Kidney International, Vol. 54 (1998), pp. 2207–2217

CLINICAL PERITONEAL DIALYSIS

What really happens to people on long-term peritoneal dialysis?

Simon J. Davies, Louise Phillips, Anne M. Griffiths, Lesley H. Russell, Patrick F. Naish, and Gavin I. Russell

Department of Nephrology, North Staffordshire Hospital Trust, Stoke-on-Trent, England, United Kingdom

What really happens to people on long-term peritoneal dialysis?

Background. Several risk factors for patients treated with peritoneal dialysis (PD) have now been identified. These include age, comorbid disease, nutritional status, loss of residual renal function (RRF) and high peritoneal solute transport. This is not the same, however, as knowing what actually happens to these patients, particularly in the long-term. The purpose of this review was to give as complete a description as is currently possible of the long-term PD patient.

Methods. The literature was surveyed for publications that provide longitudinal cohort data of either selected or unselected patient groups. Detailed data from the Stoke PD Study is presented in the context of these studies. Three principle aspects of what really happens to patients were considered: (*1*) death, both cause and mode of death; (*2*) technique failure, with reference to peritoneal function and how the cause of technique failure related to patient survival; and (*3*) evolution of clinically relevant parameters of patients on PD, such as nutrition and peritoneal function.

Results. Sudden death and debilitation were the predominant modes of death, with sepsis playing a contributory role. Debilitation was important regardless of co-existent comorbid disease, and time to death was not influenced by the mode of death. Predominant causes for technique failure remain peritonitis and ultrafiltration, the latter becoming more important with time on treatment. Technical failure is associated with poorer survival, particularly when due to multiple peritonitis or failure to cope with treatment. Cox regression demonstrated that whereas low albumin, loss of RRF and high solute transport predicted patient death, only high solute transport predicted technique failure. Longitudinal changes over the first five years of treatment included loss of RRF, increasing solute transport and following an initial improvement in nutritional state, a decline after two years. Patients surviving long-term PD (at least five years, $N = 25$) were characterized by prolonged RRF, maintained nutrition and lower solute transport in the medium term.

Conclusions. Several studies of long-term PD in the literature now complement each other in providing a picture of what really happens to PD patients. The links between loss of solute clearance and poor peritoneal ultrafiltration combining to exacerbate sudden or debilitated death and technique failure are emerging. For PD to be successful as a long-term therapy, strategies that maintain nutrition and preserve peritoneal membrane function must be developed.

Key words: risk factors for death, residual renal function, peritoneal solute transport, nutrition and dialysis, Stoke PD Study, death and peritoneal dialysis, patient survival on PD.

Despite the fact that continuous forms of peritoneal dialysis (PD) have been in use for 20 years and that it is a well established treatment in the medium-term [1–3], our detailed understanding of what actually happens to patients using this modality in the longer term is only now beginning to develop. The 1980s were spent addressing the more pressing problems of the technique, such as high peritonitis rates, while at the same time those factors that determine patient outcome as they relate to dialysis adequacy were beginning to be defined for the hemodialysis population [4]. The 1990s have seen these concerns addressed within the PD population, and we now have a far clearer idea of those factors that predict good outcome in these patients [5–7]. However, this is not the same thing as knowing what actually happens to these individuals, which is the focus of the present review.

There are now several large cohort studies in the literature that provide information about what actually happens to patients on PD in the medium to longer term, and these are summarized in Table 1 [2, 3, 8–16]. These studies vary in size, with the larger multicenter studies having the advantage of patient numbers that can address comparative survival (patient and technique) with hemodialysis [2, 3, 10, 13, 16], whereas the smaller or single center studies can provide greater detail on nutrition, solute kinetics and peritoneal membrane function [8, 9, 11, 12, 14, 15].

The Stoke Peritoneal Dialysis Study was set up in 1990 specifically to examine how peritoneal membrane function is influenced by the treatment and its complications with time on PD, and also to establish how it in turn influences patient outcome. In addition, the study has taken a close look at nutrition in these patients. Several important observations have already been made. These include clinical evaluation of the peritoneal equilibration test [17], the effect of comorbidity on appetite suppression [18], interaction of peritoneal function with varying comorbidities and patient survival [19], longitudinal changes in peritoneal function and the influence of peritonitis [20], and the relationship of solute transport to patient survival [7]. There are now sufficient data to provide a detailed description of what actually happens to PD patients during the first

Table 1. Summary of cohort studies of long-term peritoneal dialysis (PD)

Source	Duration	Number of patients	Type of study	Comment
Maiorca et al 1991 [2]	7 years	483	Multicenter	6 Italian Centers Comparative study with HD. Patient and technique survival.
Rotellar et al 1991 [8]	10 years	171	Single Center	Patient and technique survival.
Selgas et al 1993 [9]	11 years	56	Single Center	Selected patients on PD more than three years, solute clearance data.
Lupo et al 1994 [10]	10 years	1,990	Multicenter	Italian Cooperative Dialysis Study Group (30 Centers). Patient and technique survival.
Faller & Lamiere 1993 [9] 1994 [11]	7 years	23	Two Centers	Selected patient group. Detailed data on solute clearance and membrane function.
Selgas et al 1994 [12]	11 years	56	Single Center	Selected patients on PD more than three years, membrane function data.
Maiorca et al 1996 [13]	13 years	297	Single Center	Comparative study with HD. Patient and technique survival, with some solute clearance data.
Diaz-Buxo & Shultman 1997 [14]	5 years	22	Single Center	Selected group of patients on treatment at least 5 years, from a cohort of 734. Describes characteristics including membrane function.
Abdel-Rahman et al 1997 [15]	18 years	20	Single Center	Retrospective analysis of 20 patients on PD more than 100 months from a cohort of 165. Describes characteristics including age and dialysis prescription.
Kawaguchi et al 1997 [16]	16 years	224	Single Center	Patient and technique survival.
Fenton et al 1997 [3]	5 years	2,841	Multicenter	Canadian dialysis population, derived from registry data. Patient survival.
Stoke Study 1998	7 years	303	Single Center	Patient and technique survival. Detailed data on nutrition, solute clearance and membrane function.

five years of treatment, and this is presented below in the context of a review of the existing literature.

Three principle areas need to be considered in order to provide a complete picture of what actually happens to PD patients: (*1*) death, (*2*) transfer to hemodialysis after technique failure, and (*3*) the evolution of clinically relevant parameters that change with time on PD, such as nutrition and peritoneal membrane function. Before the latter can be interpreted, which will inevitably be shaped by patient selection associated with treatment drop-out, a thorough understanding of death and technical failure is required. This review will deal with each of these areas in turn.

METHODS

Analysis of the literature

A literature search was conducted to identify publications that might provide relevant information concerning long-term PD patients. Studies were included (Table 1) if (*1*) they were published after 1990, (*2*) they represented a prospective cohort of either selected or unselected patients, and (*3*) that they contained significant data at five years or more. In view of the tendency of authors to re-publish data once patient numbers have increased, the review was limited to one type of study per author group. During this process a number of other important studies investigating long-term PD patients were identified, and while not strictly prospective cohort studies, they are discussed in the text [21–23]. To facilitate the comparison between cohort studies, five-year patient and technique survival rates were derived from the published survival curves, as these were not always available from the text or tables. As such, the accuracy of these derivations are within a few percentage points.

Table 2. Patient and technique survival in long-term cohort studies

Source	Mean age	Proportion of patients with diabetes	Proportion of patients with cardiovascular disease	Patient survival at 5 years	Technique survival at 5 years
Maiorca et al 1991 [2]	56.2	20.2%	20–25%	50%	70%[a]
Rotellar et al 1991 [8]	47	18%	not stated	60%	64%
Lupo et al 1994 [10]	58.4	13%	31%	48%	58.5%
Maiorca et al 1996 [13]	62	13%	22–25%	60%[a]	72%
Kawaguchi et al 1997 [16]	47.6	13.8%	not stated	50%	55%
Fenton et al 1997 [3]	63[b]	31.9%	43.4%	35%	n/a
Stoke Study 1998	58.8	14.8%	32%	55%	70%

[a] Data adjusted for risk factors
[b] Estimated from published distribution

Where possible, the survival data reflect crude percentages, although occasionally the data are only represented when adjusted for risk factors (Table 2). Technical survival was derived by considering a switch to hemodialysis as the final event, treating death and transplantation as lost to follow-up.

Stoke study design

All patients new to peritoneal dialysis at this center from the beginning of 1990 were entered into the study. While they remained on PD, they had assessments as outpatients for comorbidity, dialysis adequacy, dietary protein and calorie intake, peritoneal membrane function, biochemistry, lipid profiles, weight and anthropometrics every six months. Until the latter part of 1995 this was a purely observational study. Subsequently, those patients with clinical evidence of malnutrition (SGA of B or C) received a 25% increment in their delivered peritoneal dialysis dose. For the present study the population was censored in January 1998, at which point a policy decision was made to increase the dialysis dose across the board to reach dialysis adequacy targets (Kt/V 2.0 or creatinine clearance 60 liters/week). All patients were censored to allow overall patient and technical survival to be calculated, as well as survival according to treatment modality at the time of death/censor. The clinical and dialysis records were examined to ascertain the mode of death.

Mode of death

Prior to assessment of the clinical records, six categories describing the events at the time of death were identified. These were: (*1*) sudden death, characterized by sudden collapse, being found dead at home unexpectedly, cardiorespiratory arrest in hospital or a cerebrovascular event resulting in rapid decline and death within the next few days; (*2*) debilitation, a death characterized by frequent hospital admissions, always expected and often associated with treatment withdrawal at the point at which the outlook was considered hopeless; (*3*) sepsis, an uncontrolled infection at the time of death resulting in septic shock; (*4*) peritonitis, active PD peritonitis at the time of death, or requiring Tenckhoff catheter removal during the previous 14 days; (*5*) recent amputations, fulfilled if the patients had undergone a recent amputation, or were still hospitalized following amputation, even if the duration was several months; and (*6*) non-compliance, in this context it was defined as an overt inability or refusal to comply with treatment. One or more of the above categories could be identified as relevant in contributing to the mode of death in each patient, but where more than one category was fulfilled, one was identified as being the predominant mode. Hospital records were examined by two independent observers, and where a difference in categorization was obtained, the evidence was re-examined in order to obtain consensus.

Weight and mid-arm circumference

Actual body weight on the day of clinical assessment was used. The mid-arm circumference (MAC) was measured by one of a team of experienced renal dieticians, using a standard technique [24]. Intra-observer error between dieticians was re-assessed every two months, and found to be consistently within 2 mm (<1%).

Diet

Dietary protein (DPI) and calorie intake (DCI) were assessed by an experienced renal dietician who was blinded to the urea kinetic data, and who used a detailed dietary interview to establish the protein and calorie intake at home over the previous 24 hours. Data from this interview were analyzed by a dietetic software package, Microdiet (copyright University of Salford, 1983, 1988, Mark 7.10). This method of assessing protein and calorie intake has been carefully evaluated in our unit, and validated by an independent dietician working with a different group of CAPD patients and normal controls.

Peritoneal equilibration test

The peritoneal equilibration test (PET) was utilized to measure peritoneal kinetics, and this was performed as described previously [17, 20, 25]. Briefly, a standard four-hour dwell period was used (first exchange of the day), with a 2.27% glucose concentration-2 liter volume exchange. Patients used their usual overnight dialysis regime, and both the overnight and test drainage volumes were measured. Net ultrafiltration (UF) was calculated as the difference between the 2 liters of instilled dialysate and the volume drained after the four hour dwell. The dialysate: plasma creatinine ratio of creatinine at the completion of the four-hour dwell period (D/P_{Cr}) was used as the estimate of low molecular weight solute transfer. As glucose interferes with the assay for creatinine in a linear fashion, concentrations for both these solutes were measured at four hours, and the true value for creatinine obtained by subtracting the glucose concentration multiplied by a correction factor derived locally by our laboratory (0.47). Using this method, the four-hour D/P_{Cr} is a highly reproducible measure of low molecular weight solute transfer across a wide range of values (0.45 to 0.9), in the short term (3 months or less, provided there has been no clinical event such as peritonitis or surgery), with a coefficient of variation of 3 to 5%. Normal ranges $\pm$ 95% confidence interval (CI) for D/P_{Cr} were 0.635 ± 0.25 and net ultrafiltration 498 ± 409 ml.

Comorbid disease

The approach to identification of significant comorbid disease has been described previously, where it has been shown to predict patient survival [18, 19]. The following categories of active comorbid disease were: (*1*) malignancy, defined as an active, non-cutaneous disease, such as myeloma and breast cancer; (*2*) ischemic heart disease, as evidenced by previous myocardial infarction, angina pectoris, positive coronary angiography or the presence of ischemic changes on the resting ECG; (*3*) peripheral vascular

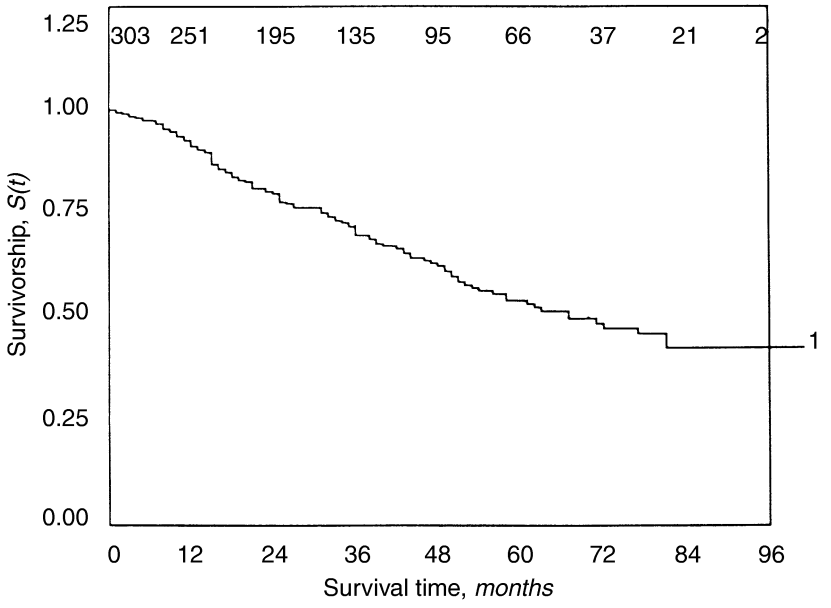

Fig. 1. Actuarial survival of the whole patient population ($N = 303$), representing all patients treated with peritoneal dialysis since 1990. The actual numbers of patients alive at each 12 month time point are shown.

disease, to include distal aortic, lower limb and cerebrovascular disease; (*4*) left ventricular dysfunction, defined as clinical evidence of pulmonary edema, not attributable to errors in fluid balance, and/or left ventricular dysfunction on echocardiography; (*5*) diabetes mellitus (Type 1 and Type 2); (*6*) systemic collagen vascular disease, such as vasculitis, rheumatoid arthritis and systemic sclerosis; (*7*) other significant pathology, for example, chronic obstructive airways disease, cirrhosis.

Dialysis dose

The dialysis dose (Kt/V) was assessed by calculating the weekly Kt/V_{urea} from the 24-hour urinary and dialysate clearances, by direct measurement of urea in urine and each dialysate exchange. The volume of distribution for urea was calculated as 58% of the body wt. Results are expressed as the total weekly Kt/V_{urea} (peritoneal and renal components), or for the residual renal function (RRF) alone.

Protein nitrogen appearance

Protein nitrogen appearance (PNA) was calculated using the equation derived from detailed nitrogen balance studies in CAPD patients [26]:

$$\text{PNA (g/day)} = [0.261 \cdot \text{UA (mmol/day)}] + 13 + \text{TPL (g/day)}$$

where UA is the total (urine plus dialysate) urea appearance and TPL is the total (urine plus dialysate) protein loss over 24 hours.

Analytical methods

Plasma and dialysate concentrations of urea, creatinine and glucose were determined on an automated discrete random access analyzer (DAX 72; Bayer Instruments, Basingstoke, UK). Plasma triglycerides were measured by enzymatic determination, using the GPO-POD reagent. Urine and dialysate total protein estimations were made using the biuret method. Plasma albumin levels were measured using the Bromocresol green method.

Statistical analysis

Univariate analysis of actuarial survival following entry to the study was performed using the Kaplan-Meier method, and the log-rank test was used to compare survival between subgroups. Longitudinal comparisons in clinical parameters were made using paired or unpaired *t*-tests where appropriate. The χ^2 test was used to compare the distribution of mode of death according to different comorbid conditions. Multivariate analysis of solute clearance, plasma albumin and peritoneal solute transport, and their prediction of patient and technique survival (excluding deaths) were performed using Cox proportional hazard modeling.

PATIENT SURVIVAL AND MODE OF DEATH ON PERITONEAL DIALYSIS

Patient survival

A comparison of the five-year survival rates for those studies that did not apply patient selection are summarized in Table 2. While the differences are apparent, these are not large and can be explained by the variability in the case

Table 3. Analysis of mode of death in 93 patients

Mode of death	Proportion of patients on PD at death	Predominant mode of death	Contributory to mode of death
Sudden	62%	41%	42%
Debilitation	57%	45%	53%
Sepsis	50%	6.8%	19.3%
Peritonitis	50%	4.5%	21.6%
Recent amputations	—	0%	3.4%
Non-compliance	50%	2.2%	3.4%
Mean	58%		

Table 4. Relationship of mode of death to pre-existing comorbid diseases

Comorbid disease	*N*	Sudden death	Debilitation
Ischemic heart disease	38	52%	48%
Peripheral vascular disease	26	48%	52%
Diabetes mellitus	18	46%	53%
Left ventricular dysfunction	23	40%	55%
Collagen vascular disease	7	28%	57%
Other	14	38%	30%
Malignancy	17	21%	79%[a]

A total of 15% of patients with collagen vascular disease died of peritonitis. In patients with "other" pathologies, sepsis accounted for 15% of deaths and peritonitis 10%.

[a] Proportionately more patients debilitated, χ^2, $P < 0.04$

mix, as indicated by the mean age and the proportion of patients treated who had diabetes mellitus and cardiovascular disease. The actuarial patient survival curve, and numbers of patients at risk as defined for the Stoke Study, in which 98% of patients were white Caucasian and 58% were male, are shown in more detail in Figure 1.

Cause and mode of death in peritoneal dialysis patients

The majority of studies in long-term PD patients do not provide detailed information as to how these patients die, and yet if we are to understand what really happens to these individuals, this information is vital. The best data describing the cause of death come from the Italian studies, in which sudden or cardiovascular deaths account for 45 to 47%, cachexia and malignancy for 23 to 25%, sepsis for 12 to 13%, and miscellaneous causes comprising the rest [2, 10, 13].

In the analysis of our own data, we chose to describe the mode of death, rather than ascribe a specific cause. The purpose of this approach was to define as clearly as possible those factors contributing to death, as well as the influence of the current treatment modality. Of 106 consecutive deaths, detailed information was available from the hospital notes or dialysis records in 93 (88%) of the events surrounding death. Of these, the independent observers agreed on categorization of contributory factors in 92% of cases. Of the total number of deaths, 58% occurred when the patient was on PD and 42% after transfer to hemodialysis or transplantation. The contribution of each category describing the mode of death, that is, whether it was the predominant or a contributory factor, is summarized in Table 3. It can be seen that sudden death and debilitation are by far the two most important categories, and that the proportions of patients still on PD verses alternative treatment modalities are very similar, and reflect the whole population. While sepsis and peritonitis were important contributors to the mode of death, it was much less common for them to be the predominant mode. These observations are certainly compatible with the ascribed causes of death in the literature (see above), although the role of debilitation appears to be important, and this is of course not specific to the cause. When the predominant mode of death was analyzed according to the pre-existing comorbid disease states (Table 4), it can be seen that there is a spectrum of balance between sudden and debilitated death. The proportion is approximately equal for those with ischemic heart disease, vascular disease and diabetes, with increasing debilitation seen in those with left ventricular dysfunction, and the majority of those with cancer being debilitated. Sepsis and peritonitis were more likely to be the predominant factors in patients with collagen vascular disease or other pathologies. Debilitated patients tended to die earlier, the median time to death being 15 months compared to 24 months if death was sudden, but this was not significant ($P = 0.27$).

Technique survival

Overall technique failure rates seen in the cohort studies are summarized in Table 2. While at first sight these rates appear to be quite good, it must be remembered that these exclude PD patients whose death may have been a consequence of a "failure" of the technique. Furthermore, in the case of comparative studies with hemodialysis, PD technique failure has been found consistently to be worse, a difference that gets progressively greater with time on treatment [2, 13]. In the study with the longest follow-up, 18% of the PD patients had switched modality as compared to 2.8% of the hemodialysis patients [13].

The reasons for technique failure are summarized in Table 5. It is clear that recurrent or severe peritonitis continues to be an important cause, although improvements in technique survival have been observed in some studies with time, primarily due to a reduction of this problem. Multiple or severe peritonitis events are probably an important risk factor for the development of sclerosing peritonitis [27]. The development of sclerosing peritonitis is, however, best correlated with time on treatment. Increasing, although anecdotal, evidence in centers having significant experience with long-term PD patients suggest that while sclerosing peritonitis may be precipitated by an infectious episode, its occurrence does not necessarily correlate with its severity or with the patient's previous

Table 5. A comparison of causes of technical failure in long-term PD studies

Source	Cause of technical failure					
	Recurrent peritonitis	Ultrafiltration failure	Solute removal	Leak/catheter	Other/clinical	Choice/not managing
Maiorca et al 1991 [2]	48.8%	22.1%		10.9%	11.9%	13%
Lupo et al 1994 [10]	29%	16.4%		8.5%	13.3%	11%
Maiorca et al 1996 [13]	37%	9%	9%	4%	13%	37%
Kawaguchi et al 1997 [16]	13.6%	23.5%	—	2.3%	44%	15.2%
Stoke Study 1998	54%	27%	—	2%	—	17%

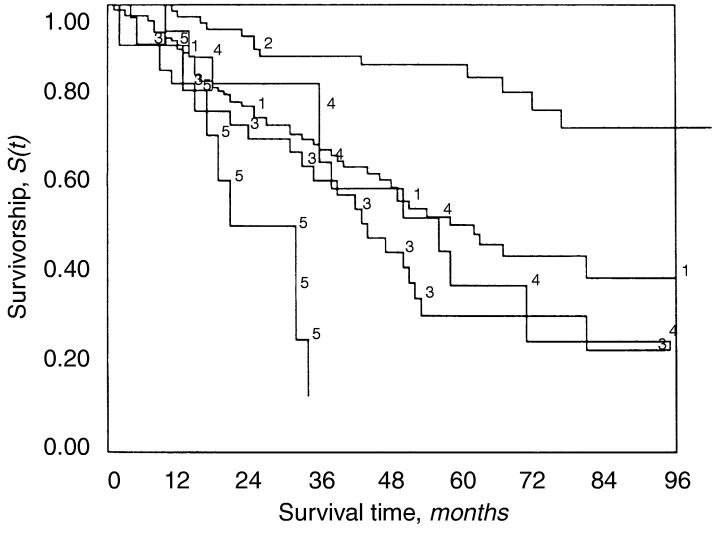

Fig. 2. Actuarial survival of patients according to the treatment modality (Group 1 is PD; Group 2 is transplant; Groups 3 to 5 are on hemodialysis at the time of death or censor (January 1998). Survival in Group 2 was better than for all other groups, $P < 0.001$ (Log-rank test). Survival for patients remaining on PD was also favorable when compared to all forms of technical failure: Group 3 (multiple peritonitis), $P < 0.05$; Group 4 (ultrafiltration failure), $P = 0.32$ and Group 5 (failure to thrive or manage), $P < 0.007$.

infection history. These data suggest that other factors, such as continuous exposure to unphysiological solutions and/or possible genetic predisposition, may be important in its etiology.

Longevity of treatment is also thought to be a risk factor, but it can occur early in treatment, and cases are so sporadic that none of the cohort studies reviewed here is able to define this problem more clearly [27, 28].

In our own patient cohort, two cases have occurred in which severe staphylococcal infections were the apparent precipitating factor.

Ultrafiltration failure, although not always clearly differentiated from solute clearance, appears to be the next most important treatment-related cause for drop-out. Definitions of ultrafiltration vary, and usually combine clinical features such as an inability to maintain dry weight without excessive utilization of hypertonic glucose solutions, with a membrane function definition as established by PET or the equivalent, often related to high solute transport [17, 28, 29]. There is increasing evidence that ultrafiltration failure increases with time on PD [20, 30], such that it becomes the predominant cause of technique failure in long-term patients [16].

We were interested to see how the type of technique failure related to patient survival. When actuarial survival curves are plotted according to treatment modality at death or censor (Fig. 2), it can be seen that survival in the transplanted patients was 84% at five years, which is significantly better ($P < 0.001$) than the survival of those on PD (50% at five years) and all other causes of technical failure. Five-year actuarial survival for patients who switched therapies were less good (32% for peritonitis, $P = 0.005$; 38% for ultrafiltration failure, $P = 0.3$) when compared to those who remained on PD. The group that fared worst, despite a treatment switch, were those who failed to thrive or cope with PD ($P < 0.002$ compared to all other groups). It would appear, therefore, that if PD is stopped for multiple peritonitis or failure to thrive, this is a marker

Table 6. Cox proportional hazard models predicting patient death and technical failure by Kt/V, plasma albumin and peritoneal solute transport

Treatment variable	Prediction of patient death		Prediction of technical failure		Risk comparitor
	Relative risk (95% CI)	*P* value	Relative risk (95% CI)	*P* value	
Total weekly Kt/V_{urea}	0.48 (0.28–0.86)	0.016	0.86 (0.44–1.67)	0.65	Decrease per weekly unit
Plasma albumin	0.95 (0.9–1.02)	0.057	1.07 (0.97–1.18)	0.13	Decrease per g/liter
Solute transport (D/P_{Cr} at 4 hr)	1.49 (1.04–2.12)	0.025	1.54 (1.06–2.24)	0.02	Increase per 0.1 unit in D/P ratio

for poor survival despite the treatment transfer. Prevention of treatment drop-out, with the exception of transplantation, must remain a continuing goal for the future.

Prediction of patient survival and technical failure

All of the studies under review agree that age and comorbid disease are important determinants of long-term patient survival on PD. Shorter-term cohort studies, most notably the CANUSA study, have identified a number of additional risk factors that predict poor clinical outcome in PD patients [5, 9]. More recently, we have extended these observations to patients remaining up to five years on treatment, confirming the importance of residual renal function as the most important treatment related factor [7]. We also found high peritoneal solute transport to predict death independently on multivariate analysis. Similar findings have been reported from Sweden [31] and continuing analysis of the CANUSA study data has shown that in the short-term, high solute transport predicts technique failure [32]. In view of this relationship to technique failure, we have repeated this analysis on the Stoke cohort for the purposes of this review. Using multiple Cox regression (Table 6), patient survival is predicted by Kt/V (residual renal function being responsible for the inter-patient variability), plasma albumin and solute transport characteristics measured six months into treatment. In contrast, technique failure (excluding deaths on PD) was predicted by high solute transport alone. It therefore appears that high peritoneal solute transport characteristics early in the course of treatment predict both reduced patient survival and technical failure in patients observed for up to seven years.

Longitudinal changes in clinical parameters

In general, studies that have performed detailed longitudinal analyses of clinical parameters such as solute clearance, nutrition and peritoneal function tend to be smaller with respect to patient numbers, and frequently describe selected sub-groups of patients [9, 11, 12, 33, 34]. One of the strengths of the Stoke Study is that this detail exists for an unselected population of sufficient size and length of follow-up to allow us to begin to answer the question: what really happens to these patients?

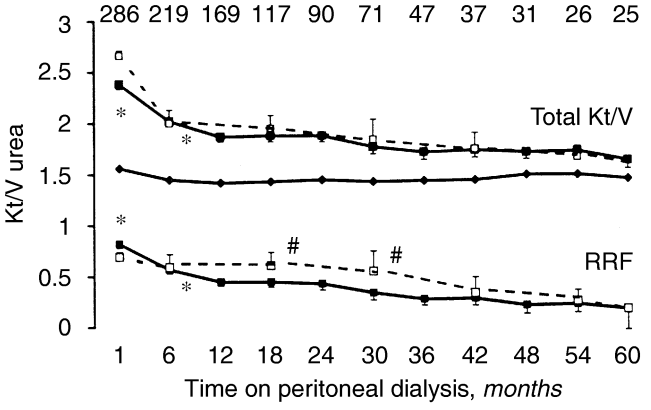

Fig. 3. The longitudinal changes in urea clearance are shown for the whole population (solid lines) and for the subgroup of long-term survivors on PD, $N = 25$, (dashed lines). Data are mean ± SE. The initial clearances are significantly greater ($^*P < 0.02$) compared to later measurements, due to the decline in residual renal function. In the medium term residual renal function is relatively well maintained in the long-term patients, ($^{\#}P < 0.05$). Net PD clearances are also shown (diamonds) for the whole population.

Solute clearance

One of the principle achievements of CANUSA was to draw attention to the considerable consequences of loss in residual renal function in PD patients, in particular its effect on solute clearance [5]. Other studies have indicated the value of prolonged residual renal function in long-term PD patients to their survival [9, 33, 34]. One of the positive features of peritoneal dialysis as a treatment modality is that it tends to permit RRF to persist [35], and this is particularly the case for the long-term group in the Stoke patients, a proportion of whom (25%) still had some function at five years. The longitudinal changes in total urea clearance (Kt/V_{urea}) and residual renal function (RRF) are shown in Figure 3, along with the actual number of data points collected at each time point. Data are shown both for the whole population regardless of final treatment outcome, and for a subpopulation of long-term survivors on PD ($N = 25$). It can be seen that the loss in RRF is entirely responsible for the drop in total Kt/V_{urea}, with an early exponential phase during the first 18 months, a time when most patients are experiencing a graded loss in their renal function. This is followed by a more prolonged linear phase

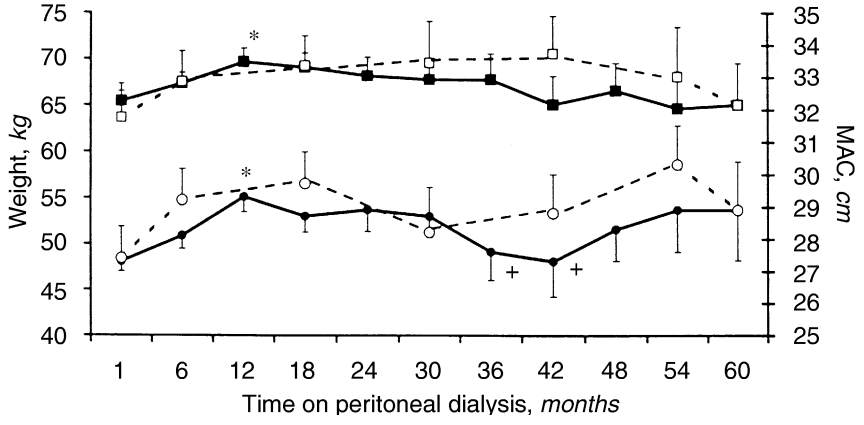

Fig. 4. Data for the whole population and long-term subgroup are shown as for Figure 3. Data are mean ± SE. Weight measurements are shown as square symbols and mid-arm circumference (MAC) as circles. There is a significant rise in weight and MAC during the first year of treatment ($^*P < 0.02$), following which both decline, although this is only significant for MAC ($^+P < 0.05$). Both weight and MAC are relatively well maintained in the long-term group, which is responsible for the late relative improvement in MAC.

Table 7. Longitudinal changes in clinical parameters during the first five years of peritoneal dialysis

Clinical variable	Months on peritoneal dialysis										
	1	6	12	18	24	30	36	42	48	54	60
Number	286	219	169	117	90	71	47	37	31	26	25
PNA *g/day*	80.9 ± 1.6	78.8 ± 1.6	76.1 ± 1.8	75.2 ± 2.0	73.5 ± 2.2[a]	74.5 ± 3.0[a]	68.3 ± 3.0[b]	68.6 ± 3.4[b]	72.1 ± 4.0[b]	66.6 ± 3.3[b]	67.4 ± 4.0[b]
DPI *g/day*	69 ± 2.4	69.6 ± 2.1	65.9 ± 2.5	66 ± 2.8	62.5 ± 2.5	69 ± 3.4	64.5 ± 4.7	68 ± 5.9	66.4 ± 3.8	60.4 ± 5.2[a]	50.2 ± 11.4[a]
DCI *cal/day*	1701 ± 51	1699 ± 54	1642 ± 58	1648 ± 56	1509 ± 56	1531 ± 65[a]	1656 ± 97[a]	1773 ± 137	1628 ± 97	1771 ± 90	1473 ± 112
UF vol. *ml*	441 ± 15	444 ± 17	461 ± 44	395 ± 20	395 ± 28	425 ± 25	360 ± 37[a]	391 ± 37[a]	454 ± 51	405 ± 39	367 ± 53[a]
Triglycerides *mmol/liter*	2.06 ± 0.08	2.43 ± 0.15	2.85 ± 0.24[a]	2.62 ± 0.18[a]	2.82 ± 0.27[b]	3.1 ± 0.46[b]	2.7 ± 0.38[a]	2.51 ± 0.24[a]	2.37 ± 0.28[a]	2.25 ± 0.38	2.33 ± 0.37

Abbreviations are: PNA, protein nitrogen appearance; DPI, dietary protein intake; DCI, dietary caloric intake; UF vol, ultrafiltration volume obtained from net drainage on Peritoneal Equilibration Test.

[a] Different to baseline, $P < 0.05$

[b] Different to baseline, $P < 0.02$

beyond two years that is still apparent at five years. The use of mean values to represent RRF in this latter phase is somewhat misleading, as the majority of patients are then anuric, so that the continued decline is confined to a small proportion only. It can be seen that RRF is relatively well preserved in the long-term survivors.

Nutritional status

The longitudinal evolution of the nutritional parameters over five years observed in the Stoke Study again support and extend those made by CANUSA [36]. Changes in weight and MAC are shown in Figure 4. During the first 12 months of treatment there was an increase both in weight and MAC, implying increase in dry weight, both for the whole population, and for those remaining on PD for five years. After 18 months there was a steady decline in weight that was delayed in the long-term group, although this was not statistically significant. The parallel drop in MAC was significant, however, suggesting that these patients were losing proportionately more dry body weight, and by implication may be becoming relatively fluid loaded. Again, the long-term survivors appeared to maintain dry weight better, and this was responsible for the apparent rise in MAC beyond four years.

The longitudinal changes in PNA, DPI and DCI are shown in Table 7. These parameters all show a similar trend, suggesting that the highest protein and calorie intake occurs at the beginning of time on PD, prior to the weight gain, followed by a decline. The fall in PNA is very gradual, and although there may be some mathematical coupling with the Kt/V_{urea}, the drop is linear rather than exponential. DPI is much more variable between individuals, but even this shows a significant decline by five years. DCI is also variable, but there is a significant fall by two to two years, after which the numbers become too small to demonstrate further change. The changes in plasma triglycerides with time in PD are shown in Table 7. There is an increase during the first twelve months of treatment, after which they remain stable, with a non-significant trend to reducing after 42 months. These changes reflect those in the weight and MAC.

There is therefore a very significant early improvement in nutrition, with evidence of good dietary intake, increase in dry body wt and plasma triglycerides. These observations were also found in the selected population of long-term PD patients reported by Faller and Lameire [11, 34], who, like the long-term subpopulation in the present analysis, had a relatively well maintained nutrition for several years. The evidence, however, that poor nutrition remains or becomes an increasing problem for the majority of patients is very

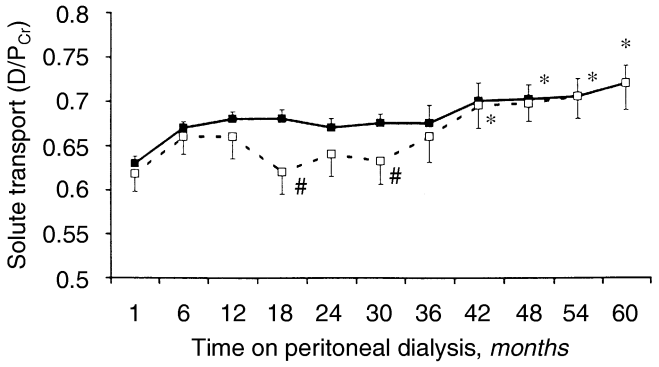

Fig. 5. Data for the whole population and long-term subgroup are shown as for Figure 3. Solute transport increases with time on PD ($^{*}P < 0.05$, compared with 6 months duration). The long-term subgroup has a significantly lower solute transport in the medium term ($^{\#}P < 0.05$).

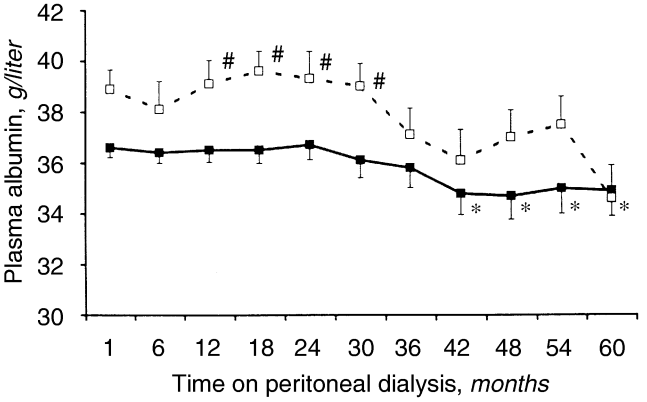

Fig. 6. Data for the entire population and long-term subgroup are shown as for Figure 3. There is a downward trend in the plasma albumin with time, which reaches significance beyond 42 months ($^{*}P < 0.05$). Plasma albumin is relatively well preserved in the long-term group, as it is significantly higher between 13 and 30 months of treatment ($^{\#}P < 0.05$).

strong. Loss of dry body wt begins to occur after two years; there is a downward trend in protein nitrogen appearance and estimates of dietary intake, and this is despite a steady loss of patients who die in a debilitated state. It is not simply due to a progressive loss of well-nourished patients to transplantation, as these patients tend to be younger and less overweight than their counterparts.

Peritoneal membrane function

There is now increasing evidence from cross sectional studies, selected and unselected longitudinal cohort studies that peritoneal solute transport increases with time on PD, at least for a proportion of patients [7, 12, 20, 23, 37]. Longitudinal changes in peritoneal solute transport (Fig. 5) demonstrate that for the whole group, after an initial early increase in D/P$_{Cr}$, the membrane function would appear to be stable for up to three years, after which there is a significant increase in transport associated with a reduction in the peritoneal ultrafiltration capacity (Tables 6 and 7). The membrane function in the long-term PD group is different, in that solute transport rates are significantly lower between 18 and 30 months of treatment, before the subsequent rise.

The period of peritoneal membrane stability between 12 and 42 months may be more apparent than real. As discussed above, high solute transport early in treatment is associated with increased treatment dropout due to death and technical failure. There is, therefore, a systematic loss of patients with high solute transport occurring throughout this period. Added to this is the fact that patients with prolonged survival on PD had lower transport rates during this time period, perhaps contributing to better fluid balance at this stage of treatment, which will further distort the apparent mean values for the whole group. Indirect evidence that low solute transport in long-term survivors may be protective is the relatively well maintained plasma albumin is these patients during the same time interval (Fig. 6). It is equally tempting to speculate that solute transport was relatively stable in this group of patients due to their persisting RRF, resulting in a lesser requirement for hypertonic glucose exchanges. Finally, long-term survival appears to be associated with peritoneal solute transport stability, typically with a D/P$_{Cr}$ ratio in the region of 0.68 at four hours [7, 12, 14].

The gradual decline in plasma albumin (Fig. 6) with time on PD is clearly a matter for concern. Low plasma albumin has been repeatedly linked to poor clinical outcome [5, 6, 21, 38], and predicts worsening cardiovascular morbidity [39]. While it reflects a combination of poor prognostic features, namely comorbidity [6, 18, 33], high solute transport (due to both increased protein clearances and impaired ultrafiltration) and poor nutritional status, which of these is the predominant cause for the decline in plasma concentrations cannot be determined with certainty from this study. There is certainly circumstantial evidence that PD patients become progressively fluid loaded with time on PD [40–42], supported here by the fall in MAC being more pronounced than the drop in actual body weight. This is in keeping with the view that because salt and water removal are directly proportional to net ultrafiltration [43], that peritoneal membrane function becomes critically important to fluid balance once RRF has gone.

CONCLUSION

This review has attempted to describe in as much detail as possible what actually happens to patients treated with peritoneal dialysis over a period of several years. It must be borne in mind that all the studies referred to here belong to a period in the development of the treatment modality in which few, if any, specific measures were taken to take account for the loss in residual renal function. Consequently, all these patients were progressively disadvantaged in terms of their small solute clearances, and potentially their salt and water removal as well.

In summarizing what actually happens to patients treated for several years on PD it is possible to produce a synthesis from the studies discussed. Those who do well have less comorbid disease, have maintained residual renal function, and proceed to transplantation. Those who die usually suffer either a sudden cardiac death or a slower debilitation period to their eventual death, and it is easy to see how progressive malnutrition, under-dialysis, and poor salt and water handling will contribute to these outcomes. Evidence for an important role for peritoneal membrane function is also increasingly compelling. High solute transport predicts death and technical failure, and increases with time on treatment. Once the patient is anuric, as is the case for the vast majority of long-term PD patients, high membrane solute transport will influence ultrafiltration and thus salt and water balance. It must be hoped that with strategies designed to preserve and optimize peritoneal membrane function, the future for long-term peritoneal dialysis can be assured.

ACKNOWLEDGMENTS

We gratefully acknowledge the financial support of the Renal Division of Baxter UK. We are very grateful to all those who have made this study possible. These include Rod Hunt (Computer Software), Professor Peter Jones (Statistics), Gill Savage (Nurse and Unit Manager), Janet Bryan who co-ordinated data collection between 1991 and 1993, and in particular Sister Val Rowley and her primary PD Nursing Team. We also express our gratitude to all the patients involved, who have willingly given of their time.

Reprint requests to Dr. S.J. Davies, Department of Nephrology, North Staffordshire Hospitals Trust, Princes Road, Hartshill, Stoke-on-Trent, ST4 7LN England, United Kingdom.
SimonDavies1@compuserve.com

REFERENCES

1. Maiorca R, Cancarini GC, Camerini C, Brunori G, Manili L, Movilli E, Feller P, Mombelloni S: Is CAPD competitive with haemodialysis for long-term treatment of uraemic patients? *Nephrol Dial Transplant* 4:244–253, 1989
2. Maiorca R, Vonesh E, Cavalli PL, De Vecchi A, Giangrande A, La Greca G, Scarpione LL, Bragantini L, Cancarini GC, Cantaluppi A, Castelnovo C, Castiglioni A, Poisetti P, Viglino G: A multi-centre, selection adjusted comparison of patient and technique survivals on CAPD and hemodialysis. *Perit Dial Int* 11:118–127, 1991
3. Fenton SSA, Schaubel DE, Desmeules M, Morrison HI, Mao Y, Copleston P, Jeffrey JR, Kjellstrand CM: Hemodialysis versus peritoneal dialysis: A comparison of adjusted mortality rates. *Am J Kidney Dis* 30:334–342, 1997
4. Gotch F, Sargent JA: A mechanistic analysis of the National Cooperative Dialysis Study. *Kidney Int* 28:526–534, 1985
5. Churchill DN, Taylor DW, Keshaviah PR: Adequacy of dialysis and nutrition in continuous peritoneal dialysis: Association with clinical outcome. *J Am Soc Nephrol* 7:198–207, 1996
6. Struijk DG, Krediet RT, Koomen GCM, Boeschoten EW, Arisz L: The effect of serum albumin at the start of continuous ambulatory peritoneal dialysis treatment on patient survival. *Perit Dial Int* 14:000–000, 1994
7. Davies SJ, Phillips L, Russell GI: Peritoneal solute transport predicts survival on CAPD independently of residual renal function. *Nephrol Dial Transplant* 13:962–968, 1998
8. Rotellar C, Black J, Winchester JF, Rakowski TA, Mosher WF, Mazzoni MJ, Amiranzavi M, Garagusi V, Alijani MR, Argy WP: Ten years experience with continuous ambulatory peritoneal dialysis. *Am J Kidney Dis* 17:158–164, 1991
9. Selgas R, Bajo MA, Fernandez-Reyes MJ, Bosque E, Lopez-Revuelta K, Jimenez C, Borrego F, De Alvaro F: An analysis of adequacy of dialysis in a selected population on CAPD over three years: The influence of urea and creatinine kinetics. *Nephrol Dial Transplant* 8:1244–1253, 1993
10. Lupo A, Tarchini R, Cancarini GC, Catizone L, Cocchi R, De Vecchi A, Viglino G, Salomone M, Segoloni G, Giangrande A: Long-term outcome in continuous ambulatory peritoneal dialysis: A 10-year survey by the Italian Cooperative Peritoneal Dialysis Study Group. *Am J Kidney Dis* 24:826–837, 1994
11. Faller B, Lamiere NH: Evolution of clinical parameters and peritoneal function in a cohort of CAPD patients followed over 7 years. *Nephrol Dial Transplant* 9:280–286, 1994
12. Selgas R, Fernandez-Reyes MJ, Bosque E, Bajo MA, Borrego F, Jimenez C, Del Peso G, De Alvaro F: Functional longevity of the human peritoneum: How long is continuous peritoneal dialysis possible? Results of a prospective medium long-term study. *Am J Kidney Dis* 23:64–73, 1994
13. Maiorca R, Cancarini GC, Zubani R, Camerini C, Manili L, Brunori G, Movilli E: CAPD viability: A long-term comparison with hemodialysis. *Perit Dial Int* 16:276–287, 1996
14. Diaz-Buxo JA, Shultman DS: Characteristics of long-term peritoneal dialysis patients. *Adv Perit Dial* 13:104–108, 1997
15. Abdel-Rahmen EM, Wakeen M, Zimmerman SW: Characteristics of long-term peritoneal dialysis survivors: 18 years experience in one centre. *Perit Dial Int* 17:151–156, 1997
16. Kawaguchi Y, Hasegawa T, Nakayama M, Kubo H, Shigematsu T: Issues affecting the longevity of the continuous peritoneal dialysis therapy. *Kidney Int* 52(Suppl 62):S105–S107, 1997
17. Davies SJ, Brown B, Bryan J, Russell GI: Clinical evaluation of the peritoneal equilibration test. A population based study. *Nephrol Dial Transplant* 8:64–70, 1993
18. Davies SJ, Russell L, Bryan J, Phillips L, Russell GI: Comorbidity, urea kinetics and appetite in continuous ambulatory peritoneal dialysis: Their interrelationship and prediction of survival. *Am J Kidney Dis* 26:353–361, 1995
19. Davies SJ, Bryan J, Phillips L, Russell GI: The predictive value of KT/V and peritoneal solute transport in CAPD patients is dependent on the type of comorbidity present. *Perit Dial Int* 16:S158–S162, 1996
20. Davies SJ, Bryan J, Phillips L, Russell GI: Longitudinal changes in peritoneal kinetics: The effects of peritoneal dialysis and peritonitis. *Nephrol Dial Transplant* 11:498–506, 1996
21. Avram MM, Mittman N, Bonomini L, Chattopadhyay J, Fein PA: Markers for survival in dialysis: A seven-year prospective study. *Am J Kidney Dis* 26:209–219, 1995
22. Hung KY, Hsu WA, Tsai TJ, Yen CJ, Hou CH, Yen TS: Continuous ambulatory peritoneal dialysis in the elderly: A seven-year experience. *Postgrad Med J* 71:160–163, 1995
23. Struijk DG, Krediet RT, Koomen GC, Hoek FJ, Boeschoten EW, VD Reijden HJ, Arisz L: Functional characteristics of the peritoneal membrane in long-term continuous ambulatory peritoneal dialysis. *Nephron* 59:213–220, 1991
24. Bennett SE, Russell GI, Williams AJ, Wilson JM, Walls J: Accurate assessment of dry weight in haemodialysis and continuous peritoneal dialysis patients. *Proc ENTNA-ERCA* 12:137–140, 1983
25. Twardowski ZJ, Nolph KD, Khanna R, Prowant BF, Ryan LP, Moore HL, Nielsen MP: Peritoneal Equilibration Test. *Perit Dial Bull* 7:138–147, 1987
26. Bergström J, Furst P, Alvestrand A, Lindholm B: Protein and energy intake, nitrogen balance and nitrogen losses in patients treated continuous ambulatory peritoneal dialysis. *Kidney Int* 44:1048–1057, 1993
27. Campbell S, Clarke P, Hawley C, Wigan M, Butler J, Wall D: Sclerosing peritonitis: Identification of diagnostic, clinical, and radiological features. *Am J Kidney Dis* 24:819–825, 1994
28. Krediet RT, Ho-Dac-Pannekeet M, Struijk DG: Preservation of peritoneal membrane function. *Kidney Int* 50(Suppl 56):S62–S68, 1996
29. Ho-Dac-Pannekeet MM, Atasever B, Struijk DG, Krediet RT: Analysis of ultrafiltration failure in peritoneal dialysis patients by means of standard peritoneal permeability analysis. *Perit Dial Int* 17:144–150, 1997
30. Heimburger O, Waniewski J, Werynski A, Tranaeus A, Lindholm B: Peritoneal transport in CAPD patients with permanent loss of ultrafiltration capacity. *Kidney Int* 38:495–506, 1990

31. Wang T, Heimburger O, Waniewski J, Bergström J, Lindholm B: Increased peritoneal permeability is associated with decreased fluid and small-solute removal and higher mortality in CAPD patients. *Nephrol Dial Transplant* 13:1242–1249, 1998
32. Churchill DN, Thorpe KE, Nolph KD, Keshaviah PR, Oreopoulos DG, Page D: Increased peritoneal membrane transport is associated with decreased patient and technique survival for continuous peritoneal dialysis patients. *J Am Soc Nephrol* 9:1285–1292, 1998
33. De Alvaro F, Bajo MA, Alvarez-Ude F, Vigil A, Molina A, Coronel F, Selgas R: Adequacy of peritoneal dialysis: Does KT/V have the same predictive value as in HD? A multicenter study. *Adv Perit Dial* 8:93–97, 1992
34. Lamiere NH, Vanholder R, Veyt D, Lambert M, Ringoir S: A longitudinal, five year survey of urea kinetic parameters in CAPD patients. *Kidney Int* 42:426–432, 1992
35. Lysaght MJ, Vonesh EF, Gotch F, Ibels L, Keen M, Lindholm B, Nolph KD, Pollock CA, Prowant B, Farrell PC: The influence of dialysis treatment modality on the decline of remaining renal function. *ASAIO J* 37:598–604, 1991
36. McCusker FX, Teehan BP, Thorpe KE, Keshaviah PR, Churchill DN: How much peritoneal dialysis is required for the maintenance of a good nutritional state? *Kidney Int* 50(Suppl 56):S56–S61, 1996
37. Struijk DG, Krediet RT, Koomen GCM, Boeschoten EW, Hoek FJ, Arisz L: A prospective study of perioneal transport in CAPD patients. *Kidney Int* 45:1739–1744, 1994
38. Blake PG, Flowerdew G, Blake RM, Oreopoulos DG: Serum albumin in patients on continuous ambulatory peritoneal dialysis—Predictors and correlations with outcomes. *J Am Soc Nephrol* 3:1501–1507, 1993
39. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE: Hypoalbuminaemia, cardiac morbidity, and mortality in end-stage renal disease. *J Am Soc Nephrol* 7:728–736, 1996
40. Amann K, Mandelbaum A, Schwarz U, Ritz E: Hypertension and left ventricular hypertrophy in the CAPD patient. *Kidney Int* 50(Suppl 56):S37–S40, 1996
41. Tzamaloukas AH, Saddler HC, Murata GH, Malhotra D, Sena P, Simon D, Hawkins KL, Morgan K, Nevarez M, Wood B, Elledge L, Gibel LJ: Symptomatic fluid retention in patients on continuous peritoneal dialysis. *J Am Soc Nephrol* 6:198–206, 1995
42. Saldanha LF, Weiler E, Gonick HC: Effect of continuous ambulatory peritoneal dialysis on blood pressure control. *Am J Kidney Dis* 21:184–188, 1993
43. Wang T, Waniewski J, Heimburger O, Werynski A, Lindholm B: A quantitative analysis of sodium transport and removal during peritoneal dialysis. *Kidney Int* 52:1609–1616, 1997