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Microbiological Diagnosis of Peritonitis in Patients Undergoing Peritoneal Dialysis: Review of 10 Years at Ege University Single Centre Experience

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Abstract

Introduction. Peritonitis as a complication of peritoneal dialysis (PD) may cause a technique failure, hospitalization, and even death and the responsible microorganisms have to be evaluated to direct the treatment.
Methods. Three hundred and four patients with the mean age of 48±14 years, 51.6% male, 16.8% diabetics, 14.8% on automated PD program, with mean PD time of 28±26 months, were recruited in this retrospective, observational cohort study.
Results. A total of 384 episodes of peritonitis occurred from January 1999 to June 2009. The peritonitis incidence has been 1 episode every 22.1 patient–months. Gram positive microorganisms were the leading cause 173 (45.1%), in which 111 (28.9%) of Coagulase negative staphylococcus (CoNS), 28(7.3%) of Staphylococcus aureus followed by gram negatives 67 (17.4%), composed mostly of E. coli 23(6%) and Klebsiella pneumoniae 8(2.1%) as causative agents of peritonitis. Proportion of negative dialysate cultures was 24.6 % at 1999 but reduced to 10% at 2009. Methicilline resistant CoNS were found in 50.5% of cases. There was a significant decrease in the proportion of peritonitis due to MR-CoNS from 61.8% (34/55) in 1999-2003, to 39.3% (22/56) in 2004-2009 ($p<0.05$). The proportion of strains resistant to Ampicilline among E. coli was 36.4% (4/11) in 1999-2003 to 75% (9/12) in 2004-2009 ($p<0.05$).
Our policy regarding the initial treatment was cefazoline plus ceftazidime or aminoglycosides so there were no vancomycine resistance in the staphylococci infections.
Conclusion. There has been an increasing resistance to antimicrobials in the world so it is important to determine causative agents of peritoneal attacks and their susceptibilities to antibiotics in order to develop current treatment protocols.

Key words: peritoneal dialysis, peritonitis, culture and antibiogram

Introduction

Peritonitis is a serious complication of peritoneal dialysis (PD) [1-3]; it probably is the most important cause of technique failure in PD [2-5]. Eighteen percent of the infection related mortality in PD patients is the result of peritonitis in the United States [6].
Although the incidence of peritonitis varies from center to center, it decreased dramatically in the 1990s to 1 episode/24 patient-months [7-10]. Widely used treatment guidelines have continually been modified by the International Society for Peritoneal Dialysis (ISPD), and the most recent modification being made in 2010 [11].
Treatment guidelines should be changed depending on the causative organisms because empirical antimicrobial regimens for peritonitis are established by the major causative organisms. Even though cross-sectional studies on the causative organisms of peritonitis have been reported frequently, long-term studies on changes in the causative organisms of peritonitis are scarce [12,13]. There have been only a few studies, conducted at a single center, which analyzed the changes in infecting pathogens and also their antimicrobial sensitivities [14,15].
In the present study, from 474 patient's files, we investigated the causative organisms, antimicrobial susceptibility, and catheter removal rates relative to the causative organisms in all available records of 304 PD patients with peritonitis, who were followed up at Ege University Medical Faculty Hospital, Izmir, between 1999 and 2009. Changes in the causative organisms and antimicrobial susceptibility of each causative organism were also examined.

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Patients and Methods

Between January 1999 and June 2009 at Ege University Medical Faculty Division of Nephrology PD unit Three hundred and four patients being on PD for more than 6 months were recruited in this retrospective, observational cohort study. The mean age was 48±14 years, 51.6% were male, 16.8% diabetics, 14.8% on automated PD program with dry day, the rest CAPD with the 2 liters of dialysate solutions 4 times a day. The mean PD duration was 28±26 months. The data recorded included causative organisms of peritonitis, antimicrobial susceptibility of each organism.

PD was performed by means of disconnect systems (Baxter Healthcare, Deerfield, Illinois, USA, and Fresenius Medical Care, Deutschland GmbH, Germany), with lactate-buffered glucose-containing dialysate solutions.

Prophylactic antimicrobial was not routinely administerred prior to Tenckhoff catheter placement. PD was initiated after a break-in period of 4 weeks following whether percutaneous or surgical placement of the catheter. The standard PD training program lasted generally for a week.

An exit-site infection is defined by the presence of purulent drainage, with or without erythema of the skin at the catheter-epidermal interface. A positive culture in the absence of an abnormal appearance is accepted as colonization rather than infection [16].

A tunnel infection was diagnosed if erythema, edema, or tenderness present over the subcutaneous pathway. A tunnel infection was usually diagnosed in the presence of an exitsite infection but rarely occurred alone.

Patients were classified as having peritonitis if they satisfied at least two of the following criteria: (1) presence of clinical symptoms (pain, fever, cloudy dialysate); (2) presence of more than 100 leukocytes/mm^3 dialysate, with at least 50% polymorphonuclear neutrophils; and (3) positive culture or Gram stain. Since 1999, culture of the dialysate has been performed as recommended by the ISPD [17]. Whole dialysate (50 mL) is concentrated by centrifugation, resuspended in sterile saline, inoculated into blood culture media, and observed for at least 72 hours to document pathogens. Antimicrobial susceptibility is determined by standard disk-diffusion and automatised (api strips/VITEK 2, bioMérieux) microbiological methods.

When peritonitis was diagnosed, empirical therapy with a combination of cefazolin and cefdazidime (or amikacin) was initiated. Within 72 hours, the empirical antibiotics were adjusted based on the results of the dialysate culture and antimicrobial susceptibility test. In culture-negative peritonitis with no response to initial therapy after 72 hours, cefazolin and cefdazidime were substituted by vancomycin and amikacin. If peritonitis did not respond to adequate antibiotics after 96 hours, the catheter was removed. In addition, the catheter was removed in cases of frequent relapsing peritonitis, fungal peritonitis, and tuberculosis peritonitis.

Data are expressed as episodes/patient-months, percent, and mean±standard deviation (SD) Antimicrobial susceptibilities and catheter removal rates according to the pathogens were analyzed using chi-square analysis or Fischer's exact test.

All probabilities were two-tailed and the level of significance was set at 0.05. To further explore the effect of individual factors after excluding potential confounding variables, a Binary Logistic Regression model was constructed.

Table 1. Clinical Characteristics of Patients

Patients (n)	304
Sex (male/female)	157/147
Age (years)	48±17a
APD (%)	45 (14.8)
Mean duration of follow-up (months)	28±26
≥1 peritonitis attacks (%)	165 (54.2)
≥2 peritonitis attacks (%)	67 (40.6)
Peritonitis attacks/patients	384 / 251
Underlying disease (%)	
Others or unknown (%)	135 (44.4)
Diabetes mellitus (%)	51 (16.8)
Glomerulonephritis (%)	32 (10.5)
Amyloidosis (%)	16 (5.3)
Hypertension (%)	28 (9.2)
Polycystic kidney disease (%)	16 (5.3)
TIN (%)	13 (4.3)
Pyelonephritis (%)	8 (2.6)
Systemic lupus erythematosus (%)	5 (1.6)

a Mean ± standard deviation

Table 2. Causative Organisms of PD Peritonitis (n = 384)

	Microorganism	1999-2003		2004-2009	
		n	%	n	%
Peritonitis (patient-months)		21.4		24.4	
Dialysate cultures (+)		122	61.3	129	70
Dialysate cultures (-)		77	38.7	56	30
Gram (+) m.o		85	42.7	88	47.6
	CoNS	55	27.6	56	30
	MR-CoNS	34	17.1	22	12
	S. aureus	15	7.5	13	7
	Other gram (+)	15	7.5	19	10.3
Gram (-) m.o		35	17.6	32	17.3
	Escherichia coli	11	5.5	12	6.5
	K. pneumoniae	3	1.5	5	2.7
	P. aeruginosa	5	2.5	2	1.1
	Other gram (-)	16	8	13	7
Other	Tbc, fungi, etc.	2	1	9	4.9

Results

Demographic and clinical characteristics of patients

Of the 304 patients examined, 157 were men and 147 women, the mean age at the initiation of PD was 48±17 years, and they were followed up for a mean period of 28± 26 months. The causes of ESRD are listed in Table 1.

Causative organisms of peritonitis

A total of 384 episodes of peritonitis were recorded during this 10-year study period. The causative organisms of peritonitis are listed in Table 2.

Peritonitis rates and causative organisms

The incidence of peritonitis decreased significantly, from 1 episode/21.4 patient-months in 1999-2003 to 1 episode / 24.4 patient-months in 2004-2009. Gram positive microorganizms were the leading cause 173(45.1%), in which 111 (28.9%) of Coagulase negative staphylococcus (CoNS), 28(7.3%) of Staphylococcus aureus were followed by gram negatives 67(17.4%), composed mostly by E. coli 23(6%) and Klebsiella pneumoniae 8(2.1%) as causative agents of peritonitis. Overall proportion of negative dialysate cultures was 34.6% but decreased to 10% abruptly by the time (Figure 1).

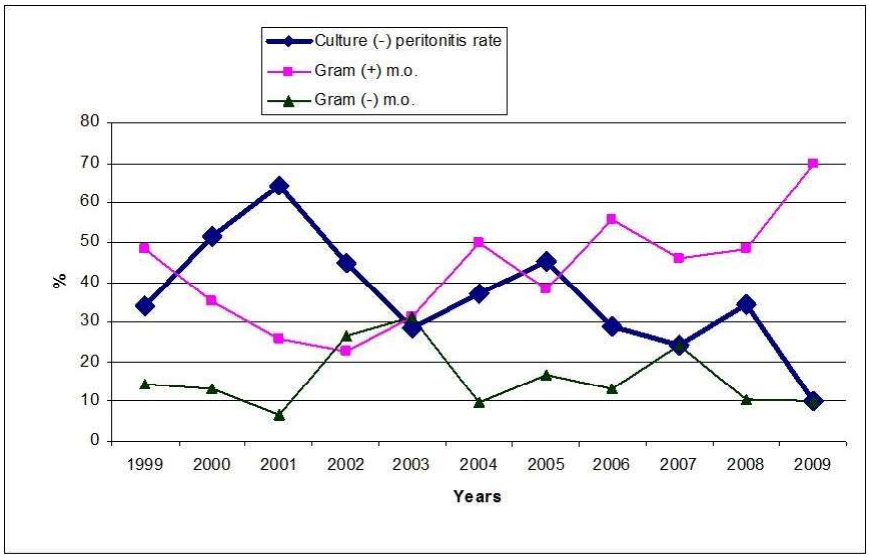

Fig. 1. Culture Negative, Gram-Positive and Gram-Negative Peritonitis Rates in Peritoneal Dialysis

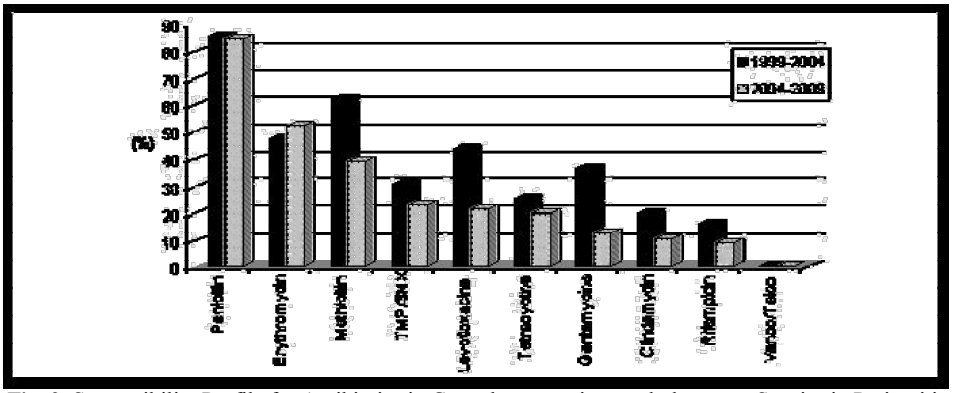

Fig. 2. Susceptibility Profile for Antibiotics in Coagulase negative staphylococcus Species in Peritonitis Episodes in Peritoneal Dialysis ***Abbreviations***: Vanco/Teico - Vancomycin/Teicoplanin

Antimicrobial resistance of gram-positive organisms decreased (Figure 2).

Coagulase-Negative Staphylococcus: Of the 111 episodes of peritonitis caused by CoNS, 49.5% (55/111) were caused by methicillin-sensitive (MS-) CoNS and 50.5% (56/111) by methicillin-resistant (MR-) CoNS. There was a significant decrease in the proportion of peritonitis due to MR-CoNS from 61.8% (34/55) in 1999-2003, to 39.3% (22/56) in 2004-2009 ($p<0.05$). There was also a significant decrease in the proportion of peritonitis

resistance to levoflaxacine from 43.6% (24/55) in 1999-2003, to 21.4% (12/56) in 2004-2009 ($p<0.05$) (Table 3).

Table 3. Susceptibility Profile for Antibiotics in Gram-Positive Species in Peritonitis Episodes in Peritoneal Dialysis

		1999-2003			2004-2009		
	Organism	**Resistance (n)**	**Isolates (n)**	**%**	**Resistance (n)**	**Isolates (n)**	**%**
Penicillin	CoNS	47	55	85,5	47	56	83,9
Methicillin*	CoNS	34	55	61,8	22	56	39,3
Erythromycin	CoNS	26	55	47,3	29	56	51,8
Levofloxacine*	CoNS	24	55	43,6	12	56	21,4
Gentamycine	CoNS	20	55	36,4	7	56	12,5
TMP/SMX	CoNS	17	55	30,9	13	56	23,2
Tetracycline	CoNS	14	55	25,5	11	56	19,6
Clindamycin	CoNS	11	55	20	6	56	10,7
Rifampicin	CoNS	9	55	16,4	5	56	8,9
Vanco/Teico	CoNS	0	55	0	0	56	0
Penicillin	S. aureus	14	15	93,3	12	13	92,3
Methicillin	S. aureus	5	15	33,3	0	13	0
Rifampicin	S. aureus	2	15	13,3	1	13	7,7
Clindamycin	S. aureus	1	15	6,7	2	13	15,4
Erythromycin	S. aureus	4	15	26,7	2	13	15,4
Levofloxacine	S. aureus	4	15	26,7	1	13	7,7
TMP/SMX	S. aureus	3	15	20	1	13	7,7
Tetracycline	S. aureus	3	15	20	3	13	23,1
Vanco/Teico	S. aureus	0	15	0	0	13	0
Penicillin	Enterococcus	4	4	100	2	2	100
Gentamycine	Enterococcus	2	4	50	2	2	100
Levofloxacine	Enterococcus	3	4	75	1	2	50
Vanco/Teico	Enterococcus	1	4	25	1	2	50

$p< 0.05$, TMP/SMX: Trimethoprim/sulfamethoxazole, Vanco/Teico: Vancomycin/teicoplanin, CoNS = coagulase-negative staphylococcus

Staphylococcus aureus: Staphylococcus aureus was the etiologic agent in 7.3% (28) episodes of peritonitis. Methicilline resistance was decreased from 33.3% (5/15) to 0% (0/13) ($p>0.05$) (Table 3). Importantly, there was no Vancomycine resistance to CoNS and S. aureus.

Enterococcus: Enterococcus species were resistant to penicilline and the resistance to aminoglycosides was increased from 50% (2/4) to 100% (2/2) ($p>0.05$) (Table 3). Of the 23 episodes of peritonitis caused by E. coli were 6%. The proportion of strains resistant to Ampicilline among

Antimicrobial resistance of gram-negative organisms increased (Figure 3).

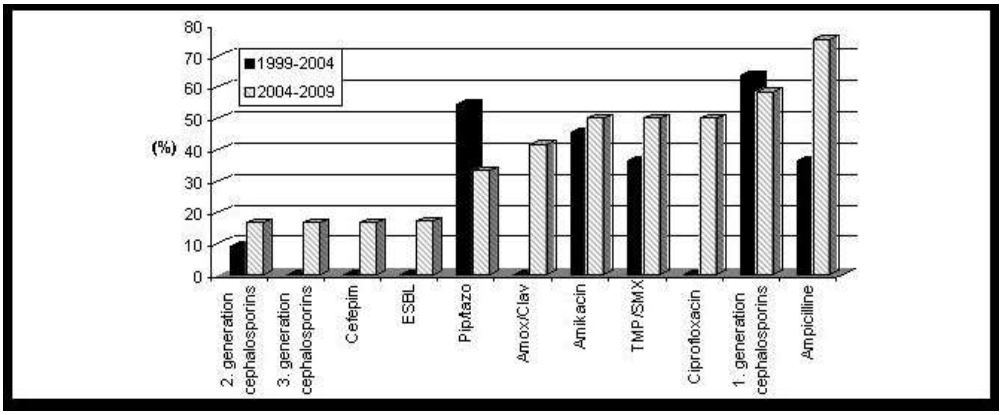

Fig. 3. Susceptibility Profile for Antibiotics in Escherichia coli Species in Peritonitis Episodes in Peritoneal Dialysis ***Abbreviations***: TMP/SMX: Trimethoprim/sulfamethoxazole

E. coli was 36.4% (4/11) in 1999-2003 and 75% (9/12) in 2004-2009, respectively ($p<0.05$) (Table 4).

Of the 8 episodes of peritonitis caused by K. pneumoniae were only 2.1%. Although there was no resistance to various antibiotics (Cephalosporins, Cefepim, ESBL, and Amikacin) in 1999-2003, by the time resistance reached 20%, while there was a 100% resistance to Ampicilline.

Table 4. Susceptibility Profile for Antibiotics in Gram-Negative Species in Peritonitis Episodes in Peritoneal Dialysis

		1999-2003			2004-2009		
	Organism	**Resistance (n)**	**Isolates (n)**	**%**	**Resistance (n)**	**Isolates (n)**	**%**
1. generation cephalosporins	E.coli	7	11	63,6	7	12	58,3
Pip/tazo	E.coli	6	11	54,5	4	12	33,3
Amikacin	E.coli	5	11	45,5	6	12	50
Ampicilline*	E.coli	4	11	36,4	9	12	75
TMP/SMX	E.coli	4	11	36,4	6	12	50
2. generation cephalosporins	E.coli	1	11	9,1	2	12	16,7
3. generation cephalosporins	E.coli	0	11	0	2	12	16,7
Cefepim	E.coli	0	11	0	2	12	16,7
Ciprofloxacin	E.coli	0	11	0	6	12	50
Amox/Clav	E.coli	0	11	0	5	12	41,7
1. generation cephalosporins	K. pneumoniae	0	3	0	1	5	20
Pip/tazo	K. pneumoniae	0	3	0	1	5	20
Amikacin	K. pneumoniae	0	3	0	1	5	20
Ampicilline	K. pneumoniae	3	3	100	5	5	100
TMP/SMX	K. pneumoniae	0	3	0	0	5	0
2. generation cephalosporins	K. pneumoniae	0	3	0	1	5	20
3. generation cephalosporins	K. pneumoniae	0	3	0	1	5	20
Cefepim	K. pneumoniae	0	3	0	1	5	20
Ciprofloxacin	K. pneumoniae	0	3	0	0	5	0
Amox/Clav	K. pneumoniae	0	3	0	0	5	0
Ceftazidime	P. aeruginosa	1	5	20	0	2	0
Ciprofloxacin	P. aeruginosa	2	5	40	0	2	0
Gentamycine	P. aeruginosa	0	5	0	0	2	0
Carbapenem	P. aeruginosa	1	5	20	0	2	0
Pip/tazo	P. aeruginosa	0	5	0	0	2	0

*$p<0.05$, Pip/tazo: Piperacillin/tazobactum, TMP/SMX: Trimethoprim/sulfamethoxazole, Amox/Clav: Amoxicilline/Clavulanic acid

Of the 7 episodes of peritonitis, the cause in 1.8% was P. aeruginosa. In the second period althought there was a decrease of Ceftazidime, Ciprofloxacin and Carbapenem resistance, it was not significant (Table 4). In addition, the proportion of strains resistant to the extended spectrum beta-lactamase among E. coli and Klebsiella was 0% to 17% (2/12) and 0% to 20% (1/5) from 1999-2003 to 2004-2009, respectively ($p>0.05$) (Table 4).

Our policy regarding the initial treatment was cefazoline plus ceftazidime or aminoglycosides as guidelines recommended so there were no vancomycine resistance in staphylococci.

As described in the Methods section, we constructed a Binary Logistic Regression model for the analysis of time to the first peritonitis episode. Variables used for modeling were patient Age, Dialysis mode whether CAPD or APD, Sex, Diabetes mellitus, Catheter insertion technique, PD time (months), Previous transplant history. Using this model, two independent factors that predicted peritonitis -free survival among our cohort were identified, namely, age (hazard ratio -0.98, 95% confidence interval 0.96-0.99; $p=0.01$) and PD time (hazard ratio -0.98, 95% confidence interval 0.97-0.99; $p = 0.000$) (Table 5).

Table 5. Binary Logistic Regression Analysis Showing Factors Associated with Dialysis-Related Peritonitis

Variables	**Hazard ratio (95% CI) of developing peritonitis**	**p Value**
Age (per 1 year decrease)	0.98 (0.96-0.99)	0.01
Sex (male vs female)	0.94 (0.57-1.58)	0.83
Diabetes mellitus	1.06 (0.52-2.14)	0.88
Catheter insertion technique	1.29 (0.78-2.15)	0.32

(medical vs surgical)		
PD time (per 1 month decrease)	0.98 (0.97-0.99)	0.000
Previous tx history	-0.68 (0.31–1.48)	0.33

Discussions

There were a few studies investigating changes in the causative organisms of peritonitis and their antimicrobial susceptibilities in PD patients for a decade [15]. This is the first study in Turkey in this field, concerning more than 300 PD patients, for 10 years follow up at a single center. Peritoneal dialysis has been performed in Turkey since 1981. The provider of renal replacement therapy in Turkey is public.

The incidence of peritonitis decreased significantly, from 1 episode/21.4 patient-months in 1999-2003 to 1 episode/ 24.4 patient-months in 2004-2009 years. It was good enough if we compare with the ISPD recommendation rate of 1 episode every 18 months (0.67/year at risk) [11]. This change may be due to the increased experience of our institution, improvement in connecting systems (usage of the double-bag system), development of the new peritoneal dialysis solutions, improvement in living environments, and finally education of patients.

The incidence of peritonitis differs according to patient characteristics, such as race [18], age [19], mode of PD (CAPD vs. automated PD) [20], and composition of dialysis solutions [21]. In the present study, all subjects were Turks, and there was a small decrease in the proportion of diabetics and the age of patients after 2003. All patients used lactate-based solutions. Therefore, we consider that the specially trained nurses and technicians at our institution, who participated in training of new PD patients and in education of patients who visited our PD unit due to peritonitis, along with the patient education program, which has been operational since 2004, all contributed to this decrease. Our education program for new PD patients consists of 1 hour for 7-10 days according to patients intelligence and learning ability. On the first day, patients learn the basic knowledge about renal replacement treatments and physiology of PD; on the second day, how to exchange dialysate and on the following days they learn PD complications and how to deal with these problems and last days perform PD with our team.

Our policy regarding the initial treatment was cefazoline plus ceftazidime (if preserved residual renal function) or aminoglycosides into peritoneal dialysate. Nevertheless, only a few studies have attempted to examine the epidemiology of the causative organisms and their antimicrobial susceptibilities [22], and there have been only two reports at a single center on changes in antimicrobial susceptibility according to each organism [14,15].

We found gram-positive microrganisms incidence and the proportion of peritonitis increased from 1999-2003 to 2004-2009 (Figure 1). However, MR-CoNS, and levofloxacine resistance to CoNS were decreased signifycantly. This may be due to our more effective education program especially avoiding the hand contact of the connecting systems and hygiene. In view of the significant changes in the antimicrobial susceptibility of CoNS observed in our present study, we suggest the use of first-generation cephalosporin as the initial empirical antibiotic, as also recommended by the ISPD [23]. In the literature for the effect of S. aureus prophylaxis on the prevention of peritonitis there have been many studies, but the results are controversial [24-27]. In our study, we could not reveal the effect of S. aureus prophylaxis in our patients because it has never been performed at our unit.

The proportion of peritonitis due to E. coli and P. aeruginosa among gram-negative organisms was found to be the second most common causative microorganisms as similar to previous studies [28,29]. On the other hand, overall proportions of peritonitis due to gram negative microorganisms were decreased, but resistance to Ampicilline was increased significantly. This high resistance to Ampicilline may be due to over use of this drug for upper respiratory tract infections in our country. Nevertheless, it's not the first choice of empiric therapy regimen.

We used BACTEC aerobic bottles (Becton Dickinson) for culture of PD fluid and encountered a high percentage of culture negativity (35%) in PD in 1999-2003 peritonitis cases but it has been decreased to 10% (Figure 1) which was in line with the recommendations by the ISPD guidelines [11].

In the present study, younger age was associated with peritonitis risk reduction. In the literature some studies support [30], some not [31,32] and in our study decreasing the PD duration time was also associated with peritonitis risk reduction. There were no significant difference among gender, diabetes mellitus, type of dialysis treatment (CAPD or APD), type of catheter and its surgical implant, and previous renal transplantation history.

The role of diabetes in peritonitis is not clear; Although Chow *et al*. showed diabetics had a higher risk of first peritonitis episode [33]. Viglino *et al*. did not observe any difference [34].

Locatelli *et al*. showed that, in Argentina, transfer of patients from CAPD to APD resulted in a significant reduction in peritonitis rate: from 1/8.3 to 1/18.9 patient-months [35]. Bevilacqua *et al*. showed in Brazil, a lower peritonitis rate in prevalent APD patients [36]. Fernandez *et al*. in Chile, a peritonitis rate of 1/75 patient-moths with APD, the lowest ever reported in Latin America [37]. In contrast, Oo *et al*. analyzing data from the United States Renal Data System (USRDS), found CAPD was associated with a slightly lower risk than APD for a first peritonitis episode [38].

Conclusions

In conclusion, the proportion of peritonitis due to gram-positive organisms increased, while gram negative organisms were decreased. Antimicrobial resistance decreesed in gram-positive organisms (CoNS) and increased in gram-negative organisms (E.coli and K. pneumoniae) during the study period.

We recommend cefazoline plus ceftazidime (if presserved residual renal function) or aminoglycosides into peritoneal dialysate as initial treatment and to avoid vancomycine as an empirical approach and tailoring the treatment according to the culture results. Consequently, it is necessary to prepare new center-based treatment guidelines for PD peritonitis.

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Conflict of interest statement. None declared.

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