested by the laboratory studies.

Other clinical advantages so far reported for the new family of biocompatible solutions as compared with conventional PDFs include less infusion pain, higher concentrations of pro-collagen I C-terminal peptide, lack of change in the levels of either VEGF or tumor necrosis factor alpha, lower serum levels of serum N\textsubscript{ɛ}-carboxymethyl-lysine and imidazolone and, most importantly, higher urine output (10,11,13). If the improvement in urine volume is reflective of better preservation of renal function, the potential benefits of biocompatible solutions could be enormous, considering the fact that residual renal function rather than peritoneal clearance has been shown to significantly influence both quality of life and patient survival (14,15).

What is on the horizon?
The next stage will be to review the longitudinal experience accrued from using biocompatible solutions in thousands of patients during the past few years. That review should include both the various cross-sectional studies underway with large populations and the more rigorous controlled trials. The areas of greatest interest are actual patient survival, technique survival, peritonitis rate, and membrane function preservation with the use of biocompatible PDFs. Also important is the potential impact of biocompatible solutions on renal function preservation.

Larger numbers of patients, longer observation periods, and use of various PDF formulations are likely to identify the specific roles of GDPs, AGEs, solution pH, lactate, glucose concentration, and osmolarity with regard to peritoneal membrane function and viability. At present, the formulations of commercially available biocompatible PDFs in selected markets fall into these categories:

- Neutral pH, low-GDP, lactate-based
- Neutral pH, low-GDP, lactate/bicarbonate mixtures
- Neutral pH, low-GDP, pure bicarbonate solutions

The theoretical, in vivo, ex vivo, and preliminary data all suggest that bicarbonate-based PDF is the best candidate for most biocompatible. However, clinical studies are necessary to confirm that notion.

References
Biocompatibility


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In the present study, we evaluated peritoneal transport characteristics during the use of icodextrin-based peritoneal dialysis (PD) solution, determining ultrafiltration (UF) and dialysate-to-plasma creatinine (D/PCr) in a peritoneal equilibration test (PET).

The subjects of the study were 8 anuric patients who, at the time of enrollment into the study, were receiving continuous ambulatory peritoneal dialysis (CAPD) and using a 2.5% glucose-based dialysis solution overnight. The mean age of the patients was 57.9 ± 6.1 years (range: 45.2 – 64.1 years), and their mean duration of CAPD was 61.6 ± 44.3 months (range: 5.6 – 140.1 months).

We changed the 2.5% glucose solution that the patients were using for the 8-hour overnight dwell to icodextrin and measured the resulting UF. We also performed a PET before and 12 weeks after the start of icodextrin. After the start of icodextrin, PETs were carried out immediately after the icodextrin dwell; after rinsing twice with 2.5% glucose solution following an icodextrin dwell; and after an 8-hour dwell with glucose solution.

The UF for 8-hour dwells increased significantly 12 weeks after the start of icodextrin (356.3 ± 102.9 mL with 2.5% glucose at baseline vs. 517.5 ± 102.8 mL with icodextrin, p < 0.001). However, the daily total UF was unchanged after the start of icodextrin (924.3 ± 281.3 mL vs. 934.6 ± 263.4 mL). As compared with the D/PCr before the start of icodextrin, the D/PCr after the start of icodextrin was significantly increased immediately after an icodextrin dwell (0.57 ± 0.1 vs. 0.63 ± 0.1, p < 0.01) and after twice rinsing with 2.5% glucose solution following an icodextrin dwell (0.57 ± 0.1 vs. 0.66 ± 0.2, p < 0.01). However, before or after the start of icodextrin, the D/PCr, after an 8-hour dwell with glucose solution did not change (0.57 ± 0.1 vs. 0.57 ± 0.1, p < 0.01).

The D/PCr measured in a PET was high immediately after a dwell with icodextrin. Those results may reflect an effect of icodextrin on the small pores. Before a PET, dialysis should be performed using a glucose solution.

Key words
Continuous ambulatory peritoneal dialysis, icodextrin-based peritoneal dialysis solution, peritoneal equilibration test, peritoneal permeability

Introduction
Dialysis solutions with icodextrin as the osmotic agent have become widely used. Unlike a glucose-based dialysis solution, icodextrin-based solution produces transport of water and solutes through a colloid osmotic pressure gradient (1). That mechanism is considered to make ultrafiltration (UF) of a given volume possible regardless of peritoneal permeability. However, peritoneal transport characteristics during icodextrin use have not been completely clarified.

The peritoneal equilibration test (PET) is the most common test of peritoneal function. In a standard PET, a glucose solution dwells overnight, and then a 2.5% glucose solution dwells for 4 hours, after which the transport of solutes from crystalloid osmotic pressure is evaluated (2). When a PET is performed after a time with an empty peritoneal cavity (3) or immediately after a dwell with icodextrin, dialysate-to-plasma creatinine (D/PCr) is reported to increase (4). Peritoneal permeability may change, depending on the nature of the solution used before the test and the state of the peritoneal cavity.
In the present study, we evaluated peritoneal transport characteristics by determining UF and D/PCr in a PET during the use of icodextrin by patients in stable condition on continuous ambulatory peritoneal dialysis (CAPD).

**Patients and methods**

**Patients**
The subjects of the study were 8 anuric CAPD patients (4 men, 4 women) who had been using a 2.5% glucose solution for the overnight dwell. Their mean age was 57.9 ± 6.1 years (range: 45.2 – 64.1 years), and the mean duration of dialysis was 61.6 ± 44.3 months (range: 5.6 – 140.1 months). In all patients, the cause of end-stage renal disease was chronic glomerulonephritis.

**Methods**
We changed the 2.5% glucose solution being used by the patients for the 8-hour overnight dwell to icodextrin, and we measured the resulting UF. We also performed a PET before and 12 weeks after the start of icodextrin. Before the start of icodextrin, the PET was performed after an 8-hour dwell with glucose solution according to the method of Twardowski et al. (2). After the start of icodextrin, the PET was performed after an 8-hour dwell with icodextrin; after washing twice with 2.5% glucose solution following an 8-hour dwell with icodextrin; and after an 8-hour dwell with glucose solution. We compared the PET results after the start of icodextrin with the results from before the start of icodextrin.

**Statistics**
Results are presented as mean ± standard deviation. Differences between results seen before and after the start of icodextrin were assessed using the paired Student t-test.

**Results**
After an 8-hour overnight dwell with icodextrin, UF was significantly greater 12 weeks after the start of icodextrin than when 2.5% glucose solution was being used (517.5 ± 102.8 mL vs. 356.3 ± 102.9 mL, p < 0.001). However, no change in the daily total UF was observed (924.3 ± 281.3 mL vs. 934.6 ± 263.4 mL)—that is, the UF during daytime glucose exchanges decreased. The approximately 200-mL increase in UF after an 8-hour dwell with icodextrin was offset by a reduction in UF with daytime glucose solution. The decrease in UF with glucose solution may have been an effect of the icodextrin (Figure 1).

**Peritoneal equilibration test**
Table I shows the PET results.

As compared with D/P Cr before the start of icodextrin, the D/P Cr after the start of icodextrin increased significantly immediately after an 8-hour icodextrin dwell (0.57 ± 0.1 vs. 0.63 ± 0.1, p < 0.01) and after rinsing twice with 2.5% glucose solution following an icodextrin dwell (0.57 ± 0.1 vs. 0.66 ± 0.2, p < 0.01). However, before or after the start of icodextrin, D/P Cr did not differ after an 8-hour dwell with glucose solution (0.57 ± 0.1 vs. 0.57 ± 0.1, p > 0.01).

The dialysate glucose concentration decreased significantly when the PET was performed after an 8-hour icodextrin dwell as compared with after an 8-hour glucose dwell both before and after the start of icodextrin. The UF volume did not vary among the PETs.

**Discussion**
Icodextrin is a polyglucose with a mean molecular weight of 16,800 Da. Unlike glucose solution, icodextrin produces transport of water and solutes by colloid osmotic pressure. Because the difference in osmotic pressure between icodextrin and blood is small, no transport of water occurs through...
aquaporins; instead, water is transported through the small pores. Also, because icodextrin is absorbed only slowly into blood, the difference in osmotic pressure is maintained. Icodextrin therefore sustains UF during a long dwell and in patients with high peritoneal permeability. Icodextrin has been shown to be effective in improving volume status and blood pressure control (5,6). However, although UF increased in our patients by about 200 mL after an 8-hour dwell with icodextrin as compared with an 8-hour dwell with 2.5% glucose solution, no change was observed in the daily total UF, because UF with daytime glucose solution decreased. That decrease in UF with daytime glucose solution may have been an effect of icodextrin.

The PET is a test of peritoneal function proposed by Twardowski et al. (2). Before a PET, glucose solution dwells overnight, then 2 L of 2.5% glucose solution dwells for 4 hours, after which the transport of solutes by crystalloid osmotic pressure is evaluated.

Our results showed that D/PCr increased and dialysate glucose concentration decreased during a PET immediately after an 8-hour icodextrin dwell. Lilaj et al. (4) reported similar results. In addition, the same authors reported that dialysate-to-plasma sodium (D/PNa) was higher and sodium sieving was reduced immediately after an icodextrin dwell as compared with after a glucose solution dwell. The authors considered that those findings were the result of an increase in solute transport through the small pores because of residual icodextrin. However, the residual volume of icodextrin solution in the peritoneal cavity was 200 – 300 mL, and the icodextrin concentration was considered to have been reduced during the long dwell. Moreover, D/PCr has been reported to be increased in a PET conducted after a time with an empty peritoneal cavity. Those results are difficult to explain by the effect of residual icodextrin alone.

To avoid the possible effects of a residual volume of icodextrin solution, we performed a PET after rinsing the peritoneal cavity twice with 2.5% glucose solution following an 8-hour icodextrin dwell. Still, the D/PCr was increased and the dialysate glucose concentration was decreased, results similar to those obtained in a PET conducted immediately after an 8-hour icodextrin dwell. The peritoneal transport characteristics after an icodextrin dwell therefore persisted even when we tried to avoid the effect of residual volume.

Although we have no evidence to explain the phenomenon, we hypothesize that some change in the small pores induced by the preceding icodextrin dwell may have persisted during the PET. Ho-dac-Pannekeet et al. (7) compared the mass transport characteristic for creatinine (MTACr) and the D/PCr in 4-hour dwells with icodextrin and with 4.25% glucose solution. From the absence of differences, those authors suggested that diffusion through the peritoneal membrane is not affected by the type of osmotic pressure or type of solution (7). However, the type of dialysis solution that they used before the 4-hour study dwell is unknown. Further evaluation is needed.

The D/PCr measured in a PET performed after an 8-hour glucose solution dwell 12 weeks after the start of icodextrin for the overnight dwell was similar to the D/PCr measured before the start of icodextrin. Lilaj et al. (4) reported similar results. Following the method of Twardowski et al. (2), a PET must be performed after a long dwell with glucose solution.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>D/PCr</th>
<th>Dialysate glucose concentration (mg/dL)</th>
<th>Dialysate drain volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-icodextrin PET</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preceding glucose dwell</td>
<td>0.55±0.1</td>
<td>1022.8±151</td>
<td>2392.7±81.1</td>
</tr>
<tr>
<td>Post-icodextrin PET</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preceding icodextrin dwell</td>
<td>0.63±0.1 a</td>
<td>882.6±97.7 a</td>
<td>2353.3±106.2</td>
</tr>
<tr>
<td>Preceding icodextrin dwell + rinsing</td>
<td>0.66±0.2 a</td>
<td>838±244.5 a</td>
<td>2334.3±123.8</td>
</tr>
<tr>
<td>Preceding glucose dwell</td>
<td>0.57±0.1</td>
<td>933.1±160.9</td>
<td>2313.3±150.4</td>
</tr>
</tbody>
</table>

a The D/PCr values post icodextrin and post icodextrin plus rinsing were significantly increased as compared with pre-icodextrin values. The dialysate glucose concentrations post icodextrin and post icodextrin plus rinsing were significantly decreased as compared with pre-icodextrin concentrations. (p < 0.01 versus pre-icodextrin PET)
Conclusion
We evaluated peritoneal transport characteristics with the use of icodextrin PD solution for the long dwell. The measured \( \text{D/PCr} \) was high and the dialysate glucose concentration was low in a PET performed immediately after an 8-hour icodextrin dwell, possibly because icodextrin exerted an effect on the small pores. That effect may also have induced a reduction in UF by glucose solution during the daytime dwells following the overnight icodextrin dwell. Glucose solution should be introduced into the peritoneal cavity before a PET. Further evaluation is needed concerning the effects of icodextrin on the peritoneal membrane.

References

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