

Peritonitis Influences Mortality in Peritoneal Dialysis Patients¹

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ABSTRACT

Mortality remains high in peritoneal dialysis (PD) patients. Known risk factors for mortality include age, diabetes, race, initial albumin level, and cardiovascular disease. Peritonitis is reported to cause death in 1 to 6% of PD patients but has not been well studied as a risk factor for mortality. This study examined 516 adults with a total of 896 yr on PD at one center to determine if peritonitis influenced mortality. Time at risk began on Day 1 of training and ended at death, transplant, or 60 days after transfer to hemodialysis or intermittent peritoneal dialysis. The overall mortality rate was 17.4/100 patient yr. Survival was lower for whites, men, diabetic patients, and older patients. Independent risk factors for mortality (by Cox proportional hazards) were race, diabetes, increased age, and increased peritonitis rate. Use of the Y-set was not associated with decreased mortality. Peritonitis was a risk factor only in whites, nondiabetic patients, and those patients over the age of 60. For every 0.5/yr increase in the peritonitis rate, the risk of death increased 10% in whites, 11% in those patients who were over the age of 60, and 4% for nondiabetic patients. Mortality rates did not decrease over time (1979 to 1995), although peritonitis rates fell significantly ($P < 0.001$). Rates of Gram-negative and fungal peritonitis showed no trend over time. Peritonitis contributed to 25 of 158 (15.8%) of deaths. Gram-negative/fungal peritonitis accounted for 14 deaths (9.5% of all Gram-negative/fungal episodes) whereas *Staphylococcus epidermidis* accounted for only 1 death (0.5% of all *S. epidermidis* episodes) ($P < 0.001$). Cardiovascular disease was more common in those patients whose deaths were unrelated to peritonitis ($P < 0.01$), whereas an infectious cause was more common in those patients whose deaths were peritonitis-related ($P < 0.001$). In this study, peritonitis was a risk factor for

death in whites, nondiabetic patients, and older patients. However, the Y-set did not improve survival, perhaps because it does not decrease Gram-negative/fungal peritonitis. To have an impact on survival, efforts are needed to reduce the peritonitis that results from these more serious pathogens.

Key Words: ESRD, chronic ambulatory peritoneal dialysis, survival, risk factors, peritonitis rate

The mortality rate in peritoneal dialysis (PD) patients remains high. Analysis of mortality for PD patients in the U.S. Renal Data System (USRDS) showed an adjusted mortality rate for the yr 1987 through 1989 of 25.3/100 dialysis yr (1). This rate was higher than the rate for hemodialysis patients (21.3/100 dialysis yr). Mortality rates have been decreasing over time for dialysis patients (2), but it is not clear if this is true for PD patients. Known independent risk factors for mortality in PD patients include: age, race, diabetes, initial albumin level, and the presence of cardiovascular disease (3–6).

Peritonitis is reported to cause death in 1 to 6% of PD patients (7–9), but has not been well studied as a risk factor for mortality. In reviews of patients that died of peritonitis, the risk of death was higher for patients with Gram-negative and fungal peritonitis, especially polymicrobial peritonitis (10). In addition, patients with cardiovascular disease may be at increased risk of death after peritonitis (11). Peritonitis rates have been decreasing over time, especially since the introduction of the Y-set (12). We examined whether peritonitis was an independent risk factor for mortality and whether use of the Y-set, which lowers the peritonitis rate, has led to a decrease in the mortality rate.

METHODS

Adult continuous ambulatory peritoneal dialysis (CAPD) and continuous cycler peritoneal dialysis (CCPD) patients at our center from 1979 to December 31, 1994 were chosen for this study. Patients over the age of 14 at the time of initiation of PD who subsequently transferred from the pediatric to the adult program were also included. The patients from two outpatient units (a Veterans Administration and an university dialysis unit) signed consent forms permitting the collection of demographic and infection data.

Peritonitis was defined as cloudy dialysate with ≥ 100 white blood cells/ μ L, 50% or more of which were polymorphonuclear leukocytes.

For analysis, the organisms were classified as Gram-negative and/or fungal, *Staphylococcus epidermidis*, or other. Multiorganism peritonitis was classified as Gram-negative/fungal if any of the organisms were Gram-negative or fungal, whereas all other multiorganism peritonitis episodes were classified as "other."

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The information on patients who died was reviewed. Patients were classified as a peritonitis-related death if they (1) died of sepsis secondary to peritonitis, (2) died with a positive dialysate culture or cloudy fluid, (3) died within 14 days of the onset of peritonitis, or (4) died during a hospital admission with peritonitis. The primary cause of death did not need to be peritonitis to be classified as a peritonitis-related death.

The causes of death were classified as cardiovascular, malignancy, neurologic, infection/sepsis, gastrointestinal hemorrhage, hyperkalemia, discontinuation of dialysis (if not related to malignancy), other, and unknown/missing.

Data Analysis

Time at risk began on Day 1 of training. Mortality rates were calculated as deaths per 100 dialysis yr. Patients were censored at the time of transplant, 60 days after transfer to hemodialysis, and at the end of the study period. Peritonitis rates were calculated as episodes per dialysis yr.

Survival was examined for all patients and for each subgroup: diabetes, age (<60, > 60 yr), gender, and race (black, white). Kaplan-Meier survival curves and the log-rank test were used to examine survival differences between groups. The chi-squared goodness-of-fit test for a uniform distribution was used for trends in mortality rates and peritonitis rates over time. For proportions, chi-squared or Fisher's exact test were used. Poisson test was used to compare peritonitis rates. The *t* test or an analysis of variance was used to compare nominal data. If the analysis of variance showed a significant difference, then Fisher's least-significant difference was used to compare the difference between individual pairs. When applicable, data were expressed as means \pm SD.

The Cox proportional hazards model was used to assess the effects of age, peritonitis rate (as a continuous variable), race, diabetes, connection system used (patients using Y-set alone or standard spike system alone), gender, and initial year of PD on patient survival. This analysis was performed on all patients and for the subgroups. The rate ratio (relative risk, RR) was determined from the Cox proportional hazards using the formula: $RR = e^{\beta(X-X')}$, where β is the regression coefficient for the variable and $(X-X')$ is the difference between two values of the variable.

Statistical analyses were performed using NCSS statistical software (Jerry L. Hintz, Kaysville, UT). For all tests, a *P* value < 0.05 was considered statistically significant.

RESULTS

There were 516 adult CAPD/CCPD patients with a cumulative dialysis time of 896.2 yr. The patient characteristics are summarized in Table 1. In 1987, the Y-set was introduced at our center. CAPD patients who were on the standard spike system were subsequently converted to the Y-set. By 1989, most CAPD patients (78%) were using the Y-set. Most catheters were double-cuffed Tenckhoff catheters.

At the close of the study period, 49 patients (9.5%) remained on PD, 170 (32.9%) had transferred to hemodialysis or intraperitoneal dialysis, 158 (30.6%) had died, 115 (22.3%) were transplanted, and 24 (4.7%) had transferred to another center and were lost to follow-up. The survival curve for all patients is shown in Figure 1. The 1-yr survival rate was 82.4%, 2-yr rate was 72.0%, and 5-yr rate was 40.8%. The

TABLE 1. Patient characteristics (*N* = 516)^a

Age (mean \pm SD)	50.0 \pm 15.2
PD Time (months; mean \pm SD)	21.5 \pm 22.9
Women (<i>N</i> (%))	209 (41%)
Race (Blacks) (<i>N</i> (%))	87 (17%)
Peritonitis Rate (episodes/dialysis yr)	0.8
PD Connection Device (<i>N</i> , (%))	
Y-set only	154 (30%)
Standard spike only	261 (51%)
CCPD only ^a	19 (4%)
More than one device	82 (16%)
Etiology of Renal Disease (<i>N</i> (%))	
Diabetes	181 (35%)
Glomerulonephritis	122 (24%)
Hypertension	68 (13%)
Polycystic kidney disease	31 (6%)
Interstitial nephritis/chronic pyelonephritis	15 (3%)
Other	58 (11%)
Unknown	41 (8%)

^a PD, peritoneal dialysis; CCPD, continuous cycler peritoneal dialysis.

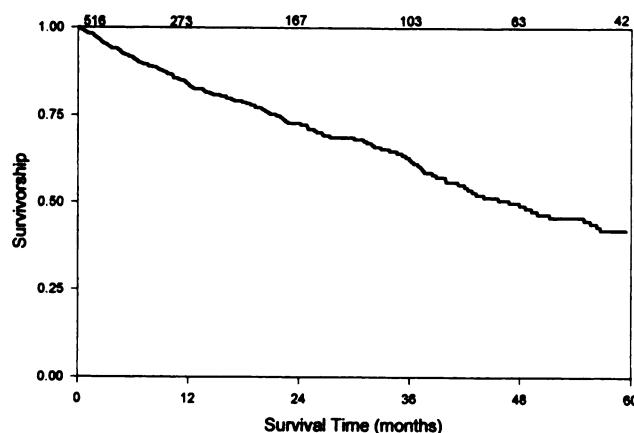


Figure 1. Overall patient survival of adult peritoneal dialysis (PD) patients. The numbers across the top represent the number of patients at risk.

survival curves for the subgroups are shown in Figures 2 through 5. Survival was significantly lower in men *versus* women, diabetic patients *versus* nondiabetic patients, and those over age 60 *versus* those under age 60.

The overall mortality rate was 17.4/100 dialysis yr. There has been no trend over time (Figure 6). Because the proportion of diabetic patients has increased over time (14.3% in 1980 to 47.8% in 1994), the patients were stratified by presence or absence of diabetes and analyzed separately for a trend in mortality. No significant trend was detected for either group. The overall peritonitis rate showed a downward trend over time, especially since the time of introduction of the Y-set (*P* < 0.001) (Figure 7). The rates of Gram-negative and fungal peritonitis have not decreased over time (Figure 8).

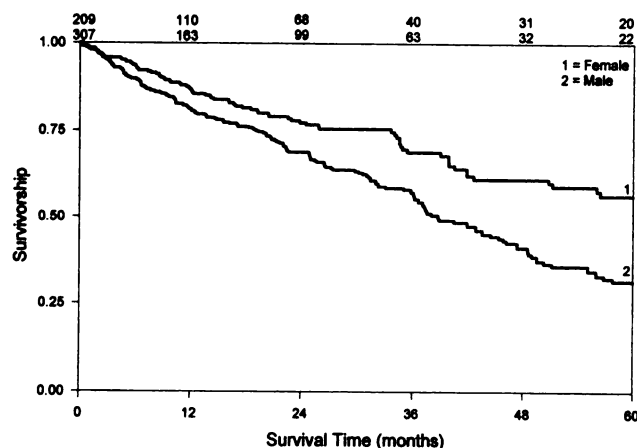


Figure 2. Survival of adult PD patients by gender ($P = 0.044$). The numbers across the top represent the number of patients at risk.

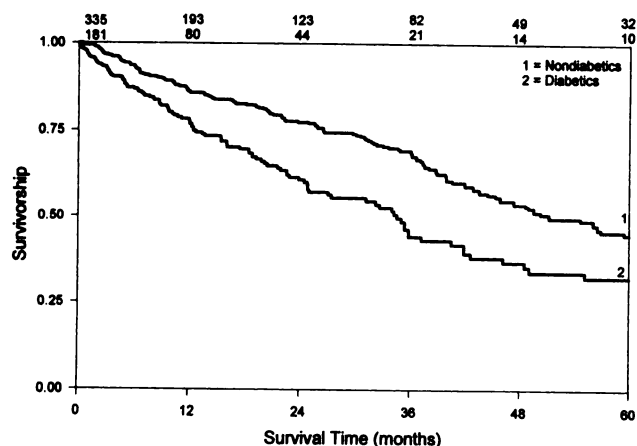


Figure 3. Survival of adult diabetic versus nondiabetic PD patients ($P = 0.004$). The numbers across the top represent the number of patients at risk.

The predictors for mortality by Cox proportional hazards for all patients were age (RR for every 10-yr increase in age, 1.57; $P < 0.001$), diabetes (RR, 2.23; $P < 0.001$), race (RR for blacks, 0.58; $P = 0.038$), and peritonitis rate (RR for every 0.5-episode/yr increase, 1.04; $P = 0.046$). Gender, year PD was started, and the connection system used were not independent predictors of death. The Cox proportional hazards model was then rerun, substituting Gram-negative/fungal peritonitis rates for overall peritonitis rate. The results were similar, with the independent predictors being age ($P < 0.001$), diabetes ($P < 0.001$), and Gram-negative/fungal peritonitis rate ($P < 0.001$). Race did not reach significance in this analysis ($P = 0.066$).

The patients were also analyzed by subgroups. Peritonitis rate was a predictor for mortality in whites ($P = 0.005$), nondiabetic patients ($P = 0.006$), and those over the age of 60 ($P = 0.009$). For every 0.5-episodes/yr increase in the peritonitis rate, the risk of

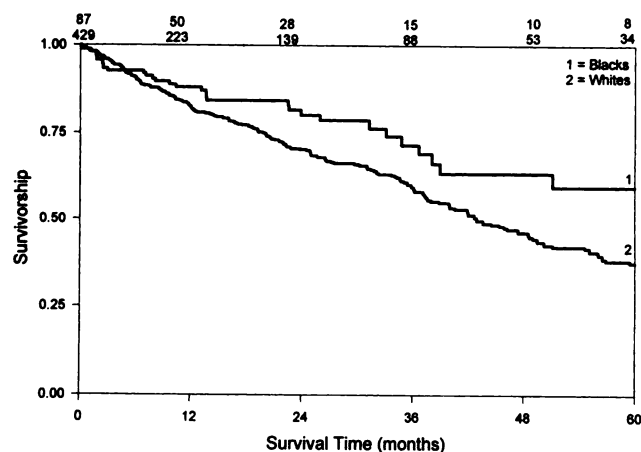


Figure 4. Survival of adult PD patients by race ($P = 0.038$). The numbers across the top represent the number of patients at risk.

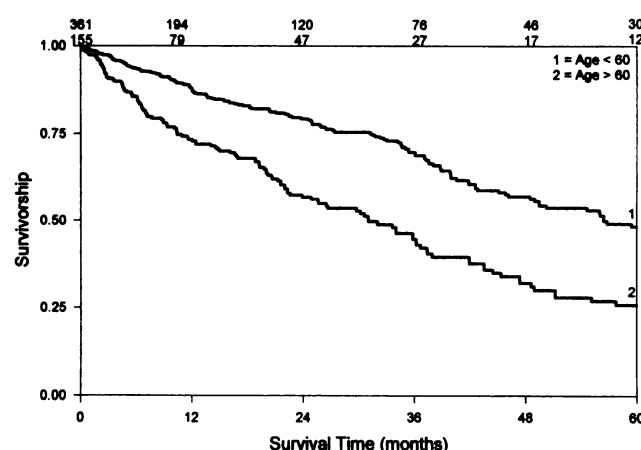


Figure 5. Survival of adult PD patients by age: over age 60 versus younger than age 60 ($P < 0.001$). The numbers across the top represent the number of patients at risk.

mortality increased 10% in whites (RR, 1.10), 4% in nondiabetic patients (RR, 1.04), and 11% (RR, 1.11) in those over the age of 60.

The patients were grouped by peritonitis rate: ≥ 1.25 episodes/yr (upper quartile) and < 1.25 episodes/yr. The survival rate for those patients in the higher peritonitis rate group was significantly worse ($P = 0.004$) (Figure 9). The two groups were not different in terms of age, race, diabetes, or gender. The survival rate for the high peritonitis rate group was worse compared with those with < 1.25 peritonitis episodes/yr in whites ($P = 0.002$), nondiabetic patients ($P = 0.002$), and those over the age of 60 ($P = 0.027$).

Of the 158 deaths, 25 (15.8%) met the definition of peritonitis-related death. The organisms involved are summarized in Table 2. The "other" category included *S. aureus*, *Enterococcus*, *Streptococcus*, uncategorized Gram-positive organism, unknown (one each), and

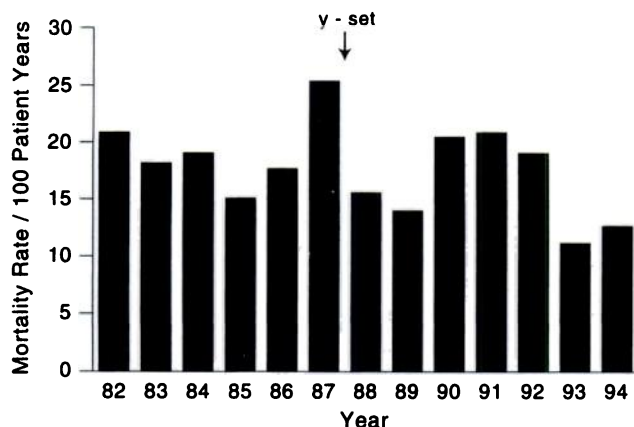


Figure 6. Unadjusted mortality rate of PD patients for the years 1982 through 1994. The arrow indicates the time of introduction of the Y-set. The overall mortality rate was 17.4/100 patient years.

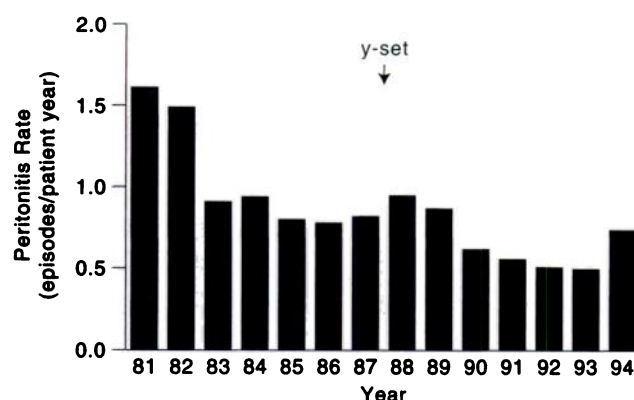


Figure 7. Yearly peritonitis rates in adult PD patients for the years 1981 through 1994. The arrow indicates the time of introduction of the Y-set.

five sterile episodes. The five sterile episodes all occurred before 1986. Three of the 14 Gram-negative/fungal peritonitis-related deaths involved multiple organisms. Of the 14 Gram-negative/fungal cases, two were secondary to colonoscopy and one was secondary to bowel perforation from colon cancer. In the remaining 11 patients, the precipitating cause of the peritonitis was not known. The characteristics of the patients who died are summarized in Table 3. The patients who died and were categorized as peritonitis-related deaths had a higher peritonitis rate and were less likely to be diabetic than those whose deaths were unrelated to peritonitis. Compared with those who survived, the patients with peritonitis-related deaths were older, more likely to be male, and had a higher peritonitis rate.

The causes of death are summarized in Table 4. The patients whose deaths were unrelated to peritonitis were more likely to have died of a cardiovascular etiology ($P < 0.01$), whereas patients with peritonitis-

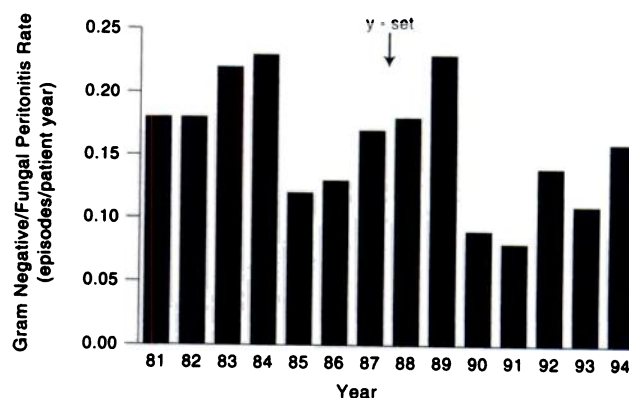


Figure 8. Yearly Gram-negative/fungal peritonitis rates in adult PD patients for the years 1981 through 1994. The arrow indicates the time of introduction of the Y-set.

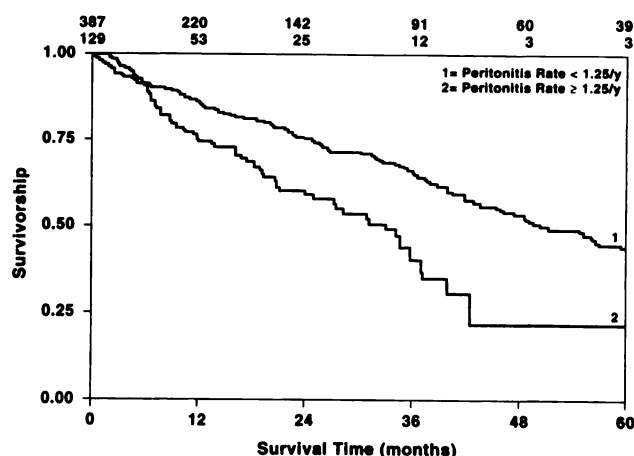


Figure 9. Survival of adult PD patients classified by peritonitis rate: < 1.25 episodes/dialysis year versus ≥ 1.25 episodes/dialysis year ($P = 0.004$). The numbers across the top represent the number of patients at risk.

related deaths were more likely to have died of an infectious/septic cause ($P < 0.001$). The two groups did not differ in terms of malignancy, neurologic, gastrointestinal hemorrhage, hyperkalemia, or discontinuation of dialysis as causes of death.

DISCUSSION

Using a PD database, this study examined risk factors for mortality in adult PD patients. We found higher mortality for whites, men, diabetic patients, and those over the age of 60, which is consistent with the USRDS results (2). The majority of studies (3,5,9,13,14,15) have shown diabetes and age to be risk factors for mortality. Race has not been consistently shown to be a predictor of mortality. Nolph *et al.* (5) showed that black patients had a higher mortality than white patients, whereas other studies showed no effect of race on mortality (6,14). Our study showed that race was a predictor of mortality but, unlike those

TABLE 2. Organisms in peritonitis-related deaths

Organism	Number of Deaths	Total Number of Episodes	Percentage of Episodes Associated with Death ^a
<i>Staphylococcus epidermidis</i>	1	190	0.5
Gram-Negative/Fungal	14	144	9.7
Other	10	394	2.5

^a $P < 0.001$.

TABLE 3. Characteristics of patients with peritonitis-related deaths

Characteristic	Peritonitis-Related Deaths (N = 25)	Deaths Unrelated to Peritonitis (N = 133)	Survivors (N = 358)
Diabetes	4 (16.0%) ^a	58 (43.6%)	119 (33.2%) ^b
Female	8 (32.0%)	38 (28.6%)	163 (45.5%) ^c
Black	4 (16.0%)	13 (9.8%)	70 (19.6%) ^b
Peritoneal Dialysis Time (months)	28 ± 27	21 ± 20	21 ± 24
Age	59 ± 11	56 ± 13	47 ± 15 ^d
Peritonitis Rate (episodes/dialysis yr)	1.48 ^e	0.74	0.77

^a Patients with peritonitis-related deaths versus those with deaths unrelated to peritonitis ($P < 0.05$).^b Patients with deaths unrelated to peritonitis versus those who survived ($P < 0.05$).^c Patients with deaths unrelated to peritonitis versus those who survived ($P < 0.001$).^d Patients that survived versus those with peritonitis-related deaths or those with deaths unrelated to peritonitis ($P < 0.001$).^e Patients with peritonitis-related deaths versus those with deaths unrelated to peritonitis or those that survived ($P < 0.001$).

TABLE 4. Causes of death

	Peritonitis-Related Deaths	Deaths Unrelated to Peritonitis
Infection/Sepsis ^a	11 (44%)	16 (12.0%)
Cardiovascular ^b	6 (24.0%)	70 (52.6%)
Neurologic	2 (8.0%)	9 (6.8%)
Malignancy	2 (8.0%)	13 (9.8%)
Gastrointestinal hemorrhage	1 (4.0%)	2 (1.5%)
Hyperkalemia	1 (4.0%)	2 (1.5%)
Discontinued dialysis	0	4 (3.0%)
Other	2 (8.0%) ^c	7 (5.3%) ^d
Unknown/Missing	0	10 (7.5%)

^a $P < 0.001$.^b $P < 0.01$.^c Includes one case of pulmonary embolism, and one case of pancreatitis.^d Includes two cases of pancreatitis, two cases of ruptured abdominal aneurysms, one case of postoperative respiratory arrest, one case of cholesterol emboli, and one case of embolism (site not specified).

patients in the study by Nolph *et al.*, black patients had a better survival rate. Cardiovascular disease and decreased serum albumin levels have also been shown to be risk factors for mortality (6,13,15), but we had insufficient data on these variables to analyze their impact on mortality in our patients.

Our overall mortality rate was lower than that found in the analysis of mortality in PD and hemodialysis patients of Bloembergen *et al.* (1). This is despite beginning time at risk on Day 1, not at 90 days as in the USRDS data, which should substantially increase the mortality rate. Differences in group characteristics may account for part of the difference. Our patients were younger (mean age, 50 versus 56 yr) and this would lead to a lower mortality rate. However, com-

pared with the Bloembergen *et al.* study, the higher percentage of diabetic patients in our study (35% versus 25%) and the lower percent of women (41% versus 49%) and blacks (17% versus 22%) should increase the unadjusted mortality rate. The lower mortality rate may be a center effect, *i.e.*, from a center with an interest in PD, or may be secondary to unstudied variables such as adequacy of PD.

In our study, peritonitis rate was a predictor of mortality. This was true for both the overall peritonitis rate and for the Gram-negative/fungal rate. Peritonitis rate has been shown to be the major determinant of technique survival (15–17), but has rarely been examined as a predictor of patient survival. Ataman *et al.* found that peritonitis rate was an independent predic-

tor, with a relative risk of 1.33 for every one-episode/yr increase in peritonitis rate (16). This relative risk is higher than that in our study but the populations studied differ, with the Ataman *et al.* study having few diabetic patients and had a higher overall peritonitis rate (average, 1.8 to 2.9 episodes/patient yr). Viglino *et al.* (17) found that patients with a peritonitis rate > 1.0 had a higher mortality than those with a rate < 0.5 , but this was only when those patients with no peritonitis were excluded. In the USRDS (18), PD patients had a higher death rate from septicemia than did hemodialysis patients (38.8/1000 patient yr versus 23.4/1000 patient yr). This difference could be the result, in part, of peritonitis. This hypothesis would be consistent with our study, which found that patients with peritonitis-related deaths were more likely to die of an infectious or septic cause. It is not clear from this study, however, if peritonitis is causally related to death. It has been previously noted that patients with cardiovascular disease are at increased risk for death after peritonitis (11). Future studies are needed to assess the impact of comorbid diseases and peritonitis on survival.

We did not find a significant change in mortality rates over time despite a decrease in peritonitis rates. The Y-set has led to a decrease in peritonitis rates (19) by decreasing touch contamination and, thus, *S. epidermidis* peritonitis (12). Gram-negative and fungal peritonitis rates are not affected by the Y-set (12) and, in our study, there was no decrease over time in Gram-negative/fungal peritonitis. One explanation for the lack of an effect on mortality with the decrease in peritonitis is that *S. epidermidis* peritonitis follows a mild course (20). In agreement with this hypothesis, Slingeneyer *et al.* (10) showed that peritonitis associated with a break-in technique (which would be decreased with the Y-set) was associated with a more favorable outcome. Mortality in this previous study was particularly high for peritonitis because of hematogenous spread or intra-abdominal pathology (that is, secondary peritonitis). Although the mortality associated with secondary peritonitis appears to be increased, other studies have also found an increased risk of death in Gram-negative peritonitis, even without a known gastrointestinal cause (11,21). Digenis *et al.* (22) reported an increased risk with multiorganism Gram-negative and fungal peritonitis; however, they also found an increased risk with *S. aureus* peritonitis. In this study, late catheter removal appeared to contribute to death. Our study did not find an association between *S. aureus* peritonitis and death. In addition, only three of the 14 deaths associated with Gram-negative/fungal peritonitis were multiorganism-involved, perhaps reflecting the early catheter removal practiced at our center.

Certain populations are at higher risk for death from peritonitis. Previous studies have shown an association between peritonitis-related death and older age (21,23). In our study, patients with peritonitis-related death were older than those who survived, but did not differ in age

from patients whose deaths were unrelated to peritonitis. In the study presented here, peritonitis rate was a predictor of death in whites, nondiabetic patients, and those patients over the age of 60. It is not clear why these patients should be at increased risk of peritonitis-associated death. Further studies are necessary to confirm this finding. Variables reportedly associated with death from peritonitis are diabetes, malnutrition prior to infection, worsening malnutrition during infection, and cardiovascular disease (11,22). Changes in albumin and potassium are also indications of high-risk cases (21,22). Digenis *et al.* (22) did not find that diabetes was associated with increased mortality from peritonitis, in agreement with our results. The decrease in albumin level may indicate the development of malnutrition that contributes to death or may be a marker of a more severe disease with increased peritoneal permeability. We were not able to assess the change in albumin level in our study. A prospective study of the decrease in albumin level during peritonitis episodes as a risk factor for death is needed.

In summary, we found that the patient's peritonitis rate was an independent risk factor for mortality. Mortality associated with peritonitis was predominantly related to Gram-negative/fungal peritonitis. Although the Y-set has contributed to decreased peritonitis rates, it has not led to a decrease in mortality, as it does not affect Gram-negative/fungal peritonitis. To have an impact on survival, efforts are needed to decrease peritonitis resulting from these more serious pathogens.

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