PREDICTORS OF PERITONITIS AND THE IMPACT OF PERITONITIS ON CLINICAL OUTCOMES OF CONTINUOUS AMBULATORY PERITONEAL DIALYSIS PATIENTS IN TAIWAN—10 YEARS' EXPERIENCE IN A SINGLE CENTER

Yao-Peng Hsieh,^{1,2} Chia-Chu Chang,¹ Yao-Ko Wen,¹ Ping-Fang Chiu,¹ and Yu Yang^{1,3}

Division of Nephrology,¹ Department of Internal Medicine, Changhua Christian Hospital, Changhua; Kaohsiung Medical University,² Kaohsiung; and School of Medicine,³ Chung Shan Medical University, Taichung, Taiwan

◆ **Objective:** Peritoneal dialysis (PD) has become more prevalent as a treatment modality for end-stage renal disease, and peritonitis remains one of its most devastating complications. The aim of the present investigation was to examine the frequency and predictors of peritonitis and the impact of peritonitis on clinical outcomes.

◆ **Methods:** Our retrospective observational cohort study enrolled 391 patients who had been treated with continuous ambulatory PD (CAPD) for at least 90 days. Relevant demographic, biochemical, and clinical data were collected for an analysis of CAPD-associated peritonitis, technique failure, drop-out from PD, and patient mortality.

◆ **Results:** The peritonitis rate was 0.196 episodes per patient-year. Older age (>65 years) was the only identified risk factor associated with peritonitis. A multivariate Cox regression model demonstrated that technique failure occurred more often in patients experiencing peritonitis than in those free of peritonitis ($p < 0.001$). Kaplan–Meier analysis revealed that the group experiencing peritonitis tended to survive longer than the group that was peritonitis-free ($p = 0.11$). After multivariate adjustment, the survival advantage reached significance (hazard ratio: 0.64; 95% confidence interval: 0.46 to 0.89; $p = 0.006$). Compared with the peritonitis-free group, the group experiencing peritonitis also had more drop-out from PD ($p = 0.03$).

◆ **Conclusions:** The peritonitis rate was relatively low in the present investigation. Elderly patients were at higher risk of peritonitis episodes. Peritonitis independently predicted technique failure, in agreement with other reports. However, contrary to previous studies, all-cause mortality was better in patients experiencing peritonitis than in those free of peritonitis. The underlying mechanisms of this presumptive “peritonitis paradox” remain to be clarified.

KEY WORDS: Continuous ambulatory peritoneal dialysis; CAPD; microbiology; patient survival; peritonitis; technique failure.

Continuous ambulatory peritoneal dialysis (CAPD) was first described as a renal replacement therapy in the late 1970s (1), but whether peritoneal dialysis (PD) is superior to hemodialysis (HD) in terms of patient survival is still controversial. A recent review reported that, although patient survival is similar for PD and HD, a difference is seen for elderly or diabetic patients (2).

Despite a series of technological innovations and improvements in PD connectology since the early 1990s, peritonitis continues to be a devastating complication for patients undergoing PD. Peritonitis is often caused by periluminal or intraluminal contamination with skin bacteria. It can also result from the trans-visceral or hematogenous spread of micro-organisms. The incidence of peritonitis varies from center to center, and significant differences in rates are seen in different countries. The most common microbial causes of PD-associated peritonitis are gram-positive organisms, mainly coagulase-negative staphylococci (3,4). Several predictors of peritonitis have been reported in the literature, but studies in Taiwanese CAPD patients are scarce.

Peritonitis damages the peritoneal membrane, interfering with ultrafiltration and dialysis capacity (5). Peritonitis thus remains the leading cause of technique failure for patients on PD in spite of declines in peritonitis rates, development of new PD techniques, and identification of risk factors with subsequent implementation of strategies to prevent infection. Peritonitis also contributes to patient mortality.

In the present study, we retrospectively reviewed incident CAPD patients for a period of 10 years in a single medical center in Taiwan. The primary objective of the study was to identify factors associated with CAPD

Perit Dial Int 2014; 34(1):85–94 www.PDIConnect.com
ePub ahead of print: 01 Oct 2013 doi:10.3747/pdi.2012.00075

Correspondence to: Y. Yang, Division of Nephrology, Internal Medicine, Changhua Christian Hospital, 135 Nanxiao Street, Changhua City 500 Taiwan.

2219@cch.org.tw

Received 3 April 2012; accepted 13 January 2013

peritonitis. Secondary objectives were to investigate factors affecting mortality and technique failure, and to determine whether the occurrence of peritonitis had detrimental effect on technique and patient survival.

METHODS

Our study included all patients who received PD in Changhua Christian Hospital in Taiwan between 1 January 2001 and 31 December 2010. All patients received a double-cuff Tenckhoff catheter inserted by the standard surgical technique, with prophylactic antimicrobial cefazolin being administered in all cases. A CAPD disconnect system (Baxter Healthcare Corporation, Deerfield, IL, USA, or Fresenius Medical Care, Bad Homburg, Germany) was used in all patients.

In Taiwan's health care system, choice of the modality of renal replacement therapy is based on the treating nephrologist's recommendation and patient preference. The final decision is individualized depending on a combination of unit facilities and practice, and patient factors. Topical antibiotics were not used for prophylaxis of exit-site infection, and exit-site care was performed daily. Patients were followed till death, transfer to HD, renal transplantation, or the end of the study (31 December 2010), at which time data were censored.

The data collected included demographics, smoking status, education status, cause of end-stage renal disease, relevant biochemical data, comorbid conditions at the start of dialysis therapy [coronary artery disease (CAD), cerebrovascular disease (CVD), peripheral vascular disease (PVD), diabetes mellitus (DM), and hypertension], original modality before CAPD, relevant PD-related parameters, and microbiologic characteristics of peritonitis episodes.

CLINICAL OUTCOMES

The outcomes examined in this study were the first peritonitis episode, all-cause mortality, and technique failure and drop-out from CAPD. Patient survival was defined as the probability of patients surviving on PD, with only death considered to be an endpoint event; other reasons for drop-out, such as transfer to HD, transplantation, or renal function recovery, were censored observations. Technique failure was defined as permanent transfer to HD because of inadequate dialysis, peritonitis, ultrafiltration failure, exit-site or tunnel infection, and mechanical or operational problems; transplantation, death, and recovery of renal function were censored observations. In the "stay on

PD" analysis (composite endpoint of patient survival and technique survival), the pertinent events were a switch to HD or death on PD; transplantation was a censored observation.

STATISTICAL ANALYSIS

Categorical variables are expressed as numbers and percentages, and continuous variables, as mean $\pm$ standard deviation. Differences between groups of patients were analyzed using a chi-square or Fisher exact test for categorical data and the Student t-test for continuous data. The univariate Cox proportional hazards model analysis of predictors of a first peritonitis episode used a selection of baseline demographics, biochemical and PD-related data, exit-site infection, duration on CAPD, original modality before CAPD, and comorbidities at the start of CAPD. Significant variables from the univariate analysis were incorporated into a multivariate model to determine independent factors associated with a first peritonitis episode. The Kaplan-Meier method and log-rank statistics were used to compare clinical outcomes between patient groups based on the presence or absence of peritonitis. The average values of the study parameters—including hemoglobin level, biochemical data, PD-related data, and accumulated comorbidities (cardiovascular disease, chronic lung disease, liver cirrhosis, cancer, and dementia), which were updated during the follow-up period—were used for a Cox regression analysis of clinical outcomes. A two-tailed *p* value less than 0.05 was considered statistically significant. All statistical analyses were conducted using the SAS statistical software package (version 8.2: SAS institute, Cary, NC, USA).

RESULTS

POPULATION CHARACTERISTICS

The study enrolled 391 incident CAPD patients with mean age of 55.8 ± 16 years (44.2% men), who were studied over a total observation period of 969.5 patient-years. The mean follow-up period was 35.5 ± 27.6 months. At the end of the observation period, 178 patients (45.5%) were still on CAPD, 85 (21.7%) had died, 92 (23.5%) had been switched to HD, 29 (7.4%) had received a renal graft, and 7 (1.8%) had recovered renal function. Table 1 shows baseline patient characteristics at the commencement of CAPD.

Glomerulonephritis accounted for 30.4% of primary renal disease, followed by diabetic nephropathy (28.6%) and hypertensive nephrosclerosis (14.6%). No difference

TABLE 1
Demographic, Clinical, and Biochemical Data at Baseline and Outcomes on Follow-Up^a

Variable	Overall	Patient group Peritonitis-free	Experienced peritonitis	<i>p</i> Value ^b
Patients	391	267	124	—
Sex (men)	173 (44.2)	122 (45.7)	51 (41.1)	0.39
Mean age (years)	55.8±16.0	55.3±16.2	56.9±15.5	0.35
Education level ^c				0.13
Body mass index (kg/m ²)	23.1±3.9	23.0±3.7	23.4±4.1	0.31
Icodextrin use	118 (30.3)	77 (29.1)	41 (33.1)	0.42
Duration on CAPD (months)	3.0±2.3	2.6±2.2	3.8±2.3	<0.001
Daily exchanges	4.0±0.5	4.0±0.5	4.1±0.5	0.13
ESI/100 pt-yrs	30.6±67.1	30.2±72.0	31.4±56.2	0.88
Secondary peritonitis/100 pt-yrs	0.7±6.3	0.7±6.4	0.8±5.9	0.82
Smoking status				0.25
Never	318 (81.3)	215 (80.5)	103 (83.1)	
Former	70 (17.9)	51 (19.1)	19 (15.3)	
Current	3 (0.8)	1 (0.4)	2 (1.6)	
Modality before CAPD				0.38
Pre-dialysis	385 (98.5)	261 (97.8)	124 (100.0)	
Hemodialysis	2 (0.51)	2 (0.8)	0 (0)	
Failed transplant	4 (1.02)	4 (1.5)	0 (0)	
Diabetes mellitus	128 (32.7)	90 (33.7)	38 (30.7)	0.55
Hypertension	319 (81.6)	212 (79.4)	107 (86.3)	0.10
Cardiovascular disease ^d	86 (22.0)	60 (22.5)	26 (21.0)	0.74
Coronary artery disease	64 (16.4)	44 (16.5)	20 (16.1)	0.93
Cerebrovascular disease	35 (9.0)	26 (9.7)	9 (7.3)	0.42
Peripheral artery disease	7 (1.8)	3 (1.1)	4 (3.3)	0.21
Serum albumin (g/dL)	3.5±0.7	3.5±0.7	3.5±0.7	0.86
Hemoglobin (g/dL)	8.0±1.7	8.1±1.7	7.9±1.5	0.20
HbA1C (%)	6.2±1.6	6.2±1.6	6.2±1.6	0.97
Calcium (mg/dL)	7.8±1.2	7.8±1.2	7.7±1.1	0.35
Phosphorus (mg/dL)	6.8±2.3	6.7±2.3	6.9±2.4	0.39
BUN (mg/dL)	114.6±43.9	113.4±44.9	117.2±41.9	0.45
Creatinine (mg/dL)	12.1±5.4	11.9±5.4	12.5±5.2	0.24
Baseline PET and PD adequacy				
Kt/V urea				
Peritoneal	1.6±0.4	1.6±0.4	1.6±0.4	0.15
Renal	0.7±0.5	0.7±0.5	0.6±0.4	0.04
Total	2.3±1.3	2.3±0.6	2.5±2.2	0.26
Creatinine clearance (L/week)				
Peritoneal	41.0±11.6	40.9±12.6	41.2±9.0	0.84
Renal	35.4±28.0	37.1±29.7	31.5±23.5	0.11
Standardized total	81.3±28.6	83.1±30.0	77.0±24.7	0.09
Residual GFR (mL/min/1.73 m ²)	3.0±2.2	3.1±2.4	2.6±1.9	0.07
Daily nPNA (g/kg)	1.0±0.3	1.0±0.3	1.1±0.3	0.24
D/P creatinine at 4 hours				0.20
High	34 (11.3)	28 (13.4)	6 (6.5)	
High average	147 (48.8)	96 (45.9)	51 (55.4)	
Low	11 (3.7)	9 (4.3)	2 (2.2)	
Low average	109 (36.2)	76 (36.4)	33 (35.9)	
Follow-up outcome				
Continuing PD	178 (45.5)	139 (52.1)	39 (31.5)	<0.001

TABLE 1 (cont'd)

Variable	Patient group			<i>p</i> Value ^b
	Overall	Peritonitis-free	Experienced peritonitis	
Follow-up outcome (cont'd)				
Death	85 (21.7)	58 (21.7)	27 (21.8)	0.99
Switch to hemodialysis	92 (23.5)	39 (14.6)	53 (42.7)	<0.001
Renal transplantation	29 (7.4)	24 (9.0)	5 (4.0)	0.08
Renal function recovery	7 (1.8)	7 (2.6)	0 (0.0)	—

CAPD = continuous ambulatory peritoneal dialysis; ESI = exit-site infection; pt-yrs = patient-years; BUN = blood urea nitrogen; PET = peritoneal equilibration test; PD = peritoneal dialysis; GFR = glomerular filtration rate (estimated by the average of renal BUN and creatinine clearance); nPNA = normalized protein equivalent of total nitrogen appearance; D/P = dialysate-to-plasma ratio.

^a Values are expressed as mean $\pm$ standard deviation, or number (percentage).

^b Peritonitis versus peritonitis-free. Boldface type highlights significant differences.

^c Stratified as illiteracy, junior high school, senior high school, or more than college.

^d Defined as the presence of coronary artery disease, cerebrovascular disease, or peripheral artery disease.

was found between the patient groups with respect to sex, age, education status, body mass index, icodextrin prescription, DM, hypertension, cardiovascular disease, serum albumin, hemoglobin, HbA1C, calcium, phosphorus, blood urea nitrogen, and creatinine. Cardiovascular disease was defined as the presence of CAD, CVD, or PVD. In the peritonitis group, 16.1% had CAD, 7.3% had CVD, and 3.3% had PVD; in the peritonitis-free group, 16.5% had CAD, 9.7% had CVD, and 1.1% had PVD. Baseline results for peritoneal equilibration tests and PD adequacy were similar in the groups. Our study subjects typically used 4 – 5 dialysis exchanges daily.

PREDICTORS OF INCIDENT PERITONITIS

Table 2 depicts the univariate Cox regression analysis for predictors of a first peritonitis episode. We observed no significant correlation of the first peritonitis episode with sex, body mass index, icodextrin use, hypertension, exit-site infection, secondary peritonitis (defined as enteric peritonitis caused by underlying pathology of the gastrointestinal tract such as cholecystitis, appendicitis, and ruptured diverticulum), number of exchanges per day, serum albumin, cardiovascular disease, or residual renal function (RRF). On the other hand, age and the presence of DM were associated with the first peritonitis episode and were therefore included in the multivariate Cox proportional hazards model. In the end, age exceeding 65 years was the only independent risk factor associated with a first peritonitis episode (hazard ratio: 2.19; 95% confidence interval: 1.38 to 3.38; $p < 0.001$); DM status lost significance in the multivariate model.

ANNUAL INCIDENCE RATE AND MICROBIOLOGY OF PERITONITIS

Most of our patients ($n = 267$, 68.3%) experienced no peritonitis episodes. The overall peritonitis rate was 0.196 episodes per patient-year over the total observation period of 969.5 patient-years. The 190 episodes of peritonitis that occurred in 124 patients included 49 episodes (25.8%) caused by gram-negative organisms and 78 (41.1%) caused by gram-positive organisms. Overall, 215 organisms were isolated. Gram-positive organisms were the most common isolates (45.1%), with *Streptococcus* species being the most common pathogen (17.7%). Gram-negative organisms constituted 34.4% of the organisms isolated, with *Escherichia coli* being the most common pathogen (16.7%). Fungal organisms constituted 2.3% of isolates. No *Mycobacterium* species was isolated, and 39 episodes of peritonitis remained culture-negative.

INFLUENCE OF PERITONITIS OCCURRENCE ON PATIENT MORTALITY, TECHNIQUE FAILURE, AND DROP-OUT FROM PD

Kaplan–Meier survival analysis and log-rank statistics were used to determine whether peritonitis episodes had a significant impact on the clinical outcomes of interest. Table 3 shows the mean values of the study parameters and accumulated comorbidities during the follow-up period. Those variables were used in the Cox regression model. Significant variables in the univariate Cox regression analysis were included in the multivariate analysis (Table 4).

TABLE 2
Univariate Cox Regression Analysis of
First Peritonitis Episode^a

Variable	HR	95% CI	p Value
Age	1.02	1.00 to 1.03	0.001
Sex (men)	0.92	0.64 to 1.31	0.64
Body mass index	1.04	0.99 to 1.09	0.09
Icodextrin use (ever vs. never)	1.02	0.70 to 1.48	0.92
Exit-site infection	1.03	0.99 to 1.07	0.13
Secondary peritonitis	1.07	0.73 to 1.58	0.73
Daily exchanges	0.74	0.52 to 1.07	0.11
Diabetes mellitus	1.61	1.09 to 2.39	0.02
Hypertension	1.42	0.85 to 2.37	0.18
Cardiovascular disease	1.42	0.92 to 2.20	0.11
Albumin	0.83	0.62 to 1.09	0.18
Hemoglobin	1.01	0.91 to 1.12	0.82
HbA1C	1.04	0.87 to 1.23	0.69
Calcium	1.01	0.87 to 1.16	0.94
Phosphorous	0.95	0.88 to 1.04	0.26
Blood urea nitrogen	1.00	0.99 to 1.01	0.19
Creatinine	0.98	0.95 to 1.01	0.20
Kt/V urea			
Peritoneal	1.11	0.67 to 1.84	0.68
Renal	0.62	0.38 to 1.01	0.06
Total	1.02	0.92 to 1.14	0.68
Creatinine clearance			
Peritoneal	1.00	0.98 to 1.01	0.58
Renal	1.00	0.99 to 1.01	0.34
Standardized total	0.99	0.99 to 1.00	0.15
Residual GFR	0.93	0.83 to 1.04	0.20
nPNA	0.96	0.46 to 1.98	0.91
D/P creatinine at 4 hours (H, HA vs. L, LA)	1.08	0.71 to 1.65	0.71

HR = hazard ratio; CI = confidence interval; GFR = glomerular filtration rate; nPNA = normalized protein equivalent of total nitrogen appearance; H = high; HA = high average; L = low; LA = low average.

^a Significant results are shown in boldface type.

“STAY ON PD” SURVIVAL

The “stay on PD” survival was 56.38 ± 2.65 months for patients free of peritonitis and 56.41 ± 3.44 months for patients experiencing peritonitis. Figure 1 shows the Kaplan–Meier analysis of “stay on PD” survival according to peritonitis status. No significant difference in “stay on PD” survival was observed between the patient groups (log rank $p = 0.30$). In the multivariate Cox proportional hazards model, peritonitis occurrence, icodextrin use, DM status, dementia, and total weekly Kt/V were independent risk factors for drop-out from PD (Table 4).

TECHNIQUE SURVIVAL

Figure 2 illustrates technique survival according to the presence or absence of peritonitis. As expected, the peritonitis-free group had a significantly longer technique survival (74.63 ± 2.64 months vs 68.66 ± 3.99 months for the group experiencing peritonitis, $p = 0.003$). The independent predictors of technique failure by the Cox proportional hazards model for the overall patient cohort were peritonitis occurrence, icodextrin use, and DM. Compared with the peritonitis-free group, the group experiencing peritonitis had a 130% increase in the risk of technique failure (hazard ratio: 2.30; 95% confidence interval: 1.48 to 3.57; $p < 0.0001$; Table 4).

PATIENT SURVIVAL

The Kaplan–Meier analysis of patient survival according to peritonitis status revealed that patients experiencing peritonitis tended to have better survival, but the difference did not reach significance (61.31 ± 2.18 months vs 56.12 ± 1.67 months for the peritonitis-free group, $p = 0.11$, Figure 3). In the multivariate Cox regression model, a 36% reduction in the risk of patient mortality was observed for the group experiencing peritonitis compared with the peritonitis-free group (hazard ratio: 0.64; 95% confidence interval: 0.46 to 0.89; $p = 0.006$). Age, DM, total weekly Kt/V, serum albumin, and creatinine were also independent risk factors for patient mortality (Table 4). In the overall patient cohort, infection (48.2%) was the leading cause of patient mortality, followed by cardiovascular disease (41.2%). The peritonitis-free patients died mostly of cardiovascular disease; infection was the leading cause of mortality in patients experiencing peritonitis.

DISCUSSION

Here, we report the peritonitis data for a single PD unit in Taiwan (Asia), encompassing 969.5 patient-years during an observation period of 10 years.

Predictors of peritonitis risk that have been reported in the literature include African or Aboriginal ethnicity, obesity, diabetes, hypoalbuminemia, transfer from HD to PD, improper bag exchange procedures, insufficient nursing experience, lack of RRF, and a previous peritonitis episode (which can predispose to subsequent episodes) (6–13). The association between age and peritonitis has been inconsistent in various reports. Local application of mupirocin ointment at the catheter exit site can prevent exit-site infection and peritonitis involving gram-positive organisms (14). In the present long-term

TABLE 3
Study Parameters and Accumulated Comorbidities During the Study Period^a

Variable	Patient group			<i>p</i> Value ^b
	Total (<i>n</i> =391)	Peritonitis-free (<i>n</i> =267)	Experienced peritonitis (<i>n</i> =124)	
Diabetes mellitus	148 (37.9)	103 (38.6)	45 (36.3)	0.66
Hypertension	359 (91.8)	244 (91.4)	115 (92.7)	0.65
Cardiovascular disease ^c	170 (43.5)	114 (42.7)	56 (45.2)	0.41
Chronic lung disease	107 (27.4)	61 (22.9)	46 (37.8)	0.003
Liver cirrhosis	10 (2.6)	6 (2.3)	4 (3.2)	0.73
Dementia	15 (3.8)	10 (3.8)	5 (4.0)	0.89
Cancer	35 (9.0)	22 (8.2)	13 (10.5)	0.47
D/P creatinine at 4 hours	0.7±0.1	0.7±0.1	0.7±0.1	0.40
Daily ultrafiltration (L)	0.6±0.5	0.6±0.5	0.7±0.6	0.12
Total weekly Kt/V	1.9±0.4	1.9±0.4	1.9±0.3	0.87
nPNA (g/kg/day)	1.0±0.2	1.0±0.2	1.0±0.2	0.57
Hemoglobin (g/dL)	9.4±1.1	9.5±1.1	9.2±1.0	0.03
Albumin (g/dL)	3.4±0.5	3.4±0.5	3.4±0.4	0.17
Triglycerides (mg/dL)	155.4±94.8	148.4±93.6	169.6±96.0	0.05
Cholesterol (mg/dL)	192.1±40.0	189.8±41.9	196.8±35.7	0.12
High-density lipoprotein	49.2±15.9	50.1±16.8	47.4±13.8	0.14
Low-density lipoprotein	114.1±31.8	111.7±32.9	118.7±29.1	0.05
Blood urea nitrogen (mg/dL)	63.3±16.6	63.4±17.5	63.1±14.5	0.89
Creatinine (mg/dL)	10.2±3.1	10.1±3.2	10.4±2.6	0.29
Uric acid (mg/dL)	6.7±1.1	6.7±1.1	6.7±1.1	0.80
Calcium (mg/dL)	9.0±0.6	9.0±0.6	9.1±0.6	0.08
Phosphate (mEq/L)	4.9±1.1	5.0±1.1	4.8±0.9	0.10
Ca×P	44.1±10.3	44.4±10.7	43.3±9.2	0.32
AST (U/L)	27.0±31.1	27.0±36.3	26.9±16.2	0.99
ALT (U/L)	23.8±19.9	23.2±17.1	25.1±24.8	0.38

D/P = dialysate-to-plasma ratio; nPNA = normalized protein equivalent of total nitrogen appearance; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

^a Values are expressed as mean ± standard deviation, or number (percentage). Significant results are shown in boldface type.

^b Peritonitis versus peritonitis-free.

^c Defined as the presence of coronary artery disease, cerebrovascular disease, or peripheral artery disease.

study of 391 incident CAPD patients, we demonstrated an independent effect of age on the risk of dialysis-related peritonitis. Older age (>65 years) was associated with an increased peritonitis risk.

We observed differences in terms of the peritonitis rate in the current report compared with single-center reports from other countries and regions. In the United States, the peritonitis rate was 0.37 episodes per patient-year between 1998 and 2004, and in Canada, it was 0.43 episodes per patient-year between 1996 and 2005 (4,15). A UK report involving 12 centers identified a CAPD peritonitis rate of 0.82 episodes per patient-year between 2002 and 2003 (16). Reported peritonitis rates also vary widely across countries in Asia. A Korean center reported a peritonitis rate of 0.29 episodes per patient-year

during 2004 and 2005, and the Shanghai Dialysis Registry showed a rate of 0.25 episodes per patient-year in 2006 (17,18). A Japanese study of 561 incident PD patients revealed a peritonitis rate of 0.28 episodes per patient-year from 2005 to 2007 (19). However, an audit of a single Hong Kong center reported a peritonitis rate of 0.68 per patient-year between 1995 and 2003 (3). Compared with worldwide data, we achieved the lowest reported peritonitis rate over 10 years (0.196 episodes per patient-year on average). The different peritonitis rates between Western and Asian countries may be attributable to patient age, concurrent comorbidities, social support for older patients, hygiene technique, and smaller dialysis exchanges because of the lower dialysis volumes used by Chinese patients (20–22).

TABLE 4
Multivariate Cox Regression Analysis for
Clinical Outcomes^a

Model and variable	HR	95% CI	p Value
Dropout from peritoneal dialysis			
Peritonitis episode (yes vs no)	1.47	1.03 to 2.08	0.03
Age	1.00	0.99 to 1.02	0.74
Icodextrin use	0.53	0.35 to 0.79	0.001
Diabetes mellitus	2.60	1.78 to 3.85	<0.0001
Cardiovascular disease	0.95	0.60 to 1.54	0.83
Dementia	2.23	1.11 to 4.51	0.03
Ultrafiltration	0.68	0.47 to 1.00	0.05
Total weekly Kt/V	0.33	0.14 to 0.75	0.01
nPNA	1.09	0.34 to 3.50	0.89
Albumin	0.99	0.56 to 1.78	0.97
Creatinine	0.93	0.84 to 1.03	0.16
Ca×P	0.97	0.95 to 1.00	0.05
Technique failure			
Peritonitis episode (yes vs no)	2.30	1.48 to 3.57	<0.0001
Icodextrin use	0.29	0.17 to 0.50	<0.0001
Diabetes mellitus	1.98	1.24 to 3.16	0.004
Dementia	2.24	0.80 to 6.26	0.12
Patient mortality			
Peritonitis episode (yes vs no)	0.64	0.46 to 0.89	0.006
Age	1.05	1.01 to 1.08	0.01
Diabetes mellitus	2.88	1.53 to 5.41	0.001
Cardiovascular disease	0.90	0.46 to 1.75	0.76
Dementia	1.87	0.78 to 4.45	0.16
Total weekly Kt/V	0.18	0.06 to 0.55	0.003
nPNA	2.12	0.45 to 9.89	0.34
Albumin	0.37	0.16 to 0.86	0.02
Creatinine	0.80	0.68 to 0.93	0.005
Ca×P	0.99	0.95 to 1.05	0.57

HR = hazard ratio; CI = confidence interval; nPNA = normalized protein equivalent of total nitrogen appearance.

^a Variables significantly associated with individual clinical outcomes in univariate Cox regression analysis were incorporated into the multivariate analysis. Significant results are shown in boldface type.

Peritonitis is the most important complication of chronic PD, causing significant morbidity and mortality (23,24). Peritonitis associated with concurrent exit-site or tunnel infection is more likely to proceed to catheter loss (25). In our 10-year observational study, the technique survival of incident CAPD patients was significantly worse in patients with DM than in those without DM, which accords with a previous study on the prognosis of DM patients on PD therapy (26). Icodextrin,

Figure 1 — Kaplan-Meier “stay on PD” survival, by peritonitis occurrence: experiencing peritonitis (open circles) or peritonitis-free (open triangles).

Figure 2 — Kaplan-Meier technique survival by peritonitis occurrence: experiencing peritonitis (open circles) versus peritonitis-free (open triangles).

a glucose polymer, is able to assist in the maintenance of the osmotic gradient, producing adequate ultrafiltration capacity for 8–12 hours, thus prolonging CAPD treatment (27). We also identified prescription of icodextrin solution as a rescue therapy for technique failure. Peritonitis was another independent risk factor for technique failure in our study, which is also in keeping with an audit of PD patients in the United Kingdom (16).

Several authors have addressed the issue of risk factors for patient mortality on CAPD and have identified, mainly from observational data, various associations, including systemic inflammation, malnutrition, dialysis adequacy, peritoneal transport status, comorbidity, and rapid loss of RRF. Despite the advances in PD techniques

Figure 3 — Kaplan–Meier patient survival for the overall group, by peritonitis occurrence: experiencing peritonitis (open circles) versus peritonitis-free (open triangles).

and treatment strategies, peritonitis remains the major complication in patients on PD. Peritonitis is not only the leading cause of technique failure, but also a contributor to mortality, insofar as a higher peritonitis rate is a risk factor for patient mortality (28,29). Pérez Fontan *et al.* reported that the incidence of peritonitis is a strong predictor of peritonitis-related death and showed a clear trend predicting overall mortality (30). We studied the impact of peritonitis on patient mortality according to the presence or absence of peritonitis, not the peritonitis rate, during the observation period. An intriguing finding of our study is that CAPD patients with peritonitis were at a lower risk of mortality than were patients free of peritonitis. In the Kaplan–Meier analysis, longer survival was only a trend for the group experiencing peritonitis, but after multivariate adjustment, a significant difference was evident in patient mortality between the two groups. This paradox brings to mind the term “reverse epidemiology,” usually referring to circumstances in which previously identified associations or correlations of associated factors with known outcomes are now, in the presence of the same or new causative factors, associated with a clinical outcome in a different and often opposite direction. This phenomenon is usually proposed to address the varying relationships between numerous classical risk factors, such as obesity, hypertension, hypercholesterolemia, and clinical outcomes in dialysis patients. Recently, reverse epidemiology has been considered a misnomer and even misleading, mainly because of the complexity of the dialysis population and the oversimplification of risk factors preceding the clinical disease (31).

We have some hypotheses that may explain this presumptive “peritonitis paradox” in our data. First, once the PD patients in the current study developed a peritonitis episode, they were categorized into the group experiencing peritonitis, among whom only 4 of 124 died within 2 weeks of the first peritonitis episode (defined as “peritonitis-associated deaths”). Patients surviving a first peritonitis episode were offered exceptional education on self-care and management of PD complications, possibly facilitating their survival to a higher degree than in the patients free from peritonitis. Second, the peritonitis rate was markedly lower in Taiwan than in Western countries, and the predictors of a first peritonitis episode were also distinct. Differences in race, ethnicity, and the patient’s awareness of PD complications may play a role in this phenomenon. Third, RRF has recently emerged as an important factor for predicting mortality in PD patients, and thus preservation of RRF is of paramount importance in prolonging patient survival. We did not find a correlation between RRF and patient survival, even in the univariate Cox regression model, and so RRF was not included in the multivariate analysis. The peritonitis paradox cannot be confidently confirmed until all dialysis-related factors (PD adequacy, fluid and blood pressure control, mineral metabolism) and all non-dialysis related factors (psychosocial, comorbidities, family support, nutrition) can be taken into account, although we did make efforts to incorporate many factors into the analysis, such as average values of the study parameters and accumulated comorbidities. In short, given that patients in our unit experiencing an episode of peritonitis unexpectedly tended to survive better than did those free of peritonitis, more effort should be made to clarify the mechanisms underlying this “peritonitis paradox.”

The independent prediction of technique failure by a peritonitis episode suggests that the incidence of peritonitis needs to be lowered to reduce PD withdrawal. Elderly patients and those with DM are prone to develop peritonitis and also already have a lesser survival. Improving the institution’s education system for end-stage renal disease patients and medical staff, and providing support for at-risk patients may lower the incidence of peritonitis and thus prevent PD withdrawals.

The strengths of the present study include its homogenous population, limited exclusively to incident CAPD patients, and its long follow-up period of up to 10 years. In addition, all the data analyzed were validated against patient charts. Patients using automated PD were excluded because of the small number of such patients at our center. On the other hand, although the analytic model incorporated several potentially important factors linked

with peritonitis risk or clinical outcome, we could not detect any effect of factors previously linked to peritonitis risk, such as socio-economic status or nasal carriage of *Staphylococcus aureus*. As a result, we cannot exclude the possibility of residual confounding from variables not included in the present study. Moreover, because this is a retrospective observational study with a relatively small sample size, the causal relations implicated in the analysis should be treated with caution.

CONCLUSIONS

In our study population, the peritonitis rate was notably low, at 0.196 episodes per patient-year. Older age (>65 years) was the only identified risk factor for peritonitis. Although DM affects prognosis in CAPD treatment (patient mortality, drop-out from PD, and technique failure), it does not affect the incidence of peritonitis. Peritonitis not only predicts technique failure, it also influences patient mortality. The beneficial effect of a first peritonitis episode on patient survival (the "peritonitis paradox") and its underlying mechanisms remain to be clarified.

ACKNOWLEDGMENTS

We thank Ms. Shu-Chuan Wang for help with statistical analyses and data collection, and all the PD nursing teams for their help in collecting data.

DISCLOSURES

The authors have no financial conflicts of interest to disclose.

REFERENCES

- Oreopoulos DG, Robson M, Faller B, Ogilvie R, Rapoport A, deVeber GA. Continuous ambulatory peritoneal dialysis: a new era in the treatment of chronic renal failure. *Clin Nephrol* 1979; 11:125–8.
- Vonesh EF, Snyder JJ, Foley RN, Collins AJ. Mortality studies comparing peritoneal dialysis and hemodialysis: what do they tell us? *Kidney Int Suppl* 2006; (103):S3–11.
- Szeto CC, Leung CB, Chow KM, Kwan BC, Law MC, Wang AY, et al. Change in bacterial aetiology of peritoneal dialysis-related peritonitis over 10 years: experience from a centre in South-East Asia. *Clin Microbiol Infect* 2005; 11:837–9.
- Mujais S. Microbiology and outcomes of peritonitis in North America. *Kidney Int Suppl* 2006; (103):S55–62.
- Coles GA, Topley N. Long-term peritoneal membrane changes. *Adv Ren Replace Ther* 2000; 7:289–301.
- Dong J, Chen Y. Impact of the bag exchange procedure on risk of peritonitis. *Perit Dial Int* 2010; 30:440–7.
- Yang Z, Xu R, Zhuo M, Dong J. Advanced nursing experience is beneficial for lowering the peritonitis rate in patients on peritoneal dialysis. *Perit Dial Int* 2012; 32:60–6.
- Oo TN, Roberts TL, Collins AJ. A comparison of peritonitis rates from the United States Renal Data System database: CAPD versus continuous cycling peritoneal dialysis patients. *Am J Kidney Dis* 2005; 45:372–80.
- Golper TA, Brier ME, Bunke M, Schreiber MJ, Bartlett DK, Hamilton RW, et al. Risk factors for peritonitis in long-term peritoneal dialysis: the Network 9 Peritonitis and Catheter Survival studies. Academic Subcommittee of the Steering Committee of the Network 9 Peritonitis and Catheter Survival studies. *Am J Kidney Dis* 1996; 28:428–36.
- Lim WH, Johnson DW, McDonald SP. Higher rate and earlier peritonitis in Aboriginal patients compared to non-Aboriginal patients with end-stage renal failure maintained on peritoneal dialysis in Australia: analysis of ANZDATA. *Nephrology (Carlton)* 2005; 10:192–7.
- Chow KM, Szeto CC, Leung CB, Kwan BC, Law MC, Li PK. A risk analysis of continuous ambulatory peritoneal dialysis-related peritonitis. *Perit Dial Int* 2005; 25:374–9.
- Han SH, Lee SC, Ahn SV, Lee JE, Kim DK, Lee TH, et al. Reduced residual renal function is a risk of peritonitis in continuous ambulatory peritoneal dialysis patients. *Nephrol Dial Transplant* 2007; 22:2653–8.
- Prasad N, Gupta A, Sharma RK, Sinha A, Kumar R. Impact of nutritional status on peritonitis in CAPD patients. *Perit Dial Int* 2007; 27:42–7.
- Wong SS, Chu KH, Cheuk A, Tsang WK, Fung SK, Chan HW, et al. Prophylaxis against gram-positive organisms causing exit-site infection and peritonitis in continuous ambulatory peritoneal dialysis patients by applying mupirocin ointment at the catheter exit site. *Perit Dial Int* 2003; 23(Suppl 2):S153–8.
- 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* 2009; 4:1195–200.
- Davenport A. Peritonitis remains the major clinical complication of peritoneal dialysis: the London, UK, peritonitis audit 2002–2003. *Perit Dial Int* 2009; 29:297–302.
- Han SH, Lee SC, Ahn SV, Lee JE, Choi HY, Kim BS, et al. Improving outcome of CAPD: twenty-five years' experience in a single Korean center. *Perit Dial Int* 2007; 27:432–40.
- Yao Q, Zhang W, Qian J. Peritoneal dialysis in Shanghai. *Perit Dial Int* 2008; 28(Suppl 3):S42–5.
- Mizuno M, Ito Y, Tanaka A, Suzuki Y, Hiramatsu H, Watanabe M, et al. Peritonitis is still an important factor for withdrawal from peritoneal dialysis therapy in the Tokai area of Japan. *Clin Exp Nephrol* 2011; 15:727–37.
- Li PK, Szeto CC. Success of the peritoneal dialysis programme in Hong Kong. *Nephrol Dial Transplant* 2008; 23:1475–8.
- Szeto CC, Kwan BC, Chow KM. Peritonitis risk for older patients on peritoneal dialysis. *Perit Dial Int* 2008; 28:457–60.

22. Fang W, Qian J, Lin A, Rowaie F, Ni Z, Yao Q, *et al.* Comparison of peritoneal dialysis practice patterns and outcomes between a Canadian and a Chinese centre. *Nephrol Dial Transplant* 2008; 23:4021–8.
23. Digenis GE, Abraham G, Savin E, Blake P, Dombros N, Sombolos K, *et al.* Peritonitis-related deaths in continuous ambulatory peritoneal dialysis (CAPD) patients. *Perit Dial Int* 1990; 10:45–7.
24. Tzamaloukas AH, Murata GH, Fox L. Peritoneal catheter loss and death in continuous ambulatory peritoneal dialysis peritonitis: correlation with clinical and biochemical parameters. *Perit Dial Int* 1993; 13(Suppl 2):S338–40.
25. Yang CY, Chen TW, Lin YP, Lin CC, Ng YY, Yang WC, *et al.* Determinants of catheter loss following continuous ambulatory peritoneal dialysis peritonitis. *Perit Dial Int* 2008; 28:361–70.
26. Kuriyama S. Peritoneal dialysis in patients with diabetes: are the benefits greater than the disadvantages? *Perit Dial Int* 2007; 27(Suppl 2):S190–5.
27. Wolfson M, Piraino B, Hamburger RJ, Morton AR on behalf of the Icodextrin Study Group. A randomized controlled trial to evaluate the efficacy and safety of icodextrin in peritoneal dialysis. *Am J Kidney Dis* 2002; 40:1055–65.
28. Fried LF, Bernardini J, Johnston JR, Piraino B. Peritonitis influences mortality in peritoneal dialysis patients. *J Am Soc Nephrol* 1996; 7:2176–82.
29. Sipahioglu MH, Aybal A, Unal A, Tokgoz B, Oymak O, Utas C. Patient and technique survival and factors affecting mortality on peritoneal dialysis in Turkey: 12 years' experience in a single center. *Perit Dial Int* 2008; 28:238–45.
30. Pérez Fontan M, Rodríguez-Carmona A, García-Naveiro R, Rosales M, Villaverde P, Valdés F. Peritonitis-related mortality in patients undergoing chronic peritoneal dialysis. *Perit Dial Int* 2005; 25:274–84.
31. Levin NW, Handelman GJ, Coresh J, Port FK, Kaysen GA. Reverse epidemiology: a confusing, confounding, and inaccurate term. *Semin Dial* 2007; 20:586–92.