

# Significant issues in PD therapy

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## Contents

- 1. Benefits of biocompatible PD fluid for preservation of residual renal function in incident CAPD patients: a 1-year study**
- 2. Rate of decline of residual renal function is associated with all-cause mortality and technique failure in patients on long-term peritoneal dialysis**
- 3. A positive effect of ACE inhibitors on peritoneal membrane function in long-term PD patients**
- 4. Predictors of peritonitis in patients on peritoneal dialysis: Results of a large, prospective Canadian database**
- 5. Similar survival on automated peritoneal dialysis and continuous ambulatory peritoneal dialysis in a large prospective cohort**

## Preface

Peritoneal dialysis has been advancing in terms of technique, new exchange systems, and a new generation of solutions. Nevertheless significant issues and questions for PD therapy remain.

The pivotal contribution of residual renal function to survival and well-being of PD patients has been underlined by several studies. **Kim et al.** and **Liao et al.** point to several mechanisms accounting for an accelerated RRF loss and offer strategies oriented towards better preservation of RRF in PD.

The long-term success of PD as an adequate renal replacement therapy also clearly depends on the function of the peritoneal membrane as the intracorporeal dialyzing organ. **Kolesnyk et al.** demonstrate a beneficial long-term effect on small-solute transport using ACE inhibitors and angiotensin II receptor blockers. **Nessim et al.** looked for factors that are associated with peritonitis to identify the patients who are at increased risk for developing a peritonitis which remains a major cause of PD treatment failure and transfer to haemodialysis.

The study by **Michels et al.** confirms recent findings, also from a meta-analysis, that there is no difference in overall mortality and technique failure between CAPD and APD patients. Therefore the authors suggest, the decision which PD modality to start should be based on the patient's preference, quality of life, or available resources.

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## 1. Benefits of biocompatible PD fluid for preservation of residual renal function in incident CAPD patients: a 1-year study

Conventional peritoneal dialysis fluids (CF) with acidic pH and a high content of glucose degradation products (GDPs) have been identified as contributing causes for a progressive loss of peritoneal membrane function. In comparison, more biocompatible PD fluids (LF) with neutral pH and a low content of GDPs seem to better preserve mesothelial cell mass/function. However, few clinical trials have investigated the effect of LF with regard to residual renal function (RRF). This prospective, randomized, multicentre, controlled Korean study from **S Kim et al.** investigated the impact of CF in comparison to LF with regard to RRF (determined by glomerular filtration rate, GFR).

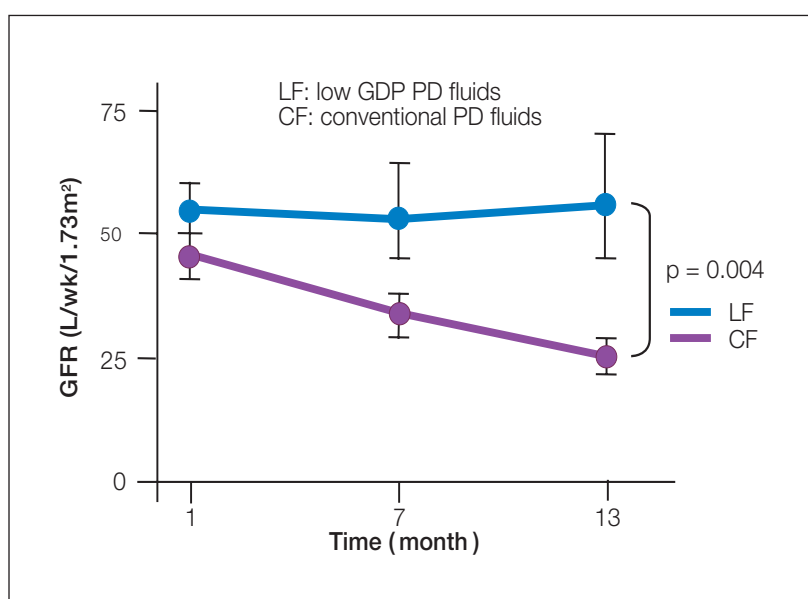
Between 2004 and 2006, 91 incident PD patients were randomized to receive - following a run-in phase of one month on CF - either LF (Balance<sup>®</sup>, Fresenius Medical Care, n = 48) or CF (CAPD/DPCA<sup>®</sup>, Fresenius Medical Care, n = 43) on a continuous ambulatory (CAPD) basis. RRF, peritoneal solute transport rate and solute clearances were measured every 6 months.

Baseline demographics of both groups were similar. There were no differences in age, gender, comorbidity score, prior requirement for HD, aetiology of ESRD and eGFR at month 0. At month 13, GFR was  $39.6 \pm 50.2$  L/week/1.73 m<sup>2</sup> in the LF group and  $22.4 \pm 18.6$  L/week/1.73 m<sup>2</sup> in the CF group ( $p=0.065$ ). When analyzed by the mixed model with adjustments for age, gender, Davies comorbidity score and GFR at month 1, GFR at month 13 for the LF group was significantly higher

( $p = 0.048$ ). In per-protocol analysis, GFR did not decrease over the 12-month period in the LF group, while it decreased significantly in the CF group (LF:  $0.13 \pm 33.4$  L/week/1.73 m<sup>2</sup> vs. CF:  $-13.6 \pm 19.4$  L/week/1.73 m<sup>2</sup>,  $p = 0.049$ ).

In a *subgroup* of patients (n = 67) with baseline GFR of  $\geq 2$  mL/min/1.73 m<sup>2</sup>, GFR was significantly higher ( $p = 0.004$ ) in the LF group than in the CF group at month 13,  $57.5 \pm 55.8$  L/week/1.73 m<sup>2</sup> versus  $26.1 \pm 18.7$  L/week/1.73 m<sup>2</sup> (**Figure 1**). Over time, there was an obvious tendency to a wider divergence of GFR values between the groups. The authors state that this study suggests a beneficial effect of low GDP fluid on GFR for the first time in a prospective, randomized, controlled study with parallel arms.

In the LF group, the dialysate CA-125 (cancer antigen 125) levels increased significantly over the 12-month period (month 13:  $31.6 \pm 19.5$  U/ml), and were higher than those of the CF group ( $12.7 \pm 8.98$  U/ml,  $p < 0.001$ ), indicating a better recovery of the mesothelial cell mass. Effluent interleukin-6 levels were similar between the groups.



**Fig. 1:** Effect of LF on RRF in a subgroup of patients with GFR at month 1  $\geq 2$  mL/min/1.73m<sup>2</sup>

In conclusion, this controlled study suggests that low GDP PD fluids compared with conventional PD fluids may better preserve RRF in incident PD patients over a 1-year treatment period - especially in PD patients with baseline GFR of  $\geq 2$  mL/min/1.73 m<sup>2</sup>. KB

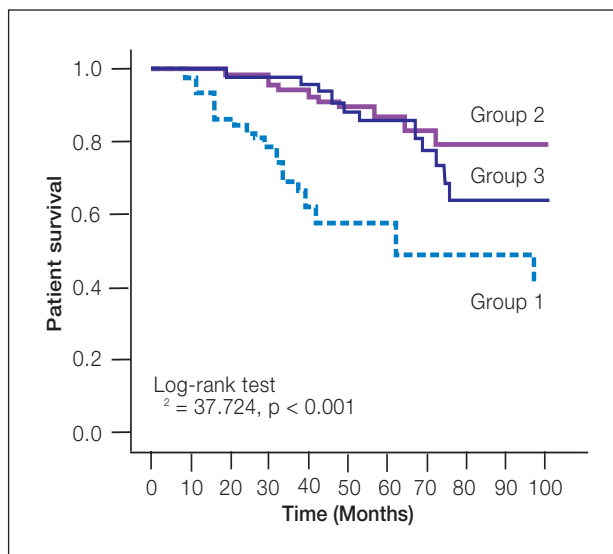
Kim Se, Oh J, Kim Su, Chung W, Ahn C, Kim SG, Oh KH: Benefits of biocompatible PD fluid for preservation of residual renal function in incident CAPD patients: a 1-year study; Nephrol Dial Transplant, 24 (9), 2899 - 2908, 2009

## 2. Rate of decline of residual renal function is associated with all-cause mortality and technique failure in patients on long-term peritoneal dialysis

Many studies have pointed to the importance of residual renal function (RRF) at the initiation of PD. However, RRF declines with time at variable rates in different patients. Thus, **CT Liao et al.** compared the impact of baseline RRF versus the rate of RRF decline on patient and technique survival.

A total of 270 patients from a medical centre in North Taiwan who began PD between January 1996 and December 2005 and who were followed until December 2007 were included in this retrospective study. RRF was determined as the arithmetic mean of 24-h urea nitrogen and creatinine clearance, which were measured within 3 months following initiation of PD, and thereafter at 3- to 6-month intervals. The study population was categorized as the 'fast' (n = 90), 'intermediate' (n = 90) and 'slow' (n = 90) decline groups according to the tertiles of the calculated RRF decline rate.

At baseline, the mean age of the 270 patients was  $50.4 \pm 15.8$  years, 19.2% were diabetics, mean RRF was  $2.75 \pm 1.72$  mL/min/1.73m<sup>2</sup>. During the average follow-up time of 45 months, 50 patients died, 67 experienced technique failure (i.e. transfer to HD) and 43 received renal transplantation. Infection and cardiovascular disease were the most common causes of death, and peritonitis and inadequate small solute clearance were the most common causes of technique failure. The Kaplan–Meier estimate of the survival curve and the log-rank test showed that patients with fast RRF decline were more likely to have worse survival (**Figure 2**) as well as worse technique survival, compared to patients with slow and intermediate RRF decline. The Cox regression model, which treated RRF and decline rate of RRF as time-dependent variables, revealed that a more rapid rate of RRF decline was more strongly associated with combined death and technique failure than a lower baseline RRF. Among the 270 patients who had RRF at the beginning of PD, 206 patients became anuric during the follow-up. The mean duration from the initiation of PD to anuria was 31 months. The median annual rate of RRF decline was 0.885 mL/min/1.73m<sup>2</sup>. The fitted multivariate propor-



**Fig. 2:** Kaplan-Meier survival curves for PD patients with different rates of RRF decline (categorized as the 'fast' (group 1, n = 90), 'intermediate' (group 2, n = 90) and 'slow' (group 3, n = 90) decline groups according to the tertiles of the calculated RRF decline rate)

tional odds polychotomous logistic regression model after adjusting age, baseline RRF and other variables showed that those who were diabetic, had a history of congestive heart failure, large body mass index, used diuretics, had peritonitis episodes and suffered hypotensive events experienced more rapid decline of RRF. The most frequent causes of hypotensive events included excessive ultrafiltration (41.7%), sepsis (23.8%), heart failure (14.3%), overuse of antihypertensive agents (9.5%), acute blood loss (4.8%), severe diarrhoea (2.4%) and other unspecified causes (3.5%).

*In conclusion, the authors could demonstrate that the rate of RRF decline is a more crucial predictive factor than baseline RRF for all-cause mortality and technique failure in PD patients. Every effort should be made to prevent the accelerated loss of RRF by avoiding overdiuresis, peritonitis, hypotensive episodes, especially in those patients with diabetes, obesity and congestive heart failure.*

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Liao CT, Chen YM, Shiao CC, Hu FC, Huang JW, Kao TW, Chuang HF, Hung KY, Wu KD, Tsai TJ: Rate of decline of residual renal function is associated with all-cause mortality and technique failure in patients on long-term peritoneal dialysis; *Nephrol Dial Transplant*, 24 (9), 2909 - 2914, 2009

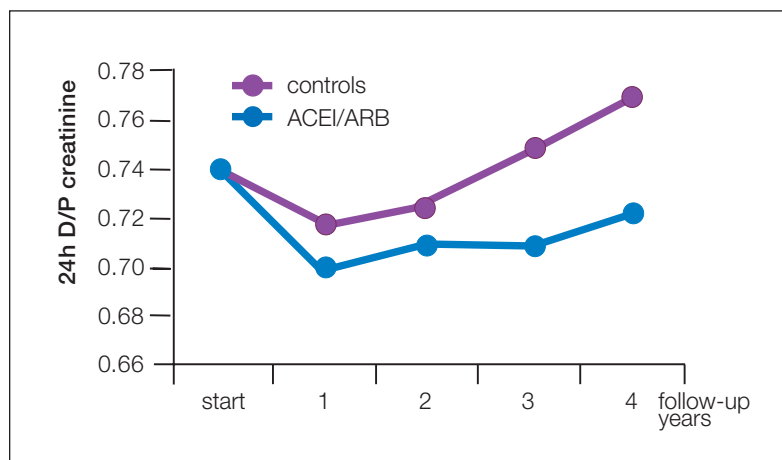
### 3. A positive effect of All inhibitors on peritoneal membrane function in long-term PD patients

Experimental studies have shown that inhibition of Angiotensin receptor II (All) positively influenced peritoneal solute transport. In a single centre study the use of ACE inhibitors (ACEI) and/or Angiotensin receptor blockers (ARBs)

could prevent the increase of small solute transport in peritoneal dialysis (PD) patients. In this study performed by **I Kolesnik et al.** the effects of All inhibition in a larger population and its influence on patient and technique survival in patients on long-term PD were investigated.

Data from 217 long-term PD patients from 38 dialysis centres were selected from the database of NECOSAD, a prospective multicentre cohort study. Included patients underwent CAPD therapy for at least 2 years, 120 of them received ACEI/ARB for at least 25% of the follow-up time. The control group consisted of 87 patients who received none of these drugs and 10 patients who had them for < 25% of their time on PD. Peritoneal transport characteristics were assessed by the dialysis adequacy and transport test (DATT), and the time course of 24h D/P creatinine was analysed in relation to the exposure to the drug.

A significant difference in the time course of peritoneal transport was found between the two groups. The value of 24h D/P creatinine was associated with the PD duration ( $p = 0.01$ ) and its time course was influenced by use of ACEI/ARB,  $p = 0.05$  (**Figure 3**). No effect of ACEI/ARB on patient survival was observed.



**Fig. 3:** Time course of 24h D/P creatinine. The number of patients in the ACEI/ARB group was 120 at first and second year, 64 at third year and 36 at fourth year. The respective values for the controls were 97 at the first and second year, 44 at third years and 28 at the fourth year of the follow-up

However, technique survival was slightly but not significantly better in the ACEI/ARB group: in a multivariate model the hazard ratio for the group with the longest use of ACEI/ARB was 0.5 (CI 0.22–1.4,  $p = 0.19$ ).

*In conclusion, the results of this study illustrate that the use of ACEI/ARB in CAPD patients may prevent or retard the increase in D/P creatinine often seen in long-term PD patients. As D/P creatinine depends on the vascular peritoneal surface area, the data suggest less peritoneal angiogenesis in patients receiving ACEI/ARB treatment. The assumed membranoprotective effect of All inhibition may positively influence PD technique survival in long-term PD patients.* UK

Kolesnyk I, Noordzij M, Dekker FW, Boeschoten EW, Krediet RT: A positive effect of All inhibitors on peritoneal membrane function in long-term PD patients; *Nephrol Dial Transplant* 24: 272-277, 2009

#### 4. Predictors of peritonitis in patients on peritoneal dialysis: Results of a large, prospective Canadian database

Despite the dropping incidence of peritonitis among peritoneal dialysis (PD) patients over time, its occurrence is still associated with significant morbidity and mortality. It is still not clear which patients are at highest risk for developing peritonitis. Thus, determining factors that are associated with peritonitis may facilitate the identification of PD patients who are jeopardized.

The primary objective of **SJ Nessim et al.** was to assess factors that are associated with peritonitis. Analyses were carried out on 2555 peritonitis episodes among 4247 incident PD patients from 25 centres across Canada. Data were prospectively collected from a database within a period from January 1, 1996,

until September 12, 2005. Of the 4247 patients, 1445 were still being followed at the end of the data collection period (median follow-up time 2 years). Relapsing or recurrent peritonitis episodes were excluded. Mean age was  $59 \pm 16$  years, 55% were males, 40% were diabetics. Median time on PD was 1.37 years. The overall peritonitis rate was one episode in 26 patient months on PD, decreasing to one episode in 33 patient months after exclusion of recurrent or relapsing events. In the multivariable regression model, the following variables were independently associated with a higher peritonitis rate: age, black race, transfer from haemodialysis (HD) to PD, diabetic females (**Table 1**). The authors remark that the increased peritonitis rate associated with transfer from HD to PD has not been previously reported. They hypothesize that this increased risk may have two reasons. On the one hand, patients with a "crash start" on HD with little pre-dialysis care subsequently chose to transfer to PD. On the other side, patients with years on HD have most probably lost their residual renal function at the time of transfer to PD. This may increase their peritonitis risk, since it has been shown that loss of residual renal function is an independent predictor of peritonitis. CAPD (continuous

**Table 1:** Multivariable regression model; APD, automated PD; CI, confidence interval; HR, hazard ratio; RR, rate ratio; <sup>a</sup>subgroup of 3180 patients who did not switch between CAPD and APD during their time on PD

Parameter	RR	95% CI	p-value
Age (per decade)	1.04	1.01 to 1.08	0.010
Black	1.37	1.00 to 1.88	0.050
Asian	0.89	0.74 to 1.08	0.240
Diabetes			
female	1.27	1.10 to 1.47	0.001
male	0.99	0.87 to 1.13	0.880
Glomerulonephritis	0.87	0.75 to 1.00	0.050
Transfer from HD	1.24	1.11 to 1.38	<0.001
Failed transplant	1.27	0.95 to 1.69	0.120
CAPD versus APD <sup>a</sup>	1.03	0.91 to 1.16	0.650

ambulatory PD) was not associated with a higher peritonitis rate than APD (automated PD). These results suggest that the choice between CAPD and APD can be guided by patient preference if the patient is able to perform both modalities. Having glomerulonephritis as the cause of endstage renal disease was associated with a lower peritonitis rate. The authors note that the possibility of residual confounding from variables that could not be incorporated in the statistical model (e.g. serum albumin, residual renal function) cannot be excluded.

Diabetes among women was associated with an increased Gram-positive peritonitis rate, as well as a higher streptococcal peritonitis rate. Patients who transferred from HD to PD also had an increased rate of Gram-positive peritonitis, mainly due to coagulase-negative Staphylococcus.

*In conclusion, predictors of peritonitis in PD patients were black race, transfer from HD to PD, and diabetes among women. In contrast to several previous studies, the authors found that CAPD and APD were similar with regard to risk of peritonitis.*

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Nessim SJ, Bargman JM, Austin PC, Nisenbaum R, Jassal SV: Predictors of peritonitis in patients on peritoneal dialysis: Results of a large, prospective Canadian database; Clin J Am Soc Nephrol 4, 1195 – 1200, 2009

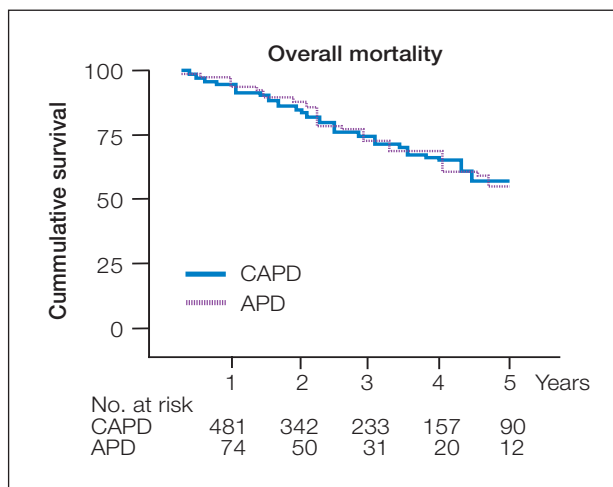
## 5. Similar survival on automated peritoneal dialysis and continuous ambulatory peritoneal dialysis in a large prospective cohort

Automated peritoneal dialysis (APD) is increasingly used in comparison with continuous ambulatory peritoneal dialysis (CAPD). The aim of the study, performed by

**WM Michels et al.** was to investigate whether overall mortality and technique failure of incident dialysis patients treated with APD differ from those treated with CAPD.

Patients on APD or CAPD at 3 months after start of dialysis were selected from the prospective multicentre cohort study NECOSAD (Netherlands Cooperative Study on the Adequacy of Dialysis) in incident dialysis patients. 38 dialysis centres in the Netherlands participated between 1997 and 2006 in the NECOSAD study. In the present analysis, 87 incident dialysis patients on APD and 562 patients on CAPD at 3 months after the start of dialysis (baseline) were included and followed up until patients received transplantation or they died. The overall mortality was studied with an intention-to-treat (ITT) design. Technique failure was studied with an as-treated design; the event was a switch of dialysis modality, either to HD or to another form of PD. Hazard ratios (HRs) were calculated with a follow-up of 5 years.

In the intention-to-treat analysis 154 (27%) CAPD and 21 (24%) APD patients died. The crude HR for overall mortality with APD was 0.98 (95% CI: 0.62–1.54), the adjusted HR was 1.09 (95% CI: 0.65–1.83) compared to CAPD. In the as-treated analysis 238 (42%)



**Fig. 4:** Kaplan-Meier curve of overall mortality on automated peritoneal dialysis compared with continuous ambulatory peritoneal dialysis.

CAPD patients and 34 (39%) APD patients switched therapy. Of these patients during follow-up 91 (16%) CAPD patients died, compared with 7 (8%) APD patients. The crude HR for technique failure with APD was 0.92 (95% CI: 0.64 – 1.31) and did not change after adjustment.

*The investigators found no difference in overall mortality and technique failure for APD compared with CAPD in incident dialysis patients. Therefore, the choice to start either one of these therapies should be based on other factors than survival, such as quality of life, patients' preference, or available resources.* UK

Michels WM, Verduijn M, Boeschoten EW, Dekker FW, Krediet RT: Similar survival on automated peritoneal dialysis and continuous ambulatory peritoneal dialysis in a large prospective cohort; Clin J Am Soc Nephrol 4: 943 – 949, 2009



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