Predictors of Peritonitis in Patients on Peritoneal Dialysis: Results of a Large, Prospective Canadian Database

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Background and objectives: Despite the decreasing incidence of peritonitis among peritoneal dialysis (PD) patients over time, its occurrence is still associated with significant morbidity and mortality. Determining factors that are associated with PD peritonitis may facilitate the identification of patients who are at risk.

Design, setting, participants, & measurements: Using data collected in the multicenter Baxter POET database between 1996 and 2005, the study population included incident Canadian PD patients. Potential predictors of peritonitis were sought using a negative binomial model and an Andersen-Gill model. Study variables included age, gender, race, cause of renal disease, diabetes status, transfer from hemodialysis (HD), previous renal transplant, and continuous ambulatory PD (CAPD) *versus* automated PD (APD).

Results: Data were available for 4247 incident PD patients, including 1605 patients with a total of 2555 peritonitis episodes. Using the negative binomial regression model, factors that were independently associated with a higher peritonitis rate included age, Black race, and having transferred from HD. There was an interaction between gender and diabetes, with an increased risk for peritonitis among female patients with diabetes. The use of CAPD *versus* APD did not affect the peritonitis rate. The Andersen-Gill model for recurrent events yielded similar results.

Conclusions: Predictors of PD peritonitis included Black race, transferring from HD to PD, and diabetes among women. In contrast to previous findings, CAPD and APD were similar with regard to peritonitis risk.

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The occurrence of peritoneal dialysis (PD)-associated peritonitis is an important complication of PD. At present, our understanding of which patients are most at risk for developing peritonitis is limited.

Several predictors have been reported in the literature. Among demographic characteristics, Black race (1,2), Aboriginal race (3), diabetes (1,4,5), and obesity (3,6) have been associated with a higher risk for peritonitis. In addition, hypoalbuminemia (4,7) and lack of residual renal function (5) have been reported to be associated with a shorter time to first peritonitis. Furthermore, a previous peritonitis episode has been shown to increase the risk for developing a subsequent episode (1,2). Although the association between age and peritonitis has been inconsistent across different studies (1,3,5,8,9), we recently reported an era effect for age, such that the increased risk associated with older age disappeared among those who initiated PD after the year 2000 (10). The data regarding other important factors are conflicting. One such example is the use of continuous ambulatory PD (CAPD) *versus* automated PD (APD) as a PD modality. Several studies have reported an increased peritonitis risk with CAPD (8,9,11,12), whereas others have reported no difference (13) or an increased risk with APD (1,14).

Some of the variability in the predictors identified may relate to the patient populations studied, the varying sizes of the cohorts studied, and the different eras during which data were collected. An additional complicating factor is the type of analysis chosen to assess variables that are associated with peritonitis. Although the optimal analytic model to study peritonitis risk factors is not known, the two most common analyses, Poisson modeling and Cox proportional hazards modeling, define peritonitis outcomes using either a peritonitis rate (which takes into account all peritonitis episodes over time) or time to first peritonitis (which follows a patient only until he or she develops the first peritonitis).

The primary objective of this study was to identify factors that are associated with PD peritonitis. A secondary objective was to assess whether modeling the occurrence of peritonitis using peritonitis rates and time to peritonitis would yield similar predictors.

Materials and Methods

Patients

The study included PD patients who were from 25 centers across Canada and for whom data were available through the Peritonitis

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Organism Exit sites Tunnel infections (POET) database (Baxter Healthcare). The data from all Canadian PD centers using the POET clinical monitoring system software were collected as described previously (15). The database includes prospectively collected data on incident PD patients, as well as data on prevalent patients from as early as 1990 who were retrospectively entered into the database when their center started using the POET software. For this study, we included only incident patients for whom data were collected prospectively. The period for data collection was from January 1, 1996, until September 12, 2005. Information contained within the POET database includes patient demographics, cause of infection, catheter complications, and therapy transfers. Approval was obtained from the research ethics board at University Health Network before study initiation.

Demographic data that were available for this study include age, gender, race, cause of ESRD, diabetes status, modality before PD start (new to dialysis, transfer from HD, failed transplant, other/unknown), and PD modality (CAPD *versus* APD). A secondary analysis was performed after exclusion of any patient who switched from one PD modality to another (CAPD to APD or *vice versa*) to reduce confounding by modality switching. Given that the prospective cohort included patients who initiated PD during a 10-yr period, we defined two eras of patients to assess for an era effect: An earlier cohort consisting of those who initiated PD between 1996 and 2000 and a more contemporary cohort consisting of those who initiated PD between 2001 and 2005.

Peritonitis

Relapsing or recurrent peritonitis episodes were excluded. Although there is some controversy as to the definition of a recurrent peritonitis episode, standard International Society of Peritoneal Dialysis definitions were used, with a relapse defined as an episode that occurs within 4 wk of completion of therapy of a previous infection with negative culture or the same organism and a recurrence defined as an episode that occurs within 4 wk of completion of therapy of a previous infection but with a different organism (16). Consequently, peritonitis episodes that occurred within 60 d of a previous episode were excluded on the basis of the assumption that patients were treated with a maximum of 4 wk of antibiotic therapy.

Statistical Analysis

Continuous variables were reported as means ± SD. Two models were used to assess the predictors of peritonitis. In the first, we considered the number of peritonitis episodes per patient as the outcome, and potential predictors were tested using a multivariable negative binomial regression model. The negative binomial model, which is an extension of the Poisson model, allows one to determine the association between patient characteristics and the peritonitis rate (*i.e.*, number of peritonitis episodes divided by time on PD) when there is overdispersed count data (*i.e.*, variance is much larger than the mean). In the second model, peritonitis outcome was reported as the time to each peritonitis event and analyzed using an Andersen-Gill model (an extension of the Cox proportional hazards model) for ordered recurrent events. This model allows information on all events to be included but assumes that each event is independent. The Andersen-Gill model determines the association between patient characteristics and the hazard of the occurrence of peritonitis. *A priori* selected variables for inclusion as covariates included age, gender, race, diabetes status, glomerulonephritis as a cause of ESRD, modality before PD start (new to dialysis, transfer from HD, failed transplant), and PD modality (CAPD *versus* APD). To assess for an era effect for each of the variables, we included an interaction term between era and each variable as a method of initial screening. When the interaction was found to be statistically significant, subsequent analyses were performed for each of the two eras. Multivariable negative binomial models were used to assess for differences in the rates of peritonitis caused by specific organism categories among several patient subgroups. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed using SAS 9.1 (SAS Institute, Cary, NC).

Results

The study sample consisted of 4247 incident PD patients, 1605 of whom had 3058 episodes of peritonitis. The remaining 2642 patients had no peritonitis. Of the 3058 peritonitis episodes, 503 were excluded because they occurred within 60 d of a previous episode and were assumed to be recurrent or relapsing events. Consequently, the analyses were carried out on 2555 peritonitis episodes among 4247 patients. The overall peritonitis rate was one episode in 26 patient-months on PD, decreasing to one episode in 33 patient-months after exclusion of recurrent or relapsing events. The median time on PD was 1.37 yr with an interquartile range of 0.62 to 2.43 yr. Of the 4247 patients included in the study, 1445 (34.0%) were still being followed at the end of the data collection period (median follow-up time 2 yr), 18.4% of patients in the cohort died after a median time on PD of 1.31 yr, 27.2% transferred to HD after a median time on PD of 0.93 yr, and 12.2% received transplants after a median time on PD of 1.21 yr. Demographic characteristics of the patients are presented in Table 1.

In the multivariable negative binomial regression model, variables that were independently associated with a higher

Table 1. Patient demographics ($n = 4247$)[a]

Parameter	Value
Age (yr; mean ± SD)	59 ± 16
Male gender (%)	55
Race (%)	
White	82
Black	2
Asian	6
Other	10
Modality (% on CAPD)	
initial	74
most recent	52
Modality before PD start (%)	
new to dialysis	58
transfer from HD	24
failed transplant	3
other/unknown	15
Cause of ESRD	
diabetes	35
hypertension	17
glomerulonephritis	15
cystic kidney disease	5
other	27
Diabetes	40

[a]CAPD, continuous ambulatory peritoneal dialysis; PD, peritoneal dialysis; HD, hemodialysis.

peritonitis rate included age, Black race, and transfer from HD to PD (Table 2). Predictors of a lower peritonitis rate included having glomerulonephritis as the cause of ESRD. The association between use of CAPD *versus* APD and peritonitis was assessed in the subset of 3180 patients who did not switch modalities during their time on PD. In this subgroup, CAPD was not associated with a higher peritonitis rate than APD (rate ratio [RR] 1.03; 95% confidence interval [CI] 0.91 to 1.16; $P = 0.65$).

Similar results were seen using the multivariate Andersen-Gill model. Variables that were associated with a shorter time to peritonitis included age, Black race, and transfer from HD to PD. Having glomerulonephritis as the cause of ESRD was associated with a longer time to peritonitis (Table 2). CAPD was not associated with a shorter time to peritonitis than APD (HR 1.02; 95% CI 0.92 to 1.13; $P = 0.69$).

In both analyses, a significant interaction between gender and diabetes was seen, such that diabetes confers a higher risk for peritonitis in women but not in men ($P = 0.011$ in the negative binomial analysis and $P = 0.002$ in the Andersen-Gill model). The association between diabetes and peritonitis by gender is shown in Table 2.

Initial screening for an era effect for each of the variables revealed that the only significant interaction was for the relationship between age and era ($P = 0.006$), as has previously been reported (10). Specifically, the higher peritonitis risk associated with increasing age was present only among those who initiated dialysis before the year 2001. There was no era effect for any of the other variables in the model.

For each of the variables found to be independently associated with peritonitis, the spectrum of organisms that caused infection was assessed *post hoc*. Specifically, microbial profiles were compared between female patients with diabetes and others, between those who did and did not transfer from HD, and between Black patients and those from other racial backgrounds. Diabetes among women was associated with an increased Gram-positive peritonitis rate, as well as a higher streptococcal peritonitis rate. Patients who transferred from HD to PD also had an increased rate of Gram-positive peritonitis, accounted for by an increased coagulase-negative *Staphylococcus* peritonitis rate. In comparison with other racial groups, Black patients had a higher Gram-positive peritonitis rate, along with a higher *Streptococcus* peritonitis rate. These data are shown in Table 3. RR for peritonitis caused by individual Gram-negative organisms and yeast could not be calculated because of the small number of peritonitis episodes caused by these organisms.

Discussion

Among patients who initiated PD between 1996 and 2005, the predictors of PD peritonitis include Black race, transfer from HD to PD, and diabetes among women. In contrast to several previous studies, we found that choice of CAPD *versus* APD did not influence the peritonitis risk. Furthermore, these results were similar regardless of modeling strategy, suggesting that both rate analyses and time-to-event analyses are comparable analytic tools for studying the occurrence of PD peritonitis.

Before this study using the POET database, the two largest observational studies to have looked at variables that are associated with peritonitis used the US Renal Data System (USRDS) database and the ANZDATA registry. The former analysis included 11,975 patients who were on PD between 1994 and 1997 and identified several important predictors of peritonitis. Unfortunately, as a result of the method of data collection, patients who did not survive their first 9 mo on PD were excluded, as were patients with secondary-pay Medicare insurance or those who were insured by health maintenance organizations. Furthermore, peritonitis episodes that occurred in the first 3 mo on PD were not captured; neither could the database capture whether a patient had one or more peritonitis episodes during the 6-mo entry period. The ANZDATA analysis, which included data on 3162 patients who commenced PD between 1999 and 2003, identified Aboriginal race, obesity, and older age as predictors of peritonitis. Similar to the ANZDATA registry, advantages of the POET database include the multicenter nature of the database, the inclusion of a relatively

Table 2. Multivariable regression models ($n = 2555$ episodes in 4247 patients)[a]

Parameter	Negative Binomial Model			Andersen-Gill Model		
	RR	95% CI	*P*	HR	95% CI	*P*
Age (per decade)	1.04	1.01 to 1.08	0.010	1.03	1.01 to 1.06	0.025
Black	1.37	1.00 to 1.88	0.050	1.47	1.15 to 1.88	0.002
Asian	0.89	0.74 to 1.08	0.240	0.91	0.78 to 1.06	0.230
Diabetes						
female	1.27	1.10 to 1.47	0.001	1.31	1.17 to 1.48	<0.001
male	0.99	0.87 to 1.13	0.880	1.02	0.91 to 1.14	0.750
GN	0.87	0.75 to 1.00	0.050	0.86	0.76 to 0.97	0.015
Transfer from HD	1.24	1.11 to 1.38	<0.001	1.24	1.13 to 1.35	<0.001
Failed transplant	1.27	0.95 to 1.69	0.120	1.18	0.93 to 1.49	0.170
CAPD *versus* APD[b]	1.03	0.91 to 1.16	0.650	1.02	0.92 to 1.13	0.690

[a]APD, automated PD; CI, confidence interval; GN, glomerulonephritis; HR, hazard ratio; RR, rate ratio.
[b]Subgroup of 3180 patients who did not switch between CAPD and APD during their time on PD.

Table 3. Comparison of peritonitis rates for several organism categories among subgroups of patients with higher overall peritonitis rates[a]

Parameter	Female Patients with Diabetes			Transfer from HD			Black		
	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
Gram positive	1.33	1.09 to 1.62	0.005	1.26	1.08 to 1.46	0.003	1.72	1.15 to 2.56	0.010
Gram negative	1.04	0.77 to 1.40	0.780	1.12	0.89 to 1.42	0.350	1.39	0.73 to 2.64	0.320
Culture negative	1.37	1.04 to 1.81	0.027	1.19	0.96 to 1.49	0.120	0.70	0.31 to 1.57	0.390
CNS	1.25	0.95 to 1.63	0.110	1.33	1.09 to 1.62	0.005	1.41	0.80 to 2.47	0.240
Staphylococcus aureus	1.16	0.69 to 1.94	0.580	1.13	0.76 to 1.67	0.540	0.57	0.13 to 2.61	0.470
Streptococcus	1.57	1.06 to 2.32	0.026	1.16	0.84 to 1.60	0.370	2.75	1.35 to 5.59	0.005

[a]CNS, coagulase-negative *Staphylococcus*.

contemporary PD cohort, and the availability of data from the first day of initiation of PD. The availability of microbiology data for each peritonitis episode in the POET database is an additional advantage in that it allowed for further exploration of the basis for the increased risk for each of the identified predictors.

Among the variables that have been linked to peritonitis, the data on age have been conflicting. Whereas increasing age was associated with a higher peritonitis rate in our overall analysis, we previously identified an era effect for age, such that increasing age is associated with peritonitis only among those who initiated PD before 2001 (10). There was, however, no era effect for any of the other predictor variables, suggesting that their association with peritonitis is not related to the year in which the patient initiated PD. The finding that Black race is associated with a greater risk for peritonitis is consistent with previous studies (1,2). The higher proportion of Gram-positive peritonitis in Black patients has not been previously described but should be interpreted with caution given their relatively small number in this study.

The increased peritonitis rate associated with transfer from HD to PD has not been previously reported. We hypothesize that this increased risk may be attributable to two high-risk groups: Those who were "crash starts" on HD with little predialysis care who subsequently chose to transfer to PD, and those who had been on HD for years and had exhausted all vascular access options. For the latter group, the lack of residual renal function at the time of transfer to PD may contribute to their peritonitis risk, because it has been shown that loss of residual renal function is an independent predictor of peritonitis (5). Because we do not have information on dialysis vintage before transfer, we cannot determine with certainty which group of patients accounted for the increased peritonitis risk. Nevertheless, physicians who care for PD patients should be aware of the higher peritonitis rate among those who transfer from HD. The identification of an increased coagulase-negative *Staphylococcus* peritonitis rate in this patient population suggests that more extensive training and more frequent review of technique might be beneficial for these patients.

It is not surprising that diabetes was associated with a higher peritonitis rate, because this has been previously reported (1,4,5); however, in this study, we found for the first time a significant interaction between gender and diabetes, such that the higher peritonitis rate was present only among female patients with diabetes. Although this has not previously been described with respect to peritonitis risk, several large US studies demonstrated a higher incidence of death on PD among women, in particular among female patients with diabetes (17–19). In one study that used USRDS data, Bloembergen *et al.* (17) noted a differential effect of gender on PD outcomes, with women at significantly higher risk for death as a result of infection than men. In a subsequent comparison of PD and HD outcomes by Vonesh *et al.* (18), female patients with diabetes were one of the few subgroups in which PD was associated with a higher risk for death than HD. Furthermore, Collins *et al.* (19) reported a higher risk for all-cause death for female patients who had diabetes and were ≥55 yr of age and on PD as compared with HD. In cause-specific analyses in the latter study, it was found that these patients had a significantly higher risk for infectious death on PD. A smaller single-center study subsequently reported that infection was the second leading cause of death among older women who had diabetes and were on PD (20). Our finding that female patients with diabetes have the highest peritonitis rates therefore suggests that the higher risk for infection-related death in this group may be mediated in part through a higher risk for PD peritonitis.

Several studies have addressed the issue of whether the use of CAPD *versus* APD has an effect on peritonitis risk. The majority of studies have found that CAPD is associated with a higher risk for peritonitis (8,9,11,12), including the only randomized, controlled trial to have studied the relationship between modality and peritonitis risk (11). This has been attributed to the increased number of connections and disconnections that are required relative to cycler-based therapy; however, in the largest observational study to have addressed this question, using USRDS data from 11,975 PD patients, CAPD was associated with a 6% lower risk for peritonitis relative to APD (1). Furthermore, another study of 1205 Scottish PD patients found no difference between CAPD and APD in the risk for peritonitis (13). The apparent inconsistency among these studies may relate in part to the fact that several of the

studies in which CAPD was associated with a higher peritonitis rate included patients who were on PD before the adoption of the improved PD connectology systems, which greatly reduced the risk for contamination at the time of an exchange (21–25). In our study, which included a larger and more contemporary cohort of patients than in most of the previous studies, there was no association between peritonitis and the use of CAPD or APD. These data are reassuring, because they suggest that the choice between CAPD and APD can be guided by patient preference if the patient is capable of performing both modalities.

With regard to the optimal modeling approach to studying the occurrence of peritonitis, there are few comparative data. Most studies have reported either peritonitis rates or time to first peritonitis. Only two studies have compared analytic methods, demonstrating a tight correlation between a peritonitis rate analysis using a negative binomial model and an analysis of time to first peritonitis (3,26). In other words, it was shown that patients with a high peritonitis rate also tended to have a shorter time to their first peritonitis episode. One of the limitations of the analyses of time to peritonitis reported to date is that all studies using this type of modeling have incorporated only time from initiation of dialysis until the first peritonitis episode. In our study, we used an Andersen-Gill model, which allows for modeling of time to peritonitis with the incorporation of multiple events. Using this type of modeling, information on all peritonitis episodes can be included. On the basis of the similar results between the rate and time-to-event analyses in our study, we conclude that both are appropriate analytic methods in the assessment of factors related to peritonitis.

Our study has several limitations. As with most large data sets, the data have not been validated against patient charts. As a result, we have chosen to study only variables that were most likely to have complete and accurate data entry. Although the models incorporated several potentially important demographic characteristics, we did not have data available on biochemical parameters such as serum albumin and residual renal function that might be related to peritonitis. Because we did not have detailed information on all switches between CAPD and APD during a patient's time on PD, we tested the association between the PD modality and peritonitis by performing the analysis in a subgroup of patients who did not switch between CAPD and APD during their time on PD. Despite this, the number of patients in this subgroup was still larger than the majority of studies that tested this association. Finally, it is important to note that there are many factors that influence the choice of CAPD *versus* APD. Although we adjusted for basic patient demographics and diabetes status, we did not adjust for other comorbidities that may have differed between the patient groups; neither could we adjust for nonmedical factors that contributed to modality selection. As a result, we cannot exclude the possibility of residual confounding from variables that were not included in our model.

Conclusions

Our study has identified, for the first time, transfer from HD to PD as an independent risk factor for PD peritonitis. In addition, there was an interaction between diabetes and gender, such that diabetes was associated with a higher peritonitis risk only among female PD patients. In contrast to previous studies, the choice of CAPD *versus* APD did not affect the risk for peritonitis. Finally, we have demonstrated that rate analyses and time-to-event analyses both are appropriate analytic tools to study the occurrence of PD peritonitis.

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