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Original Article

Microbiology of peritoneal dialysis-related infection and factors of refractory peritoneal dialysis related peritonitis: A ten-year single-center study in Taiwan

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Abstract *Background:* Peritoneal dialysis (PD)-related infection is a serious complication of patients with PD. Refractory peritonitis may lead to failure of PD, shift to hemodialysis (HD) or death. Besides, microbiologic resistance increased worldwide that might impact the treatment choice for such infections. Investigating the causative pathogens and risk factors of PD-related infections in Taiwan was warranted.
Methods: This is a retrospective study involving patients with PD from 2007 to 2016 in a southern Taiwan hospital. Patient characteristics, microbiological data, outcomes, and factors associated with refractory peritonitis were analyzed.
Results: There were 190 episodes of PD-related peritonitis in 110 patients from this cohort. Gram-positive organisms were the leading cause of PD-related peritonitis, but gram-negative

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organisms, esp. *Pseudomonas aeruginosa*, were predominant for exit site infection and tunnel infection. The incidence of peritonitis was 0.25 episode per patient-year (1 episode per 47.69 months). The refractory rate was 14.2% (27/190). Methicillin resistance was noted in 2 (13.3%) of 15 *Staphylococcus aureus* isolates. Of 114 isolates, 72.8% (83) were susceptible to either cefazolin or gentamicin. *Staphylococcus* spp. and *Escherichia coli* infections were significantly associated with refractory peritonitis. Baseline hyponatremia (<130 mmol/L) was independently associated with refractory peritonitis.

Conclusion: Gram-positive organisms remained major cause of PD-related peritonitis. About three quarters of causative pathogens were susceptible to the recommended empirical treatment for PD-related peritonitis. Baseline hyponatremia (<130 mmol/L) was independently associated with refractory peritonitis. *Staphylococcus* spp. and *E. coli* infections had important roles for refractory peritonitis.

Introduction

Peritoneal dialysis (PD)-related infections, such as peritonitis, exit-site infection, and tunnel infection, are serious complications to patients with PD.[1] These complications may lead to technique failure, ultrafiltration failure and inadequacy which forced PD patients to transfer to HD, significant morbidity, and even mortality.[2,3] The source of PD-related infections included periluminal or intraluminal contamination, bacterial translocation from the bowel or vagina, and hematogenous dissemination.[4] Factors associated with PD-related peritonitis included old age, smoking, obesity, diabetes, hypoalbuminemia, hypokalemia, absence of vitamin D supplement, poor training, previous exit-site infection and previous peritonitis episodes.[1] The most common microbial cause of PD-associated peritonitis is gram-positive pathogen.[5,6] However, gram-negative pathogens, especially *Pseudomonas aeruginosa* and fungi, are associated with prolonged infection, worse outcomes, and more PD failure.[6–8] However, the causative pathogens of PD-related infections in Taiwan were rarely reported.[9]

Even when properly treated, approximately 20% of all PD-related peritonitis episodes are refractory to treatment and thus, even with the reduction observed in the last decades in the incidence of peritonitis, is still the main cause of drop-out.[10] Severe, refractory and prolonged peritonitis may lead to structural and functional alterations of the peritoneal membrane and even encapsulating peritoneal sclerosis, a rare but devastating complication of long-term PD.[1,11] In the literature, old age, higher C-reactive protein (CRP), gram-negative pathogen infection, viridans streptococci infection, underlying connective tissue disease, and history of peritonitis were related to refractory PD-related peritonitis.[12,13] To our knowledge, there were few studies to reveal the association between microbiology, treatment, and refractory PD-related peritonitis in Taiwan. Herein we aimed to investigate the incidence of PD-related infections, the microbiology trend of PD-related peritonitis, and risk factors of refractory peritonitis in a 10-year cohort from a medical center in Taiwan.

Methods

Study design

The retrospective study was conducted in a 1600-bed medical center in Taiwan after the approval of Institutional Review Board [KMUHIRB-E(I)-20180028]. This study included patients aged ≧18 years who were receiving PD and had treatment for PD-related infection in a medical center in southern Taiwan between January 1, 2007, and December 31, 2016.

Patients

From January 2007 to December 2016, 336 patients received PD in this hospital. These patients received Tenckhoff catheter implantation by open surgery (n = 333) or laparoscopic surgery (n = 2). Only one patient had stepwise initiation of peritoneal dialysis (SIPD). First-generation cephalosporins as prophylactic antibiotics were administrated before operation in all the patients. Patient training was started soon after Tenckhoff catheter implantation, followed by annual training and retraining after each peritonitis episode. No routine screening was conducted for nasal *Staphylococcus aureus* colonization. Catheter wound care was performed by the patient or their caregiver using clean dressing with aqueous povidone-iodine and normal saline. There was no routine wound care with topical mupirocin or gentamicin cream or ointment. The patients will have monthly follow-up of serum biochemistry data such as albumin, sodium, and potassium. Iron profiles, uric acid, serum calcium, and phosphate were followed every 3 months. When the patient reported symptoms associated with peritonitis, such as cloudy dialysate, abdominal pain, or fever, peritoneal dialysate was collected and analyzed. Dialysate was cultured, if there was elevated leukocyte count (>100 cells/μL) or polymorphonuclear neutrophil predominance in the dialysate effluent. Empirical intraperitoneal antibiotic was administrated soon after culture collection. The choice of antimicrobial agent was at the discretion of attending clinicians.

The patients were followed up 2—7 days after the first antibiotic dose. Hospitalization was suggested in those with high fever and toxic signs, severe abdominal pain, and fluid overload. Dialysate cultures and fluid analysis were repeated if there was no clinical improvement after antibiotic treatment for 5 days.

Definitions

Peritonitis episodes were classified as refractory and non-refractory based on the definition in the 2016 International Society for Peritoneal Dialysis (ISPD) guideline.[11] Refractory peritonitis was defined as the failure of the dialysate effluent to be clear after 5 days of appropriate antibiotic treatment.[11] Outcomes of peritonitis episodes were classified as cures (*i.e.*, recovery from peritonitis and continuation of PD) or drop-outs (transfer to hemodialysis or death).

Data collection

Data were collected retrospectively from medical charts and daily records from our PD center. Baseline patient data included age, sex, body weight, height, PD modality (continuous ambulatory PD or automated PD), underlying disease, date of starting PD, and date of PD catheter implantation. The biochemistry data within 3 months before the infection episode including complete blood count, serum albumin, protein, sodium, potassium, phosphate, and iron profiles, based on the routine follow-up schedule mentioned above, were collected. Dialysate analysis on the first day of treatment (including cell count and differential count), first reported symptoms, initial and follow-up antibiotic regimen, dialysate culture result, and antibiotic susceptibility test result were also recorded. Peritonitis episodes caused by 2 or more pathogens were regarded as polymicrobial infections. In the episodes of bacterial peritonitis, only monomicrobial infections were included for in the analysis of causative pathogens of refractory and non-refractory peritonitis. First empirical antibiotic regimens and drug susceptibility test were recorded to determine whether the initial treatment is adequate. Antibiotic susceptibility test (AST) results of gentamicin, amikacin, cefazolin, third-generation cephalosporins (ceftriaxone or ceftazidime), and fluoroquinolones (ciprofloxacin or levofloxacin) were recorded.

Statistical analyses

Study results were expressed as frequencies and percentages for categorical variables, and means ± standard deviations or data ranges for continuous variables. The baseline patient characteristics were analyzed using the Pearson chi-square test and Fisher exact test. Risk factors of refractory peritonitis were analyzed using univariate and multivariate logistic regression analyses. A p value of $\leqq 0.05$ was thought to be significant. Variants with a p value of $\leqq 0.1$ will be included in multivariate analysis. Data were analyzed using SPSS Statistics version 24 for Windows (IBM, New York, U.S.).

Results

From January 2007 to December 2016, 336 patients received PD in this hospital. There were fifty episodes of exit-site infection and thirty-three episodes of tunnel infection. A total of 190 peritonitis episodes occurred in 110 (33%) patients. Among them, 14.2% (27/190) were refractory peritonitis. The incidence of peritonitis was 0.25 episodes per patient-year (1 episode per 47.69 months).

Microbiology and antibiotic susceptibility tests of peritonitis

The pathogen distribution of exit-site infection, tunnel infection, and peritonitis was listed in Table 1. Causative pathogens were identified in 73.7% (140 episodes) in this cohort, and of them monomicrobial episodes accounts for 92.1% (129 episodes). There were 6 fungal peritonitis episodes and 3 episodes due to mycobacteria (one *Mycobacterium tuberculosis* complex and two *Mycobacterium abscessus*). *P. aeruginosa* was the most common pathogen for both exit-site and tunnel infections. Gram-positive pathogens were more common than Gram-negative pathogens in peritonitis cases. There were 15 episodes due to *S. aureus*, and 2 episodes were caused by methicillin-resistant *S. aureus* (MRSA). With analysis of the pathogens and the occurrence of refractory peritonitis, *Staphylococcus* spp. and *Escherichia coli* infections were significantly associated with refractory peritonitis (Table 2).

The available susceptibility data of all isolated pathogens were presented in Table 3. All gram-positive organisms were susceptible to vancomycin and all gram-negative organisms susceptible to amikacin. However, in coagulase-negative staphylococci, methicillin susceptible rate was 41.5% (17 of 41 isolates). In gram-negative organisms with available ASTs, 63.3% (19 of 30) were susceptible to cefazolin, 88.6% (39 of 44) gentamicin. Of all bacteria, 72.8% (83 of 114) were susceptible to either cefazolin or gentamicin. The trends in antimicrobial susceptibility of the first and last 5 years of the study revealed no significant change of antimicrobial resistance in the two periods (Table S1).

Patient characteristics and clinical symptoms

The mean age of patients with PD-related peritonitis was 51.26 ± 13.24 years and the mean Karnofsky score (±standard deviation) was 92.28 (±13.3). Among 110 patients with peritonitis, 68 (62%) were female, and 95 (86.4%) received continuous ambulatory PD (CAPD). Concomitant exit-site or tunnel infections were not associated with refractory peritonitis in the study.

The characteristics of patients with refractory and non-refractory PD-related peritonitis were presented in Table 4. Patients being male, with diabetes mellitus, automated PD (APD), higher baseline ferritin levels, baseline serum sodium level less than 130 mmol/L, initial higher platelet counts (>250000/mL) were related to refractory peritonitis in the univariate analysis. Turbid dialysates were more common in the non-refractory group than refractory group

Table 1 Organisms isolated from patients with peritonitis, exit-site infection, and tunnel infection.

Organisms	Peritonitis, n = 190	Exit-site infection, n = 50	Tunnel infection, n = 33
No growth	50 (26.3%)	2 (4%)	4 (12.1%)
Gram-positive pathogens	100 (52.6%)	16 (32%)	12 (36.4%)
Staphylococcus aureus	15 (7.9%)	10 (20%)	8 (24.2%)
Methicillin resistance	2 (1%)	0	3 (9.1%)
Coagulase-negative staphylococci	33 (17.4%)	5 (10%)	2 (6%)
Methicillin resistance	19 (10%)	0	1 (3%)
Streptococci	30 (15.8%)	1 (2%)	0
Enterococci	7 (3.7%)	0	0
Other gram-positive organisms	9 (4.7%)	0	2 (6.1%)
Gram-negative	40 (21.1%)	32 (64%)	14 (42.4%)
Escherichia coli	12 (6.3%)	3 (6%)	0
Klebsiella species	5 (2.6%)	3 (6%)	1 (3%)
Pseudomonas aeruginosa	8 (4.2%)	20 (40%)	12 (36.4%)
Enterobacter cloacae complex	1 (0.5%)	3 (6%)	0
Acinetobacter baumannii complex	1 (0.5%)	0	0
Other GNB	3 (1.6%)	3 (6%)	1 (3%)
Candida species	3 (1.6%)	0	0
Aspergillus species	2 (1%)	0	0
Mycobacterium	3 (1.6%)	0	0
Polymicrobial infection	11 (5.8%)	0	3 (9.1%)

(93.9% *vs.* 85.2%, p = 0.003). Other symptoms, including fever, abdominal pain, nausea, and diarrhea, were similarly noted in two groups. In the multivariate analysis, only baseline hyponatremia (<130 mmol/L) was independently associated with refractory peritonitis (Table 5).

Treatment and outcomes

The empirical intraperitoneal and parenteral antimicrobial regimens did not impact the chance of refractory PD-related peritonitis. Compared to the non-refractory

Table 2 Microbiology of refractory and non-refractory peritoneal dialysis-related peritonitis[a].

Pathogens	Non-refractory n = 163 (%)	Refractory n = 27 (%)	*p* value
Polymicrobial infection	11 (6.7%)	0	0.369[a]
Gram-positive pathogens	81 (49.7%)	19 (70.4%)	0.046
Staphylococci	34 (20.9%)	14 (51.9%)	0.001
Staphylococcus aureus	5 (3.1%)	10 (37%)	<0.001
Methicillin resistance	2 (1.2%)	0	1[a]
Coagulase-negative staphylococci	29 (17.8%)	4 (14.8%)	1[a]
Methicillin resistance	19 (11.7%)	0	0.081[a]
Streptococci	25 (15.3%)	5 (18.5)	0.775
Viridans streptococci	21 (12.9%)	4 (14.8%)	0.761[a]
Enterococci	7 (4.3%)	0	0.596[a]
Other gram-positive pathogens	9 (5.5%)	0	0.363
Gram-negative pathogens	32 (19.6%)	8 (29.6%)	0.306
Escherichia coli	7 (4.3%)	5 (18.5%)	0.005
Pseudomonas aeruginosa	6 (3.4%)	2 (7.4%)	0.318[a]
Klebsiella species	5 (3.1%)	0	1
Enterobacter cloacae complex	1 (0.6%)	0	1
Acinetobacter baumannii complex	1 (0.6%)	0	1
Other gram-negative pathogens	2 (1.2%)	1 (3.7%)	0.37[a]
Fungi[b]	6 (3.4%)	0	0.597[a]
Mycobacterium[c]	3 (1.8%)	0	1

[a] Fisher's exact test.
[b] Included 1 co-infection with gram-negative bacteria.
[c] Included 1 co-infection with gram-negative bacteria.

Table 3 Susceptibility of peritonitis-causing bacteria with available susceptibility results[a].

Bacteria	Cefazolin	Gentamicin	Penicillin	Oxacillin	3rd-generation cephalosporins[d]	Fluoroquinolones[e]
Gram-positive pathogens						
Staphylococcus aureus	10/11 (90.9%)		4/15 (26.7%)	13/15 (86.7%)		13/14 (92.9%)
Coagulase-negative staphylococci	13/26 (50%)		6/41 (14.6%)	17/41 (41.5%)	1/2 (50%)	27/38 (71.1%)
Streptococci			30/33 (90.9%)		31/31 (100%)	6/6 (100%)
Enterococci[b]			3/11 (27.3%)			10/12 (83.3%)
Other gram-positive organisms			2/2 (100%)			
Gram-negative pathogens						
Escherichia coli	14/17 (82.4%)	15/17 (88.2%)			14/17 (82.4%)	14/17 (82.4%)
Klebsiella species	5/8 (62.5%)	8/8 (100%)			8/9 (88.9%)	7/7 (100%)
Pseudomonas aeruginosa		8/10 (80%)			9/10 (90%)	8/10 (80%)
Enterobacter cloacae complex	0	2/2 (100%)			1/2 (50%)	2/2 (100%)
Acinetobacter species[c]	0	3/3 (100%)			1/3 (33.3%)	3/3 (100%)
Other gram-negative bacilli	0	3/4 (75%)			3/4 (75%)	4/4 (100%)

[a] Data are presented as susceptible/total tested isolate numbers (susceptibility percentages of available results). All gram-positive organisms were susceptible to vancomycin and all gram-negative organisms susceptible to amikacin.
[b] One enterococcal isolate was susceptible to ampicillin and was not counted as a penicillin-susceptible isolate.
[c] Two isolates of *Acinetobacter baumannii* complex, one *Acinetobacter lwoffii*.
[d] Ceftriaxone for gram-positive organisms and ceftazidime for gram-negative organisms.
[e] Levofloxacin or ciprofloxacin.

group, the admission, drop-out, or catheter-removal rate was significantly higher in the refractory group (Table 6). After exclusion of three mycobacterial episodes, which were regarded as outliners, the duration of treatment was significantly longer in the refractory group ($p < 0.001$). With further analysis of the pathogens and the outcomes (Table S2), *S. aureus* infections were related to more likely to be hospitalized, longer duration treatment and hospitalization when compared to peritonitis episodes due to pathogens other than *S. aureus*. None of the other bacterial pathogens was significantly associated with hospitalization and longer duration of hospitalization (data not shown).

Discussion

We presented epidemiologic data of PD-related infections, including peritonitis, exit-site infections, and tunnel infections in a Taiwan medical center in 10 years. The overall incidence rate of PD-related peritonitis was 0.25 episode per patient-year at risk, which is no more than the 0.5 episode per patient-year standard of ISPD peritonitis recommendations.[11] Monomicrobial episodes, esp. those due to coagulase-negative staphylococci and *S. aureus*, predominated for PD-related peritonitis. Among gram-negative pathogens, *E. coli* was the most common pathogen, followed by *P. aeruginosa* and *Klebsiella pneumoniae*. Such results of the predominance of gram-positive bacteria were similar to the studies in America, Canada, Scotland, and Hong Kong, in which gram-positive bacteria accounted for up to 66% of causative pathogens of peritonitis.[6,14–16]

In this study, more than 70% of the isolates with available ASTs were susceptible to either cefazolin or gentamicin that supported the empirical regimen for PD-related peritonitis recommended by ISPD, first-generation cephalosporin and gentamicin.[11] In current study, methicillin resistance rate, 13.3%, was low among 15 *S. aureus* isolates, in accordance with the reports from northern Taiwan (11.5%)[12] and Canada (11.1%).[14] Our results and the northern Taiwan report[12] suggested to have no need to use glycopeptides empirically for PD-related peritonitis in Taiwan.

As for *P. aeruginosa*, they were typically associated with concomitant exit-site or tunnel infection and linked to worse outcomes.[10] Removal of PD catheter was usually suggested for PD-related *P. aeruginosa* infections.[10] Of 10 *P. aeruginosa* isolates causing mono- and polymicrobial episodes, there were nine isolates susceptible to ceftazidime. In a recent study in Taiwan, Liu et al. reported that only 10% of 892 *P. aeruginosa* isolates had reduced susceptibility to ceftazidime (minimum inhibitory concentration, MIC $\geqq$ 8).[17] Though the *P. aeruginosa* isolate number is small, the proportion of non-susceptible in this study is close to that presented in Liu's study.[17] Our results supported ceftazidime could be an option when the empirical gentamicin for Gram-negative bacteria did not reveal clinical improvement.

In spite of adequate treatment, refractory peritonitis was the main cause of drop-out from PD in literature.[10] In current study, the refractory rate was 14.2%, and refractory peritonitis was common in *Staphylococcus* species and *E. coli* infections. Multivariate analysis of host factors revealed that only baseline hyponatremia (<130 mmol/L) was independently associated with refractory peritonitis. Our results alert clinicians to closely monitor the cases of PD-related peritonitis due to *Staphylococcus* spp. or *E. coli* and those with hyponatremia.

Table 4 Patient characteristics of refractory and non-refractory peritoneal dialysis (PD)-related peritonitis[a].

Clinical variables	Non-refractory n = 163 (%)	Refractory n = 27 (%)	*p* value
Female gender	118 (72.4%)	14 (51.9%)	0.032
Age (year)	52.28 ± 12.94	51.11 ± 1.03	0.659
Body weight (kg)	57.14 ± 11.66	60.7 ± 12.99	0.191
Body mass index	22.59 ± 3.49	23.68 ± 3.81	0.188
Karnofsky score	93.14 ± 11.56	92 ± 12.91	0.654
Months after initiating PD	49.14 ± 43.6	60.91 ± 51.98	0.208
Months after implanting PD catheter	48.73 ± 38.75	62.56 ± 51.43	0.105
PD modality			0.033
Continuous ambulatory peritoneal dialysis	149 (91.4%)	21 (77.8%)	
Automated peritoneal dialysis	14 (8.6%)	6 (22.2%)	
Underlying disease			
Diabetes mellitus	20 (12.3%)	8 (29.6%)	0.018
Hypertension	95 (58.3%)	14 (51.9%)	0.531
Heart failure	9 (5.5%)	0	0.363[b]
Coronary artery disease	5 (3.1%)	0	1[b]
Cerebral vascular disease	4 (2.5%)	0	1[b]
Chronic liver disease	9 (5.5%)	1 (3.7%)	1[b]
Malignancy	1 (0.6%)	1 (3.7%)	0.265[b]
Tuberculosis	1 (0.6%)	0	1[b]
Gout	25 (15.3%)	1 (3.7%)	0.134[b]
Autoimmune disease	19 (11.7%)	0	0.081[b]
Other[c]	21 (12.9%)	2 (7.4%)	0.540[b]
Laboratory data on infection onset			
Cell counts in dialysate effluent (cells/uL)	2467.45 (1–26,200)	3965.37 (90–13,392)	0.148
WBC (x1,000 cells/mL)	10.05 ± 4.11	11.88 ± 6.69	0.056
Hemoglobin (g/dL)	9.86 ± 1.9	9.53 ± 1.59	0.400
Platelet (x1,000/mL)	210.74 ± 68.48	250.52 ± 99.29	0.01
Platelet >250,000/mL	43 (26.4%)	12 (44.4%)	0.055
Baseline serum biochemistry data			
Blood urea nitrogen (mg/dL)	66.97 ± 17.85	70.5 ± 34.88	0.420
Creatinine (mg/dL)	10.4 ± 2.47	10.61 ± 3.13	0.694
Protein (mg/dL)	7.04 ± 0.69	7.06 ± 0.86	0.909
Albumin (mg/dL)	3.75 ± 0.47	3.58 ± 0.52	0.102
Phosphate (mg/dL)	4.84 ± 1.13	4.96 ± 1.45	0.623
Sodium (mmol/L)	134.65 ± 4.8	132.84 ± 4.45	0.068
Sodium <130 mmol/L	25 (13.3%)	9 (33.3%)	0.024
Potassium (mmol/L)	3.99 ± 2.82	3.76 ± 0.87	0.680
Uric acid (mg/dL)	6.33 ± 1.11	6.78 ± 1.49	0.066
Iron (ug/dL)	70.12 ± 32.45	74.41 ± 54.54	0.571
Ferritin (ng/mL)	440 ± 368.48	601 ± 518.65	0.05
Feritin >500 ng/mL	50 (31.1%)	13 (48.1%)	0.081
Initial symptoms and signs			
Turbid dialysate fluid	153 (93.9%)	23 (85.2%)	0.003
Abdominal pain	115 (70.6%)	22 (81.5%)	0.252
Fever	72 (44.2%)	11 (40.7%)	0.674
Diarrhea	31 (19%)	6 (22.2%)	0.707
Nausea	28 (17.2%)	7 (25.9%)	0.305
Concurrent bacteremia	2 (1.2%)	1 (3.7%)	0.380[b]

[a] Data were presented as number (%), mean ± standard deviation, or medium (range).
[b] Fisher's exact test.
[c] Patients with underlying disease other than diabetes, hypertension, heart failure, coronary artery disease, cerebral vascular disease, chronic liver disease, malignancy, tuberculosis, gout, or autoimmune disease.

Table 5 Multivariate analysis of risk factors associated with refractory peritoneal dialysis-related peritonitis.

Variables	OR	95% CI	*p* value
Gender (male)	1.75	0.62–4.78	0.280
Continuous ambulatory peritoneal dialysis	2.36	0.62–7.94	0.180
Diabetes mellitus	2.37	0.69–7.70	0.155
Laboratory data on first day of infection			
White blood cell >10,000/mL	0.86	0.32–2.23	0.758
Platelet >250,000/mL	1.54	0.54–4.13	0.400
Baseline laboratory data			
Serum sodium < 130 mmol/L	2.79	0.98–7.64	0.048
Serum uric acid > 7 mg/dL	1.20	0.42–3.25	0.730
Serum ferritin >500 ng/mL	2.12	0.80–5.66	0.129
Turbid dialysate effluent	0.26	0.03–2.04	0.200

OR = odds ratio; CI = confidence interval.

Table 6 Outcomes of refractory and non-refractory peritoneal dialysis-related peritonitis.

Clinical outcomes	Non-refractory (n = 163)	Refractory (n = 27)	*p* value
Treatment duration (median days)	14 (6–235)	30 (7–71)	0.152
Treatment duration[a] (median days)	14 (6–125)	30 (7–71)	<0.001
Days of admission (median days)	6 (1–235)	14 (4–56)	0.579
Concomitant exit-site or tunnel infection	9 (6.3%)	1 (5%)	1[b]
Hospitalization	79 (48.5%)	22 (81.5%)	0.001
Drop-out from peritoneal dialysis	8 (5.3%)	9 (34.6%)	0.002
Removal of peritoneal dialysis catheter[c]	13 (8%)	5 (18.5%)	0.029

[a] Excluding mycobacterial episodes.
[b] Fisher's exact test.
[c] Percentage of all refractory or non-refractory peritonitis patients.

Most exit site infections were caused by gram-positive bacteria, among them, most were *Staphylococcus* species. Of gram-negative pathogens, *P. aeruginosa* and *E. coli* were the majority in literature.[18] Kuo et al. presented a study of 115 patients with exit site infections in the period from 1995 to 2008 in Taiwan.[9] The patients were instructed to perform daily wound care with normal saline wash followed by the application of povidone-iodine to the skin surface around the exit sites, as our outpatients. However, they found gram-positive pathogens, mainly *S. aureus* and *Staphylococcus epidermidis*, accounted for 80.4% of 240 pathogens from 212 episodes, and gram-negative pathogens, mainly *P. aeruginosa*, *E. coli*, and *K. pneumoniae*, accounted for 18.8%. In another study from Chen et al., 31% of MRSA associated infections were from skin and soft tissue infection.[19] Different from the above reports, we observed that most of our exit site infections were caused by gram negative infections. *P. aeruginosa* was the most common pathogen, followed by *S. aureus*, coagulase-negative staphylococci in the study. We speculated inadequately preserved normal saline might be the source, since normal saline bottle could be contaminated after wound care. *P. aeruginosa* can be found in not only high-nutrient (copiotrophic), but also low-nutrient or oligotrophic environments (saline solutions).[20,21] Further microbiological studies are warranted to identify the source of *P. aeruginosa* in clinical settings for peritoneal dialysis.

Conclusion

In PD-related peritonitis, gram-positive cocci were major pathogens, and *E. coli* was the most common gram-negative pathogen. About three quarters of causative pathogens were susceptible to empirical antimicrobial regimens (cefazolin and gentamicin) recommended by ISPD for PD-related peritonitis. *Staphylococcus* spp. and *E. coli* infections were significantly associated with refractory peritonitis. Lower baseline serum sodium level (<130 mmol/L) was independently associated with refractory peritonitis.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2018.10.013.