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Peritoneal dialysis related peritonitis; a single center results

Peritonitis relacionada con la diálisis peritoneal; resultados de un solo centro

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ABSTRACT

Introduction: Peritoneal dialysis (PD) related peritonitis is one of the most serious complications which leads to technical failure, transfer to hemodialysis and mortality. **Objective:** We aimed to evaluate peritonitis rate, clinical outcome, and mortality in PD patients' 10-year follow-up. **Methods:** PD-related peritonitis period of 2009 to 2018 were analyzed, retrospectively. Demographic features, causative microorganism, antibiotic resistance, and biochemical parameters were obtained from hospital records. Catheter removal, mortality and peritonitis rate results were evaluated. **Results:** A total of 80 PD-related peritonitis was detected. The overall peritonitis rate was 0.24 episode/year, annually was ranging from 0.14 to 0.53. Gram-positive, gram-negative and culture negative peritonitis rate was 58.8%, 21.3%, %18.8, respectively. Coagulase negative staphylococcus (30%) was the most common causative microorganism and 37.5% of them were methicillin-resistant, while 100% of Staphylococcus aureus were sensitive to methicillin. Peritoneal effluent leukocyte count at admission was significantly higher in gram-negative than gram-positive peritonitis. Peritonitis-associated catheter removal and mortality rate were 26.25% and 6.25%, respectively. C-reactive protein 0th and 3rd day, peritoneal effluent leukocytes and neutrophils 3rd day count were significantly higher and total protein and albumin 0th and 3rd day results were significantly lower in catheter removed patients. The catheter removal was significantly higher in female patients and in gram-negative peritonitis. It was found that decrease in 1g/dL of albumin increases the probability of catheter removal by 13.8 fold. **Conclusion:** Catheter removal was slightly elevated at our center. Catheter loss was associated with female gender, gram-negative strains, and hypoalbuminemia in PD-related peritonitis.

KEYWORDS: peritoneal dialysis; peritonitis rate; catheter removal; mortality; gram stain

RESUMEN

Introducción: La peritonitis relacionada con la diálisis peritoneal (DP) es una de las complicaciones más graves que conduce al fracaso técnico, el traslado a hemodiálisis y la mortalidad. **Objetivo:** Nuestro objetivo fue evaluar la tasa de peritonitis, el resultado clínico y la mortalidad en el seguimiento de 10 años de los pacientes con DP. **Material y métodos:** Se analizaron las peritonitis relacionadas con DP en el periodo 2009 a 2018. Las características demográficas, los microorganismos causantes, la resistencia a los antibióticos y los parámetros bioquímicos se obtuvieron de los registros hospitalarios. Se evaluaron los resultados de la extracción del catéter, la mortalidad y la tasa de peritonitis. **Resultados:** Se detectó un total de 80 peritonitis relacionadas con la DP. La tasa global de peritonitis fue de 0,24 episodios/

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año, oscilando anualmente entre 0,14 y 0,53. La tasa de peritonitis por gram positivos, gram negativos y cultivos negativos fue de 58,8%, 21,3% y 18,8%, respectivamente. El Staphylococcus coagulasa negativo (30%) fue el microorganismo causante más común y el 37,5% de ellos fue resistente a la meticilina. El 100% de Staphylococcus aureus fue sensible a la meticilina. El recuento de leucocitos del efluente peritoneal en la admisión fue significativamente mayor en la peritonitis por gram negativos que por gram positivos. La tasa de retirada del catéter asociada a peritonitis y de mortalidad fue de 26,25% y 6,25%, respectivamente. La Proteína C reactiva entre el día 0 y el 3 ° día y el recuento de leucocitos y neutrófilos en los efluentes peritoneales al 3° día fueron significativamente más altos y los resultados de proteína total y albúmina entre los días 0 al 3 fueron significativamente más bajos en pacientes de retirada del catéter. La retirada del catéter fue significativamente mayor en pacientes femeninas y en peritonitis por gérmenes gram negativos. Se encontró que la disminución de 1 g/dL de albúmina aumenta la probabilidad de extracción del catéter en 13,8 veces. **Conclusión:** La remoción de catéteres fue ligeramente elevada en nuestro centro. La pérdida del catéter se asoció con el sexo femenino, cepas gramnegativas e hipoalbuminemia en la peritonitis relacionada con la DP.

PALABRAS CLAVE: diálisis peritoneal; tasa de peritonitis; retirada del catéter; mortalidad; tinción de Gram

INTRODUCTION

Peritoneal dialysis (PD) is a method of renal replacement therapy used by approximately 200,000 patients worldwide.[1] All dialysis treatments in end stage renal disease patients involve a certain risk of infection due to reduced immune defense and increased potential for microbial contamination related to dialysis techniques.[2-4] Peritonitis is the most common type of infection associated with PD treatment. PD-related infectious complications may result in significant morbidity such as hospitalization, dialysis failure, catheter loss, sclerosing encapsulating peritonitis, severe pain, and poor patient comfort. Additionally, peritonitis may cause transition to hemodialysis and mortality even though the incidence has gradually decreased with the development of secure attachment systems (Y-connector, twin bag system) in the last 3 decades.[4-5] Although peritonitis episodes improve rapidly with appropriate treatment, approximately 5% of peritonitis result in death and 15-18% of PD patients die due to peritonitis.[3-4]

While the incidence of peritonitis was 3.54 per patient-year before 1980, today the worldwide incidence has declined to approximately 0.7-0.9%.[6-7] Advanced age, concomitant disease, cultural, social, environmental and financial factors, educational status, poverty, diabetes, catheter type, modality, has been reported as factors affecting the incidence.[4-5] Peritonitis remains the most serious complication and the most important cause of technical failure. We aimed to evaluate 10-year peritonitis rate, causative microorganism, clinical outcome, and mortality in PD patients' follow-up in our unit.

MATERIAL AND METHODS

Patients who were on PD treatment program in our Nephrology Clinic and had peritonitis episode between 1 January 2009 and 31 December 2018 were analyzed retrospectively. The diagnosis of peritonitis was made in the presence of two of the following three criteria.[8]

1) Abdominal pain and/or cloudy peritoneal effluent.
2) After a dwell time of at least 2 hours' peritoneal effluent leukocyte count >100/mm^3 with >50% polymorphonuclear
3) Positive peritoneal effluent culture

The definition of relapsing, recurrent and repeat peritonitis was made according to the "ISPD Peritonitis Recommendations: 2016 Update on Prevention and Treatment" guidelines.[8]

Clinical and laboratory monitoring

Patients demographic, clinical and laboratory findings were obtained from the hospital records. Body mass index, blood pressure, complaints, residual urine amount, PD modality, chronic kidney disease etiology and gender data were recorded.

Bedside dialysate blood culture bottles culture results at the admission of peritonitis episode were evaluated, causative microorganism and culture antibiograms were noted.

Patients' peritoneal effluent cell counts, hemogram, C-reactive protein, total protein, and albumin test results were evaluated at the baseline

(0^{th} day) and 3^{rd} day of the peritonitis episode. Peritoneal catheter removal and deaths due to PD-related peritonitis during hospitalization were noted. Peritonitis rate was calculated by dividing episodes of peritonitis per year by the number of patient-years at risk. Relapsing peritonitis were excluded in the calculation.

Ethics committee approval

Ethics committee approval was obtained from the local ethics committee, dated 12.09.2018 and numbered 53043469-050.04.04. Informed consent was not obtained due to the retrospective nature of the study. This study was conducted in accordance with the ethical standards of the World Medical Association Declaration of Helsinki.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Windows version 18 [SPSS Inc; Chicago, IL, USA] packet program. Data normality was evaluated with Kolmogorov-Smirnov Test. Categorical data shown as number (percentage) and Chi-Square Test was used for analysis. Qualitative variables were shown as mean ± standard deviation or median with 25^{th} - 75^{th} percentile. Student's t-test and Mann-Whitney U test were used for normal and abnormal distributions, respectively. Binary Logistic Regression Analysis was used to determine independent risk factors. P=<0.05 was considered statistically significant.

RESULTS

A total of 85 peritonitis episodes were detected during 10-year follow-up. Five of them were relapsing peritonitis, one of recurrent peritonitis and one of repeat peritonitis. Relapsing peritonitis were excluded, in the remaining 80 peritonitis episodes, the mean age was 56.18±12.98, 26 (32.5%) cases were female, diabetes mellitus was the most common cause of chronic kidney disease, 31.2% (n=25) of them were on Continuous Ambulatory Peritoneal Dialysis (CAPD) and 68.8% (n=55) of them were on Automated Peritoneal Dialysis (APD). At the admission, all the patients had symptoms of cloudy effluent; abdominal pain was seen in 93.8%, nausea in 65% and fever in 30%.

Age, blood pressure, urine amount, PD modality were similar between genders. On the other hand, 65.4% of female patients were performing PD with their family caregivers, and 11.1% of male patients were performing PD with their family caregivers, the difference was significant (p<0.001).

A total of follow-up duration was 3289 months. The 10-year mean peritonitis rate was 0.29 episode/year. Annually, peritonitis rate was the lowest with 0.14 episode/year in 2016 and the highest with 0.53 episode/year in 2009. **(Table 1)**

The most common causative microorganism

Table 1. Annual peritonitis rate results

Year	Number of Patients	Total Follow Up (Month)	Peritonitis Episodes Number	Peritonitis Rate (1/month)	Peritonitis Rate (episode/year)
2009	34	316	14	1/22.5	0.53
2010	37	296	13	1/22.7	0.53
2011	41	342	6	1/57.0	0.21
2012	42	390	11	1/35.4	0.38
2013	36	368	10	1/36.8	0.32
2014	31	326	4	1/81.5	0.15
2015	35	340	6	1/56.7	0.21
2016	31	354	4	1/88.5	0.14
2017	33	312	7	1/44.5	0.27
2018	32	245	5	1/49.0	0.24
TOTAL	352	3289	80	1/41.1	0.29

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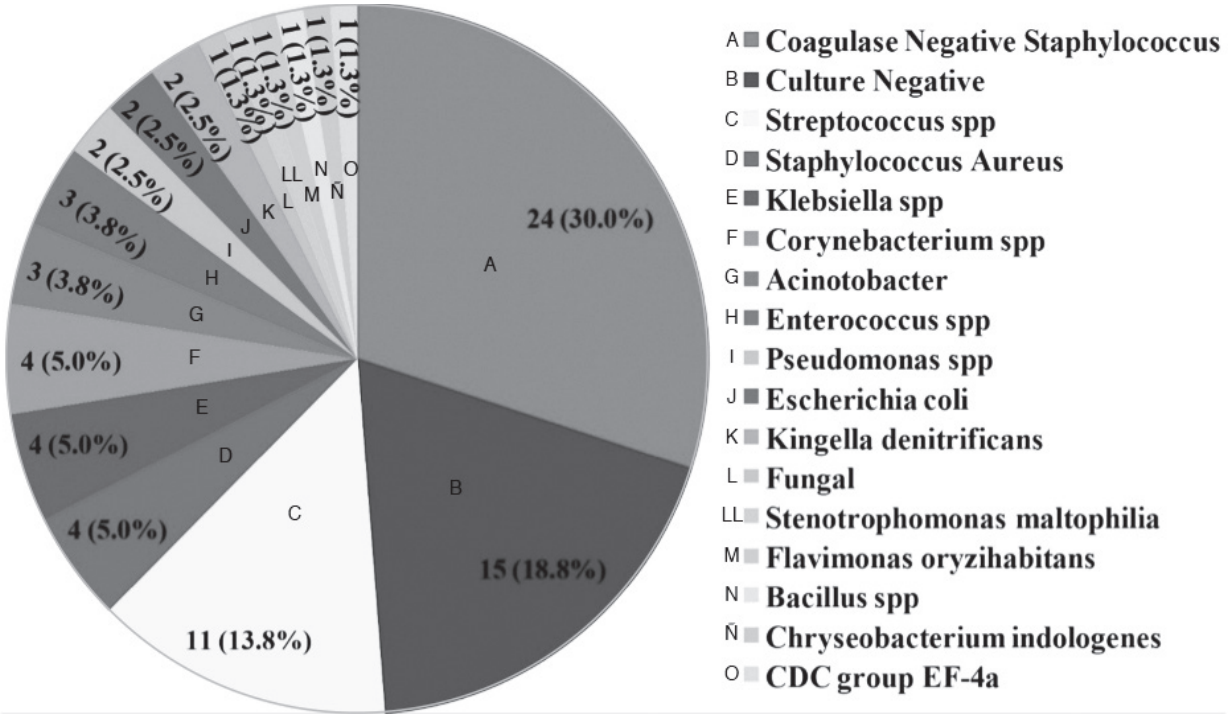
was Coagulase Negative Staphylococcus (CoNS). Additionally, 58.8% gram-positive, 21.3% gram-negative, 1.3% fungal infection was detected. Culture negative peritonitis rate was 18.8%. **(Figure 1)**

68% gram-positive and 12% gram-negative

Figure 1. Causative microorganisms of peritoneal dialysis related peritonitis



bacteria were detected in CAPD patients, 54.5% gram-positive and 25.5% gram-negative bacteria were detected in APD patients. No significant difference found between the modality of PD and gram staining (p=0.675).

It was found that 63.6% of Streptococcus spp were penicillin sensitive, 62.5% of CoNS were methicillin sensitive, 37.5% were methicillin resistant, and 100% of Staphylococcus aureus were methicillin sensitive.

Initial clinical and laboratory parameters of the patients were compared according to their bacterial growth in peritoneal effluent as gram-positive or gram-negative bacteria. Peritoneal effluent leukocyte counts were significantly higher in the patient group with gram-negative. Gender, age, body mass index, C-reactive protein, albumin, protein results was not different between gram-positive and negative groups. **(Table 2 -** Pág. 210**)**

Peritoneal catheter was removed in 21 (26.25%) of 80 peritonitis episode. Peritonitis divided as: Catheter Removed (n=21) and Catheter not Removed (n=59) group. The catheter was removed in 42.3% of female patients and 18.5% of male patients, the difference was significant (p=0.024). Leukocytes (p<0.001) and neutrophils (p<0.001) count in the 3rd day of peritoneal effluent direct examination, peritoneal effluent leukocytes count in the hemogram tube on the 3rd day (p= 0.011), the levels of C-reactive protein 0th (p=0.008) and 3rd (p=0.010) day were significantly higher in Catheter Removed group. Total protein and albumin levels were significantly higher on day 0 and day 3 in Catheter not Removed group. The catheter was removed in 19.1% of gram-positive peritonitis, 47.1% of gram-negative peritonitis (p<0.026). **(Table 3 -** Pág. 211**)**

In the analysis with Binary Logistic Regression, it was found that a decrease in serum albumin value of 1 g/dL increased the probability of removal of the catheter 13.8 fold (95% CI; 2.345-81.339), and in female gender catheter removal risk was 5.1 fold higher, while 0th day C-Reactive Protein and blood leukocytes count variables lost their significance in the model. **(Table 4)** Pág. 212

Table 2. Baseline values of patients with gram positive and negative strains

	Gram Positive (58.8%)	**Gram Negative (%21.3)**	**p**
Male/Female (n, %)	34 (77.3%) / 13 (65.0%)	10 (22.7%) / 7 (35.0%)	0.303
Age (year)	54.59±13.44	59.23±13.60	0.229
Body Mass Index (kg/m²)	26.03±6.20	26.69±4.96	0.695
CAPD / APD (n, %)	17 (85.0%) / 30 (%68.2)	3 (15.0%) / 14 (31.8%)	0.226
Urine Amount (mL)	100 (0-900)	400 (0-1350)	0.314
Systolic BP (mmHg)	125 (110-135)	130 (105-135)	0.982
Diastolic BP (mmHg)	80 (70-80)	80 (70-80)	0.777
PE-DME Leukocyte Count (mm³)	1100 (405-2730)	4160 (1237-8060)	0.022
PE-DME Neutrophil Count (%)	80 (67.5-90)	82.5 (77.5-91.25)	0.146
PE-HTA Leukocyte (x10⁹/L)	5.57±5.85	8.57±4.84	0.122
PE-HTA Neutrophil (x10⁹/L)	0.34 (0-2.37)	0 (0-1412)	0.209
C-Reactive Protein (mg/dL)	114.38±93.64	129.38±115.33	0.600
Sedimentation (mm/h)	76.98±21.74	77.93±28.73	0.899
Total Protein (g/dL)	6.31±0.78	6.09±0.63	0.317
Albumine (g/dL)	3.25±0.48	3.09±0.51	0.280
Blood Leukocyte (x10⁹/L)	12.74±5.48	9.45±4.93	0.034
Blood Neutrophil (x10⁹/L)	10.52±5.44	7.85±4.67	0.080
Blood Lymphocyte (x10⁹/L)	1.29 (0.85-1.49)	0.94 (0.61-1.50)	0.164
Blood Platelet (x10⁹/L)	274.5 (234.0-337.5)	267.0 (222.0-333.5)	0.670

(**BP:** Blood Pressure; **PE-DME:** Peritoneal Effluent Direct Microscopic Examination; **PE-HTA:** Peritoneal Effluent Hemogram Tube Analysis)

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Table 3. Comparison of patients with catheter removed and not removed

Parameter		**Catheter Removed (n=21, 26.2%)**	**Catheter not Removed (n=59, 73.7%)**	**P**
Age (year)		59.42±12.03	55.03±13.20	0.184
Male / Female (n, %)		10 (18.5%) / 11 (42.3%)	44 (81.5%) / 15 (57.7%)	0.024
Body Mass Index (kg/m^2)		26.82±5.55	25.99±6.11	0.585
CAPD / APD (n, %)		7 (28.0%) / 14 (25.5%)	18 (72.0%) / 41 (74.5%)	0.810
Systolic BP (mmHg)		120.71±23.09	122.20±18.62	0.769
Diastolic BP (mmHg)		80 (70-80)	80 (70-80)	0.915
Urine Amount (L)		0.40 (0.00-1.00)	0.35 (0.00-1.00)	0.818
PE-DME Leukocyte Count (mm^3)	Day 0.	2080 (300-3950)	1120 (495-4012)	0.980
	Day 3.	840 (490-1830)	65 (20-212)	<0.001
PE-DME Neutrophil Count (%)	Day 0.	80.0 (67.0-87.5)	80 (68.7-90.0)	0.369
	Day 3.	70.0 (70.0-80.0)	10.0 (0.0-65.0)	<0.001
PE-HTA Leukocyte (x10^9/L)	Day 0.	7.86±7.29	5.20±4.90	0.156
	Day 3.	2.30 (0.33-4.09)	0.17(0.06-0.28)	0.011
PE-HTA Neutrophil (x10^9/L)	Day 0.	0.20 (0.00-1.43)	0.10 (0.00-1.70)	0.857
	Day 3.	0.00 (0.00-1.80)	0.00 (0.00-0.00)	0.248
C-Reactive Protein (mg/dL)	Day 0.	166.95±106.17	99.77±86.97	0.008
	Day 3.	143.2 (53.2-283.7)	40.0 (29.5-121.5)	0.010
Sedimentation (mm/hour)	Day 0.	77.23±28.77	84.47±21.60	0.918
	Day 3.	76.00±24.36	0.265	0.265
Blood Leukocyte (x10^9/L)	Day 0.	9.50±4.61	12.68±5.42	0.022
	Day 3.	8.25±4.58	8.70±2.34	0.588
Blood Neutrophil (x10^9/L)	Day 0.	7.39±4.66	10.73±5.21	0.014
	Day 3.	6.23±2.38	6.23±2.38	0.599
Blood Lymphocyte (x10^9/L)	Day 0.	1.09±0.68	1.14±0.48	0.690
	Day 3.	1.12±0.48	1.46±0.62	0.033
Blood Platelet (x10^9/L)	Day 0.	313.45±113.10	289.41±83.23	0.318
	Day 3.	336.70±134.60	0.184	0.184
Total Protein (g/dL)	Day 0.	5.94±0.68	6.42±0.65	0.007
	Day 3.	5.24±0.49	5.95±0.78	<0.001
Albumin (g/dL)	Day 0.	2.87±0.52	3.35±0.42	<0.001
	Day 3.	2.33±0.46	2.95±0.42	<0.001
Gram Stain (n, %)	Positive	9 (19.1%)	38 (80.8%)	0.026
	Negative	8 (47.1%)	9 (52.9%)	

BP: Blood Pressure; **PE-DME:** Peritoneal Effluent Direct Microscopic Examination; **PE-HTA:** Peritoneal Effluent Hemogram Tube Analysis

Table 4. Logistic regression analysis of catheter removal

			Odds Ratio	95% Confidence Interval		P
C-Reactive Protein Day 0 (mg/dL)						
Catheter removed	166.95 ± 106.17		0.997		0.988-1.005	0.446
Catheter not removed	99.77 ± 86.97		1		Reference	
Albumin Day 0 (g/dL)						
Catheter removed	2.87 ± 0.52		13.811	2.345-81.339		0.004
Catheter not removed	3.35 ± 0.42		1	Reference		
Blood Leukocyte Day 0 (x10^9/L)						
Catheter removed	9.50 ± 4.61		1.000	1.000-1.000		0.010
Catheter not removed	12.68 ± 5.42		1	Reference		
Female	Catheter removed	11 (42.3%)	5.133	1.108-23.788		0.037
	Catheter not removed	15 (57.7%)				
Male	Catheter removed	10 (%18.5)	1	Reference		
	Catheter not removed	44 (%81.5)				

Five patients died due to PD-related peritonitis and the mortality rate was 6.25%. All of them were in the catheter removed group. There was no dominant microorganism in patients who died. The microorganism was different in each case; CoNS, Pseudomonas Aeruginosa, Acinetobacter Baumannii, extended-spectrum β-lactamase-producing Escherichia coli, Corynebacterium Spp were determined. Each case died due to peritonitis related septicemia within three weeks after a period of catheter removal and transfer to hemodialysis.

DISCUSSION

Despite current knowledge and technological advances, morbidity and mortality rates in dialysis patients are still high. The mortality risk of dialysis patients is 10 to 30 fold higher than the society.[9,10] The first 2-year mortality rates of PD patients are approximately 48% lower than hemodialysis patients.[11] Furthermore, PD-related peritonitis is one of the main causes of morbidity and mortality. Peritonitis rates can vary widely between individual patients, centers, regions, and countries. 0.63 in Brazil,[12] 0.37 in Argentina,[13] 0.18 in Turkey,[14] and 0.16 episode/year in China[15] have been reported. It was stated that the peritonitis rate should not exceed 0.5 episode/year in PD centers.[8] In our center, overall peritonitis rates during the 10-year was 0.24 episode/year, ranging from 0.14 to 0.53.

Studies showed either superior or similar peritonitis rate of APD in comparison with CAPD.[16-17] However, most of them were observational rather than randomized studies with a low number of cases. In our study, peritonitis rates were equal between two modalities. It has been suggested that the selection peritoneal dialysis modality should not be based on the risk of peritonitis.[8]

The most common causative microorganisms for PD-related peritonitis are gram-positive bacteria, and CoNS is the most frequent agent.[5, 18] Gram-positive and CoNS bacteria are account between 60-70% and 30-40%, respectively.[3, 4, 15, 18] It has been stated that the skin flora is the reason for gram-positive strains are dominant due to touch contamination during exchange.[5,18] Gram-negative enteric bacteria are detected at a rate of 10-25%, with the highest rate reported in Asia and Australia.[4, 13] Gram-negative percentage shows increased due to use of mupirocin in the exit site, and recent antibiotic application is a risk factor for gram-negative enteric peritonitis.[5] Lipopolysaccharide found in gram-negative bacteria increases leukocyte-endothelial

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interaction and creates a strong inflammatory response, cytokine release is 2-13 fold higher, and these patients have been reported to have more severe clinical signs and symptoms of peritonitis.[19] In our results, peritoneal effluent leukocyte and blood leukocyte counts were significantly higher at the time of admission. These findings may help foresight gram-negative peritonitis.

Microorganism isolation rates may be low in peritoneal effluent culture. Planting in blood culture bottles is recommended to increase the rate of growth in culture.[4, 8, 20] It has been reported that the automatic BACTEC culture technique increased the positive culture rate in patients with peritonitis from 73.55% to 96.55% compared to the manual technique.[13] In publications, the rate of culture negative peritonitis ranges from 15.9% to 32.1%.[13, 21-22] Our, culture negative peritonitis rate was 18.8%. Culture negative peritonitis rate should be less than 20% and it is recommended to review and improve the sampling and culture methods of the center if the rate was more than 15%.[8]

It is very important that centers know and follow antibiotic resistance rates, in the regulation of empirical treatment and in preventing the development of resistant organisms. Recent hospitalization and antibiotic therapy could increase the development of methicillin-resistant strains. Gram-positive methicillin-resistant strains increased over the three decades and methicillin-resistant CoNS was approximately 50%.[4, 23] Similarly, in this study the rate of methicillin-resistant CoNS was 37.5%, while no methicillin-resistant Staphylococcus Aureus strain was detected. Empirical antibiotic selection should be determined by the prevalence and types of resistant bacterial isolates, and vancomycin should be preferred at high methicillin resistance rate.[8]

Most of the PD-related peritonitis responds to antibiotic therapy, but a significant proportion of them may require surgical removal of the peritoneal catheter to eradicate the infection. In parallel with our study, catheter removal rates due to peritonitis have been reported in the range of 16-18% and were significantly higher in gram-negative peritonitis.[7,21] Advanced age, recurrent peritonitis, admission longer than 48 hours, paralytic ileus, hypotension, hypoalbuminemia (<3 g/dL), and causative microorganism such as Escherichia Coli, Enterobacter spp and Pseudomonas spp are important risk factors for catheter removal.[24-25] Although the relationship of hypoalbuminemia with technical failure is not clear, its low level is a marker of inflammation, malnutrition, and co-morbidity. Albumin synthesis is suppressed in the presence of infection and inflammation, and normal loss of 4-5 g/day increases 3-4 fold during peritonitis.[26-27] In our study, C-reactive protein, leukocyte and neutrophil were significantly higher in catheter removed group. In addition, serum albumin level was significantly lower in catheter removed group and the level of albumin could be determinant in predicting the catheter removal.

No death was observed in peritonitis cases responding to medical treatment, and the mortality rate in catheter removed patients was 8.9%,[25] and the cumulative mortality was seen in less than 4%.[8] Our cumulative mortality rate was close to previous studies with a rate of 6.25%, while there was no death in catheter not removed.

In conclusion, peritonitis rate may differ even among centers, determining risk factors for each center is of particular importance. Catheter removal was slightly increased at our center. Catheter loss was associated with female gender, gram negative strains and hypoalbuminemia in PD-related peritonitis. Patients should be closely monitored, and necessary precautions should be taken to prevent development of peritonitis and complications.

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