CLINICAL CHARACTERISTICS AND OUTCOMES OF “SILENT” AND “NON-SILENT” PERITONITIS IN PATIENTS ON PERITONEAL DIALYSIS

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◆ **Objectives:** We compared the clinical characteristics and outcomes of “silent” peritonitis (meaning episodes without fever and abdominal pain) and “non-silent” peritonitis in patients on peritoneal dialysis (PD).

◆ **Methods:** Our cohort study collected data about all peritonitis episodes occurring between January 2008 and April 2010. Disease severity score, demographics, and biochemistry and nutrition data were recorded at baseline. Effluent cell counts were examined at regular intervals, and the organisms cultured were examined. Treatment failure was defined as peritonitis-associated death or transfer to hemodialysis.

◆ **Results:** Of 248 episodes of peritonitis occurring in 161 PD patients, 20.9% led to treatment failure. Of the 248 episodes, 51 (20.6%) were not accompanied by fever and abdominal pain. Patients with these silent peritonitis episodes tended to be older ($p = 0.003$). The baseline values for body mass index, triglycerides, and daily energy intake were significantly lower before silent peritonitis episodes than before non-silent episodes ($p = 0.01$, 0.003 , and 0.001 respectively). Although silent peritonitis episodes were more often culture-negative and less often caused by gram-negative organisms, and although they presented with low effluent white cell counts on days 1 and 3, the risk for treatment failure in those episodes was not lower (adjusted odds ratio: 1.33; 95% confidence interval: 0.75 to 2.36; $p = 0.33$).

◆ **Conclusions:** Silent peritonitis is not a rare phenomenon, especially in older patients on PD. Although these episodes were more often culture-negative, silent presentation was not associated with a better outcome.

KEY WORDS: Peritonitis; outcomes.

Peritonitis, a common complication of peritoneal dialysis (PD), contributes to treatment failure, hospitalization, and death. It is important to diagnose PD-associated peritonitis and to initiate empiric antibiotic therapy as early as possible to prevent those serious consequences (1). Peritonitis is defined based on the presentation of symptoms, peritoneal effluent cell count, and culture of micro-organisms. Patients have to recognize their symptoms—including cloudy effluent, fever, and abdominal pain—early in the onset of peritonitis. Awareness of the symptoms of peritonitis is a key precondition for obtaining an effluent cell count and culture to promptly make the diagnosis, especially for patients who live far from the hospital and who cannot easily send dialysate samples to a lab.

In fact, the symptoms of peritonitis vary in severity across the PD population. In pediatric PD patients, disease severity scores (DSSs) at the onset of peritonitis are calculated as a points total for pain and fever (2–5). The range shows that some patients might present with cloudy effluent alone, and some might complain of severe abdominal pain or high fever, or both.

In most PD centers, DSS is not a routine measurement tool for PD-related peritonitis in adults. The DSS range for the adult PD population is not known, but we recognized that abdominal pain and fever might be absent at the onset of some peritonitis episodes. Here, we refer to those peritonitis episodes as “silent” peritonitis episodes. We coined the term silent peritonitis for this phenomenon because patients do not complain of fever or abdominal pain, and yet they have peritonitis. By contrast, we refer to peritonitis episodes with varying extents of fever and abdominal pain as “non-silent” peritonitis.

Because previous studies reported that an absence of fever in bacteremic community-acquired pneumonia

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predicts a worse outcome in elderly individuals (6,7), comparisons of the clinical characteristics and outcomes in silent and non-silent peritonitis in the PD population are of interest. In the present study, we addressed that issue in a single-center cohort of patients presenting with incident episodes of peritonitis. Specifically, we set out to determine the clinical characteristics (including demographics, biochemical and nutrition indices, effluent cell counts, and causative organisms) and final outcomes associated with these two types of peritonitis.

METHODS

SUBJECTS

This cohort study was carried out at the PD center of Peking University First Hospital. The protocol was approved by the Medical Ethical Committee of Peking University, and written informed consent was obtained from each patient.

All consecutive PD patients who presented with PD-associated peritonitis between 1 January 2008 and 30 April 2011 were recruited. All our PD patients had Tenckhoff catheters inserted. All patients were dialyzed with lactate-buffered glucose dialysate, using a twin-bag connection system (Baxter Healthcare, Guangzhou, China). No cyclers were used during the study period. Prophylactic cefazolin was administered before Tenckhoff catheter placement for most patients. (The one exception was a patient who was allergic to the drug.) Before patients and their caregivers were allowed to do exchanges by themselves, they were trained by nurses in the dialysis clinic using a standard initial training program, whose details were published in a previous paper (8).

DIAGNOSIS OF PERITONITIS

All patients attending our center were asked to contact us as soon as possible by emergency call if they experienced cloudy effluent, digestive tract symptoms, fever, or abdominal pain of either undetermined or determined origin.

Each patient had to be assessed by PD nurses and a physician. Peritonitis was defined as the presence of at least two of the following conditions: abdominal pain or tenderness; presence of white blood cells ($100/\text{mm}^3$ or more) in peritoneal effluent, with at least 50% polymorphs; and positive effluent culture results (9). In cases in which abdominal pain or tenderness was absent, cloudy fluid combined with at least one of the latter two conditions was considered diagnostic.

The DSS (range: 0–5 points) was calculated as the sum of points for pain (0, no pain; 1, moderate pain or nausea not requiring specific therapy; 2, severe pain, usually requiring analgesic therapy, or vomiting; and 3, peritoneal pain with tense abdomen or paralytic bowel, or both) and fever (0, $<37.5^\circ\text{C}$; 1, $37.5 - 38.9^\circ\text{C}$; 2, $>38.9^\circ\text{C}$). Episodes of peritonitis without fever and abdominal pain were considered to be silent peritonitis. Episodes of peritonitis with various extents of fever and abdominal pain were considered non-silent peritonitis.

BASIC DEMOGRAPHIC, LABORATORY, AND NUTRITION VARIABLES

Each episode of peritonitis was recorded in a separate database, together with the patient's age, sex, body mass index, diabetes status, previous episodes of peritonitis, and dialysis duration at the time of the peritonitis episode. The most recent biochemical, dialysis adequacy, and nutrition parameters (measured within 3 months of peritonitis onset) were also recorded. Biochemical parameters (serum albumin, prealbumin, hemoglobin, urea nitrogen, creatinine, and serum lipids) were examined using an automatic Hitachi chemistry analyzer (Boehringer Mannheim, Mannheim, Germany). High-sensitivity C-reactive protein in serum was measured by immune rate nephelometric analysis. Dialysis adequacy was calculated by collecting 24-hour dialysate and urine to measure fluid and solute clearances. The weekly total, peritoneal, and renal Kt/V urea; the weekly total, peritoneal, and renal creatinine clearance; and the residual renal function were calculated using standard methods. Peritoneal transport rate was assessed by the dialysis adequacy and transport test and represented as the 24-hour dialysate-to-plasma ratio of creatinine (10), which has been verified as a reliable method in continuous ambulatory PD patients (11).

Lean body mass by the creatinine kinetics method was used to determine muscle protein stores (12,13). A dynamometer was used to evaluate hand-grip strength in both the dominant and the nondominant arm; the measurement was repeated 3 times, and the highest value achieved was recorded in newtons. Total daily protein intake (DPI) and daily energy intake (DEI) were both calculated from 3-day dietary records checked by a skillful dietitian using a computer software program (PD Information Management System: Peritoneal Dialysis Center, Peking University, Beijing, China). Total caloric intakes included intakes from dietary and dialysate sources. The DPI and DEI were normalized to standard body weight.

Patients were instructed to bring the first cloudy effluent to the dialysis center immediately upon peritonitis being suspected. Examination of effluent included cell count, causative micro-organisms, and drug sensitivities. Two aliquots of PD effluent would be sent for cell counts (5 mL in tubes) and bacterial culture (10 mL in blood culture bottles) using the BACTEC system (BD Biosciences, Franklin Lakes, NJ, USA). For each episode of peritonitis, we recorded the initial effluent white blood cell count and then the serial white blood cell counts on scheduled follow-up visits.

TREATMENT AND FOLLOW-UP

Once diagnosed, peritonitis episodes were treated using our center's standard antibiotic protocol, modified from the guidelines (1,9) of the International Society for Peritoneal dialysis (ISPD). In general, initial antimicrobial therapy for peritonitis consisted of intraperitoneal administration of a third-generation cephalosporin plus cefazolin (both administered in a single dose of 1 g daily). Antibiotic treatment was modified once culture results and antimicrobial sensitivities became available. If peritonitis was completely resolved during the first 5 days, the standard duration of antibiotic treatment was 2 weeks for *Staphylococcus epidermidis* infection and culture-negative episodes, and 3 weeks for other bacterial and polymicrobial infections. Routine follow-up visits were scheduled on days 1, 3, 5, 7, 14, and 21 after initiation of treatment. As suggested by the ISPD guidelines (9), patients were switched to hemodialysis and their PD catheters were subsequently removed if they showed a lack of improvement after 7 – 14 days of appropriate antibiotic therapy, if effluent grew yeast species or mycobacteria at any time, or if a clinical tunnel infection was diagnosed at the start of the peritonitis episode.

Treatment success in an episode of PD-associated peritonitis was defined as complete resolution (white blood cell count of less than 100/mm³, and clinical resolution), without the need for Tenckhoff catheter removal. Conversely, treatment failure was defined as death or transfer to hemodialysis because of the peritonitis episode. Death related to peritonitis was defined as the death of a patient with active peritonitis or within 2 weeks of a peritonitis episode (1). We also recorded hospitalization status for each episode and relapses in patients who continued on PD after the first episode. Relapse of peritonitis defined as an episode that occurred within 4 weeks of completion of therapy for a prior episode with the same organism or 1 sterile episode (9).

STATISTICAL ANALYSES

Statistical analyses were performed using the SPSS software application for Windows (version 13.0: SPSS, Chicago, IL, USA). Parametric data are presented as mean $\pm$ standard deviation. Nonparametric data are presented as medians with their intervals from the 25th to the 75th percentile. Categorical variables are expressed as percentages or ratios. The clinical characteristics of silent and non-silent peritonitis episodes were compared using the chi-square test for categorical variables and the Kruskal–Wallis H-test for continuous variables. Multivariate logistic regression models were used to determine whether silent peritonitis was associated with treatment failure, including death and transfer to hemodialysis. The models were adjusted for age, sex, diabetes, duration of PD therapy, effluent white blood cell count on day 3, and causative organisms categorized into indolent organisms (culture-negative, non-*Staphylococcus aureus*, non-*Enterococcus*, and gram-positive infections) and virulent organisms (*S. aureus*, *Enterococcus*, gram-negative, and polymicrobial infections). Odds ratios and 95% confidence intervals were calculated. All probabilities were two-tailed, and the level of significance was set at 0.05.

RESULTS

Between January 2008 and April 2011, 248 episodes of peritonitis occurred in 161 PD patients [65 men (40.4%); 66 with diabetes (41%); mean age: 60.5 $\pm$ 13.4 years]. Table 1 shows the relevant patient and infection data. Of the 161 patients, 111 (68.9%) experienced just 1 episode of peritonitis during the study period. The median duration on PD of patients who presented with peritonitis episodes was 34.8 months (range: 15.7 – 56.4 months). The proportion of gram-positive organisms to total organisms examined was 47.4%. *Staphylococcus* species were the most common gram-positive organisms in our cohort. The proportions of gram-negative, polymicrobial, fungal, mycobacterial, and culture-negative infections to the total organisms examined were 18.5%, 4.3%, 2.6%, 0.4%, and 26.7% respectively.

The median DSSs for the whole cohort and for non-silent peritonitis episodes were both 1 (range: 1 – 2). In 34 patients, 51 peritonitis episodes (20.6%) were not accompanied by fever and abdominal pain (silent peritonitis episodes). No patients in our cohort with silent peritonitis had previously received prednisone or other immunosuppressants. Previous episodes of peritonitis were not significantly different between the groups with silent and non-silent episodes ($p > 0.05$). Table 2

TABLE 1
Clinical Characteristics of the Patients and Organisms
Causing Peritonitis

Variable	Value
Peritonitis episodes (n)	248
Patients (n)	161
Mean age (years)	60.5±13.4
Men [n (%)]	65 (40.4)
With diabetes [n (%)]	66 (41)
Dialysis vintage at onset (months)	
Median	34.8
Range	15.7–56.4
Causative organisms ^a [n (%)]	232 (93.5)
Gram-positive organisms ^b	110 (47.4)
CNS	67 (28.9)
<i>Staphylococcus aureus</i>	4 (1.72)
<i>Streptococcus</i> species	17 (7.33)
<i>Enterococcus</i> species	13 (5.6)
<i>Corynebacterium</i>	5 (2.2)
Others	4 (1.72)
Gram-negative organisms ^b	43 (18.5)
<i>Escherichia coli</i>	26 (11.2)
<i>Acinetobacter</i>	3 (1.3)
<i>Klebsiella</i>	6 (2.6)
<i>Pseudomonas</i>	5 (2.2)
Others	3 (1.3)
Polymicrobial ^b	10 (4.3)
Fungi ^b	6 (2.6)
Mycobacterial ^b	1 (0.4)
Culture-negative ^b	62 (26.7)

CNS = coagulase-negative staphylococci.

^a The causative organisms found in all peritonitis episodes at onset.

^b The proportion of the specific organism to the total causative organisms found at onset.

compares demographic, biochemical, and nutrition parameters between the groups with silent and non-silent peritonitis episodes. Patients with silent peritonitis episodes tended to be older (mean age: 66.0 ± 12.6 years vs 59.9 ± 12.7 years in patients with non-silent peritonitis episodes, $p = 0.003$). The distributions of sex, diabetes status, dialysis vintage, dialysis adequacy, and peritoneal transport rate were not significantly different between the groups ($p > 0.05$). In terms of parameters of nutrition, baseline values for body mass index, triglycerides, and DEI were significantly lower before silent peritonitis episodes than before non-silent peritonitis episodes [body mass index: 22.3 ± 3.6 kg/m² vs 23.9 ± 4.14 kg/m², $p = 0.01$; median triglycerides: 1.32 mmol/L (range: 1.11 – 1.88 mmol/L) vs 1.81 mmol/L (range: 1.25 – 2.93 mmol/L), $p = 0.003$; and mean

DEI: 22.7 ± 4.22 kcal/kg vs 26.3 ± 11.9 kcal/kg, $p = 0.001$]. However, mean or median hemoglobin, serum albumin, lean body mass, DPI, and hand-grip strength were not significantly different between the groups ($p > 0.05$).

The 34 patients with silent peritonitis episodes were further subdivided into two groups: 7 with more than 1 silent peritonitis episode, and 27 with only 1 silent episode. We observed no particular differences in clinical characteristics and biochemical data between those subgroups ($p > 0.05$).

Table 3 compares effluent white cell counts and the distribution of causative organisms in the patients with silent and non-silent peritonitis episodes. On day 1, effluent white cell counts for silent peritonitis episodes were significantly lower than those for non-silent episodes [641/mm³ (range: 179 – 1684/mm³) vs 1750/mm³ (range: 600 – 4000/mm³), $p = 0.002$]. On day 3, the effluent white cell counts for silent peritonitis episodes were also significantly lower than those for non-silent peritonitis episodes [130/mm³ (range: 25 – 1120/mm³) vs 600/mm³ (range: 186 – 1920/mm³), $p = 0.002$]. However, the effluent white cell counts on days 5 and 7 were not significantly different between the groups ($p > 0.05$).

With regard to causative organisms, the proportions of the organisms isolated in peritonitis episodes before antibiotic use were not significantly different between silent and non-silent episodes. The proportion of gram-negative organisms to total organisms isolated in silent peritonitis episodes was significantly lower than that in non-silent episodes (6.52% vs 21.5%, $p = 0.05$). By contrast, the proportion of culture-negative organisms to total organisms isolated in silent peritonitis episodes was significantly higher than that in non-silent peritonitis episodes (45.7% vs 22%, $p = 0.001$). We observed no significant differences in the proportions of gram-positive, polymicrobial, fungal, and mycobacterial isolates between the groups ($p > 0.05$).

In terms of outcomes, the rates of all-cause treatment failure ($p = 0.78$), peritonitis-related death ($p = 0.33$), peritonitis-related transfer to hemodialysis ($p = 0.19$), and hospitalization ($p = 0.41$) were not significantly different between the groups. The relapse rate during follow-up in patients who continued on PD after a first peritonitis episode was also not significantly different between the groups ($p = 0.3$).

The organisms in the peritonitis episodes leading to drop-out in the silent peritonitis group were *Enterococcus* species ($n = 1$), *Corynebacterium* ($n = 1$), *Escherichia coli* ($n = 1$), *Pseudomonas* ($n = 1$), fungi ($n = 1$), culture-negative ($n = 4$), and not examined ($n = 1$). The organisms

TABLE 2
Demographic, Biochemical, and Nutrition Parameters in "Silent" and "Non-Silent" Peritonitis Episodes

Variable	Peritonitis episode group		<i>p</i> Value ^a
	Silent	Non-silent	
Episodes (<i>n</i>)	51	197	
Previous episodes (<i>n</i>)			
Median	0	1	0.29
Range	0–1	0–2	
Mean age (years)	66.0±12.6	59.9±12.7	0.003
Men [<i>n</i> (%)]	19 (37.3)	76 (38.6)	0.86
With diabetes [<i>n</i> (%)]	23 (45.1)	87 (44.2)	0.91
Mean BMI (kg/m ²)	22.3±3.6	23.9±4.14	0.01
Dialysis vintage (months)			
Median	41.1	34.7	0.68
Range	11.6–60.9	15.7–56.2	
Hemoglobin (g/dL)	10.8±2.00	10.5±1.84	0.46
Albumin (g/dL)	34.4±5.50	34.9±5.78	0.79
Prealbumin (g/dL)	270±129	295±123	0.28
C-Reactive protein (mg/L)			
Median	5.86	5.11	0.62
Range	1.35–14.1	1.54–13.5	
Urea nitrogen (mmol/L)	19.2±7.94	19.7±5.69	0.67
Creatinine (μmol/L)	759±304	835±254	0.11
Triglycerides			
Median	1.32	1.81	0.003
Range	1.11–1.88	1.25–2.93	
Total cholesterol			
Median	4.57	4.90	0.97
Range	4.04–5.83	4.19–5.53	
LDL cholesterol			
Median	2.49	2.53	0.07
Range	2.21–3.35	2.07–3.11	
HDL cholesterol			
Median	1.1	0.99	0.22
Range	0.9–1.23	0.82–1.19	
Total Kt/V	1.85±0.43	1.89±0.49	0.71
Total weekly CCr (L/1.73 m ²)	57.3±22.0	58.4±21.4	0.64
RRF (mL/min)	4.09±1.59	4.17±1.53	0.64
24-Hour D/P Cr	0.73±0.18	0.74±0.15	0.65
Lean body mass (kg)	34.4±9.71	36.4±7.95	0.23
Daily protein intake (g/kg)	0.73±0.19	0.76±0.22	0.39
Daily energy intake (kcal/kg)	22.7±4.22	26.3±11.9	0.001
Hand-grip strength (N)			
Left	174±92.8	167±80.2	0.68
Right	201±94.1	192±87.6	0.59

BMI = body mass index; LDL = low-density lipoprotein; HDL = high-density lipoprotein; CCr = creatinine clearance; RRF = residual renal function; D/P Cr = dialysate-to-plasma ratio of creatinine.

^a Boldface type indicates significance for comparisons of the silent with the non-silent group.

in the peritonitis episodes leading to drop-out in the non-silent peritonitis group were coagulase-negative *Staphylococcus* (*n* = 2), *S. aureus* (*n* = 2), *Streptococcus* species (*n* = 1), *Enterococcus* species (*n* = 4), *Corynebacterium*

(*n* = 2), *E. coli* (*n* = 6), *Klebsiella* (*n* = 2), *Pseudomonas* (*n* = 3), fungi (*n* = 5), polymicrobial (*n* = 2), mycobacterial (*n* = 1), culture-negative (*n* = 6), and not examined (*n* = 6). In all drop-out episodes, we observed no significant

TABLE 3
Disease Severity Score, Dialysate White Cell Counts, and Causative Organisms for "Silent" and "Non-Silent" Peritonitis Episodes

Variable	Peritonitis episode group		<i>p</i> Value ^a
	Silent	Non-silent	
Episodes (<i>n</i>)	51	197	—
Disease severity score			
Median	0	1	<0.001
Range	0–0	1–2	
Dialysate white blood cells (<i>n</i> /mm ³)			
Day 1			
Median	641	1750	0.002
Range	179–1684	600–4000	
Day 3			
Median	130	600	0.002
Range	25–1120	186–1920	
Day 5			
Median	39	58	0.15
Range	4–111	10–504	
Day 7			
Median	12	31	0.21
Range	3–44	3–122	
Organisms found [<i>n</i> (%)] ^b	46 (90.2)	186 (94.4)	0.33
Gram-positive organisms ^c	20 (43.5)	90 (48.4)	0.38
Gram-negative organisms ^c	3 (6.52)	40 (21.5)	0.05
Polymicrobial ^c	1 (2.17)	9 (4.84)	0.69
Fungi ^c	1 (2.17)	5 (2.69)	1.00
Mycobacterial ^c	0 (0)	1 (0.54)	1.00
Culture-negative ^c	21 (45.7)	41 (22)	0.001
Outcome events [<i>n</i> (%)]			
Treatment failure ^d	10 (19.6)	42 (21.3)	0.78
Peritonitis-related death ^d	7 (13.7)	18 (9.14)	0.33
Peritonitis-related transfer to HD ^d	3 (5.88)	24 (12.2)	0.19
Hospitalization ^d	13 (25.5)	62 (31.5)	0.41
Relapse ^e	6 (14.6)	34 (21.9)	0.30

HD = hemodialysis.

^a Boldface type indicates significance for comparisons of the silent with the non-silent group.

^b The causative organisms found in all peritonitis episodes at onset.

^c The proportion of the specific organism to the total causative organisms found at onset.

^d The proportion of episodes with specific outcomes to the total episodes.

^e The proportion of relapse episodes to the total episodes in which peritoneal dialysis continued after the first episode.

difference in the combined proportion of *S. aureus*, gram-negative, and polymicrobial infections between the silent and non-silent peritonitis groups ($p > 0.05$).

In the silent peritonitis group, the rates of treatment failure, hospitalization, and relapse were not significantly different between patients with episodes that were culture-negative and culture-positive ($p > 0.05$).

Multiple logistic regressions were performed to examine the association between silent peritonitis episodes and treatment failure. As Table 4 shows, silent peritonitis

did not predict treatment failure after adjustment for age, sex, diabetes, duration of dialysis, effluent white cell count on day 3, and presence of *S. aureus*, gram-negative, or polymicrobial organisms [adjusted odds ratio (OR): 1.33; 95% confidence interval (CI): 0.75 to 2.36; $p = 0.33$]. Dialysis duration and effluent white cell count on day 3 were, independently, significant risk factors for treatment failure: respectively, adjusted OR: 1.021; 95% CI: 1.003 to 1.04; $p = 0.024$; and adjusted OR: 1.036; 95% CI: 1.009 to 1.064; $p = 0.008$. The presence of *S. aureus*,

TABLE 4
Multivariate Logistic Regression Model for Prediction
of Peritonitis Treatment Failure

Variable	Peritonitis treatment failure	
	Adjusted OR (95% CI)	<i>p</i> Value ^a
"Silent" peritonitis	1.33 (0.75 to 2.36)	0.33
Age (per year)	0.99 (0.96 to 1.04)	0.84
Male sex	2.57 (0.81 to 8.23)	0.11
Presence of diabetes	2.67 (0.79 to 8.93)	0.11
Duration of dialysis (per month)	1.021 (1.003 to 1.04)	0.024
Dialysate WBCs on day 3 (per 100/mm ³)	1.036 (1.009 to 1.064)	0.008
Causative organisms		
Group 1 ^b	1.00	NA
Group 2 ^c	1.67 (0.52 to 5.38)	0.33

OR = odds ratio; CI = confidence interval; WBCs = white blood cells.

^a Boldface type indicates significance.

^b Culture negative infections and all infections other than those in group 2.

^c *Staphylococcus aureus*, *Enterococcus*, gram negative, and polymicrobial infections.

Enterococcus, gram-negative, and polymicrobial organisms was not associated with treatment failure (adjusted OR: 1.67; 95% CI: 0.52 to 5.38).

DISCUSSION

In the present study, 20.6% of peritonitis episodes were silent episodes. Patients with silent episodes tended to be older. The silent episodes were not associated with a lower risk for treatment failure even though they presented lower dialysate white cell counts and more culture-negative results. To our knowledge, this study is the first to explore the clinical characteristics and outcomes of so-called silent and non-silent peritonitis episodes.

The DSS, a simple and practical tool, has not routinely been measured by clinicians in adult PD patients at the onset of peritonitis. Despite previous studies in the pediatric PD population showing the association of a higher baseline DSS with more severe causative organisms and worse outcome (3,14), we did not verify a similar link in our adult cohort. As the data show, peritonitis with a DSS

of 0 (silent peritonitis, or the mildest peritonitis) was not associated with a lower effluent white cell count on days 5 and 7. It was not associated with a better peritonitis outcome. Silent peritonitis should therefore not be used in adult PD patients to guide management, including antibiotic use and catheter removal.

In accord with previous studies, the data also indicate that a longer duration on dialysis and prolonged elevation of the effluent white cell count predict treatment failure in peritonitis (15–17). Chow *et al.* (15) noted the superiority of dialysate white cell count on day 3 compared with that on day 1 for predicting the outcome of peritonitis. Krishnan *et al.* (16) also reported that the odds of treatment failure were significantly higher when PD cell counts exceeded 100/mm³ for more than 5 days. Prolonged elevation of effluent white cell counts in the late course of peritonitis actually reflects a poor response to antibiotic treatment and thus predicts worse outcome.

The data show that silent peritonitis is more likely to be culture-negative and less likely to be caused by gram-negative organisms. The distribution of organisms in silent peritonitis tended to be associated with peritonitis outcome in previous studies. As reported by Zurowska *et al.* and Warady *et al.*, initial manifestations of peritonitis were uniformly severe for gram-negative causative organisms (3,14). Gram-negative organisms were more likely to require hospital admission and catheter removal and to result in technique failure (18–21). By comparison, peritonitis that is culture-negative or secondary to coagulase-negative *Staphylococcus* is generally mild-to-moderate in severity (5). Culture-negative peritonitis is associated with a significantly higher rate of cure and lower risks for hospitalization and technique failure (22–24). However, for patients presenting with silent peritonitis episodes, the milder causative organisms did not lead to better outcomes. Whether that finding is associated with lower body mass index, triglycerides, and energy intake in those patients needs to be explored. Given the strong epidemiologic data already showing lower survival with declining body mass index and lower serum lipids in maintenance dialysis patients (25–27), estimation of the health effects of silent peritonitis episodes should take the harmful consequences of deficient energy stores into account. However, we could not draw a conclusion about the relationship between silent peritonitis and malnutrition, given that lean body mass and DPI did not really vary between the silent and non-silent peritonitis groups. More research studies need to be designed to explore whether malnourished PD patients tend to present milder symptoms and fewer organisms.

Under the conditions of silent peritonitis, cloudy dialysate is the primary and unique symptom for diagnosis. Patients and their care providers have to be trained to routinely check for cloudy effluent, especially in dialysis populations that include a preponderance of elderly and diabetic patients, both groups being rapidly on the rise in China (28) and the rest of the world (29–31). Also, older and diabetic dialysis patients tend to have weaker eyesight, impaired functional abilities, and cognitive dysfunction, all of which are often regarded as major difficulties in performing PD. Also, the risk of silent peritonitis in cyclical PD could be even higher, because examination of the effluent is even more difficult. Examination of the drained fluid should therefore be one of the most important aspects covered in the training program (in addition to bag exchange and exit-site care).

The data show that 26.7% of peritonitis episodes were culture-negative, even though the culture method applied at our center is the one recommended by the ISPD (1). That percentage is similar to percentages recently reported by others from the International Pediatric Peritonitis Registry—namely, 31% in the studies by Warady *et al.* (14) and Sutherland *et al.* (4). However, we need to evaluate the culture methods in our lab, with its more than 20% culture-negative episodes, given that 10.9% – 21% culture-negative episodes have been reported in some previous studies (15,16,20,32,33). Also, given that patients with silent peritonitis tend to have a lower burden of organisms in the peritoneal cavity, leading to fewer symptoms, a lower effluent cell count, and more difficulty in culturing organisms, culture techniques that are more sensitive would likely lessen the disparity in culture-negative rates between silent and non-silent episodes.

To the best of our knowledge, the present report, which represents a large cohort of adult PD patients, is the first to set out the clinical characteristics and outcomes of silent peritonitis and the associated implications. The design and rigorous follow-up in the study are also strengths. The demographic characteristics of the patients and the distribution of causative organisms are typical of those previously reported, showing the generalizability of our findings to other PD cohorts elsewhere. The single-center design provides more complete and accurate information than can be attained in studies based on registry data. Finally, the predefined antibiotic protocol was applied in all peritonitis episodes, which precludes selection bias affecting clinical outcome because of varying antibiotic regimens.

Our study has a couple of limitations. First, examination of the immune response in our patients with silent peritonitis could not be acquired, precluding us from

exploring the potential mechanisms for the observed phenomenon. Second, in about 7% of peritonitis episodes, samples for organism culture were not obtained before the use of antibiotics because some patients lived far from the center and were unwilling to send samples, and some patients lacked the knowledge for sample collection. Also, the culture-negative percentage was up to 26.7% in the entire cohort, and it was higher in the silent group than in the non-silent group. However, the rates of treatment failure, hospitalization, and relapse were not different between the culture-positive and culture-negative episodes. Accordingly, the association between silent peritonitis and outcomes might be not influenced by that difference. Also, because the data are observational, no inference can be made about markers of nutrition causing or exacerbating outcomes of silent peritonitis episodes. We also recognize that the relatively small number of episodes with treatment failure in the multivariate model may leave the model underpowered to detect factors significantly associated with treatment failure. We did not preclude that more virulent organisms or other potential risk factors would predict treatment failure if our sample sizes increased.

CONCLUSIONS

Our study found that patients presenting with silent peritonitis tended to be older than those presenting with non-silent peritonitis. Although silent peritonitis is more likely to be culture-negative and less often caused by gram-negative organisms, it was not associated with a better prognosis. These data provide a first-time look at the clinical characteristics and outcomes of silent peritonitis. The data suggest that we have to strengthen training on examination of the effluent, especially for older patients on PD. Further explorations of the potential mechanisms of silent peritonitis and of its clinical consequences are also of interest. It is not possible to identify, at presentation, cases of peritonitis that are likely to result in drop-out from PD therapy. Clinicians should continue to rely on effluent cell counts and organism cultures to evaluate final outcomes.

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DISCLOSURES

The authors have no financial conflicts of interest to declare.

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