

Epidemiology of Culture-Negative Peritonitis in Iranian Patients on Continuous Ambulatory Peritoneal Dialysis

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Introduction. Culture-negative peritonitis is a major challenge in the treatment of peritonitis in continuous ambulatory peritoneal dialysis (CAPD). This study aimed to evaluate the culture-negative peritonitis in patients from the Iranian CAPD Registry.

Materials and Methods. Data of 1472 patients from 26 CAPD centers were analysed. Peritonitis was defined as any clinical suspicion together with peritoneal leukocyte count of 100/mL and more.

Results. The patients had been on PD for a mean of 500 ± 402 days. There were a total of 660 episodes of peritonitis observed among 299 patients (peritonitis rate of 1 episode in 34.1 patient-months). Excluding patients with both negative and positive culture results, there were 391 episodes of peritonitis in 220 patients (174 culture-positive episodes in 97 patients and 217 culture-negative episodes in 123). The 1- to 4-year patient survival rates were 85%, 75%, 69%, and 59% for the patients with culture-positive peritonitis, and 92%, 78%, 73% and 63% for the patients with culture-negative peritonitis, respectively ($P = .34$). The technique survival rates were 90%, 57%, 42%, and 27% and 95%, 85%, 74%, and 40%, respectively ($P = .001$). On follow-up, there were higher rates of active PD patients, lower rates of PD dropouts, and higher rates of kidney transplantation in patients with culture-negative peritonitis compared to those with culture-positive peritonitis.

Conclusions. In our patients, the prevalence of culture-negative peritonitis was high (55.9%). Patient survival with culture-negative peritonitis was comparable to those with culture-positive peritonitis and technique survival was higher among those with culture-negative peritonitis.

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INTRODUCTION

Peritoneal dialysis (PD) is an important modality of renal replacement therapy with increasing coverage of end-stage renal disease patients from 1.5% in 2000 to 6.5% in 2008 in Iran.¹ One of the main drawbacks of PD, however, is technique failure,²

and peritonitis, as a serious complication of PD, is probably the most frequent cause of technique failure.³⁻⁶ Although with the use of double-bag systems, its frequency has decreased to 1 episode in every 30 to 36 patient-months in western countries and to as low as 1 episode in every 50 to 60 patient-

months in eastern Asian countries,² peritonitis is still a main complication of PD, which should be diagnosed and treated urgently.

Peritonitis is usually suspected on clinical grounds with symptoms and signs such as cloudy peritoneal effluent and abdominal pain and tenderness. An effluent leukocyte count of 100/mL and more, with at least 50% polymorphonuclear cells, indicates the presence of inflammation, with peritonitis being the most likely cause.⁷ A positive culture proves the diagnosis and helps in selection of appropriate antibiotic after the initiation of empiric antibiotic therapy. However, peritoneal effluent cultures may be negative in approximately 20% of peritonitis episodes.^{8,9}

Culture-negative peritonitis is often believed to have a benign clinical course. In the study by Bunke and colleagues, there was no difference in symptoms and signs and the number of patients with cloudy bags between patients with culture-positive peritonitis and those with initially no-growth peritonitis.¹⁰ In this study, there was no significant difference between gender distribution, number of diabetics, race, or episodes of previous peritonitis episodes between patients with culture-positive and culture-negative peritonitis. Although in subsequent cultures, patients with initially no-growth peritonitis had a higher frequency of gram-negative and fungal infections, the rate of catheter removal was half in the latter group compared to patients with culture-positive peritonitis. In another study by Szeto and colleagues, the baseline demographic characteristics including age, gender, duration on dialysis, primary kidney disease, and major comorbidities were not different between patients with culture-positive and culture-negative peritonitis.¹¹ However, in this study, patients with culture-negative peritonitis did not have a favorable outcome with initial response in two-third and complete cure in only one-third of the patients. Whatever the clinical course may be, culture negativity may lead to uncontrolled use of broad-spectrum antibiotics with their unwanted side effects such as ototoxicity or loss of residual kidney function due to aminoglycosides, secondary fungal peritonitis, or development of resistant strains such as vancomycin-resistant enterococci or extended-spectrum beta-lactamase-producing *Escherichia coli*.^{8,12,13}

The aim of this study was to evaluate the prevalence of culture-negative peritonitis in a

cohort of continuous ambulatory PD (CAPD) patients from Iranian CAPD registry, the possible risk factors for culture-negative peritonitis, and its effect on patient and technique survival rates.

MATERIALS AND METHODS

Study Population

Demographic characteristics and laboratory data of 1472 patients from 26 CAPD centers in Iran, collected through questionnaires on a monthly basis, were used for this study. Iranian CAPD Registry was founded in 1995. We present the data related to January 1, 1995 to December 1, 2006 in this study. All of the patients who had a history of a single or multiple episodes of culture-positive or culture-negative peritonitis according to the questionnaires filled by PD centers were included in this study. These were 97 patients with 174 episodes of culture-positive peritonitis and 123 patients with 217 episodes of culture-negative peritonitis. Seventy-nine patients with 269 episodes of both culture-positive and culture-negative peritonitis were excluded from the study because of impossibility to be categorized.

Peritonitis

Peritonitis was defined as clinical suspicion based on any of the following symptoms or signs (cloudy PD effluent, fibrin clots in PD effluent, abdominal pain, nausea, vomiting, diarrhea, constipation, fever sensation, chills, abdominal tenderness, rebound tenderness, weakness, and oral temperature $\geq 37.8^{\circ}\text{C}$) together with peritoneal leukocyte count of 100/mL or more. Culture-positive and culture-negative peritonitis were defined according to the culture results reported by the PD centers. Peritoneal fluid culture is performed through injection of 5 to 10 millilitres of peritoneal fluid effluent into 1 blood culture bottle, without prior centrifugation.

Peritoneal dialysis-related death was defined as death due to peritonitis, uremia following technique failure, mechanical problems of the catheter or sclerosing peritonitis. Death due to other causes included cardiovascular disease, cerebrovascular accident, vehicle accidents, and cancer.

Statistical Analyses

Data were collected through a 18-sheet form on a monthly basis from 26 CAPD centers throughout Iran, including demographic information, monthly

laboratory findings, clinical course, survival and mortality data, peritonitis data, and data regarding catheter complications, were sent to Shafa CAPD Registry Center and entered in Hakim software specifically designed for the registry by Pegahsoft Co, Khorasan Science and Technology Park, Mashhad, Iran. The data used for this study were extracted from the Hakim database and analysed by the STATA 9.0 software (Stata Corp, College Station, Tx, USA). Parametric values were expressed as mean \pm standard deviation. The chi-square test and the Fisher exact test were used for comparison of proportions. The Kaplan-Meier method and the log rank test were used to assess patient and technique survival rates. *P* value less than .05 was assumed significant.

RESULTS

There were a total of 1472 patients who had been on PD for a mean of 500 ± 402 days. Among these patients, 624 (42.4%) were men and 848 (57.6%) were women. There were a total of 660 episodes of peritonitis observed among 299 patients. The total follow-up period was 22 517 patient-months, corresponding to a peritonitis rate of 1 episode in 34.1 patient-months. Excluding 79 patients with both culture-negative and culture positive peritonitis episodes, there were 391 episodes of peritonitis in 220 patients which were either culture positive (97 patients with 174 episodes; 44.6%) or culture negative (123 patients with 217 episodes; 55.4%). Among the

97 patients with culture-positive peritonitis, 38 had more than 1 episode of peritonitis, and among the 123 patients with culture-negative peritonitis, 52 had more than 1 episode of peritonitis.

Among 220 included patients, the underlying diseases were diabetes mellitus (30.8%), hypertension (22.0%), glomerulonephritis (6.7%), nephrolithiasis (2.6%), polycystic kidney disease (2.6%), reflux nephropathy (2%), familial diseases (2.0%), others (8.2%), and unknown (21.5%). The organisms identified in cases of culture-positive peritonitis were *Staphylococcus epidermitis* (24.8%), *S aureus* (24%), *Pseudomonas aeroginosa* (10%), fungi (10%), *Klebsiella pneumoniae* (7.0%), and other organisms (24.2%). Gender distribution, mean age, frequency of different symptoms and signs at presentation, and type of underlying disease were compared between the culture-positive and culture-negative peritonitis groups. None of the comparisons showed any significant differences except for a higher leukocyte count in peritoneal fluid of culture-positive compared to culture-negative episodes ($3.20 \pm 5.32 \times 10^9/L$ versus $1.84 \pm 3.88 \times 10^9/L$; Table 1).

The 1-, 2-, 3-, and 4-year patient survival rates were 85%, 75%, 69%, and 59%, respectively, for the 97 patients with culture-positive peritonitis, and these rates were 92%, 78%, 73% and 63%, respectively, for the patients with culture-negative peritonitis (*P* = .34; Figure 1). The 1-, 2-, 3-, and 4-year technique

Table 1. Comparison of Demographic and Clinical Characteristics of Patients on Peritoneal Dialysis With Culture-Negative and Culture-Positive Peritonitis*

Characteristics	Patients With Peritonitis		<i>P</i>
	Culture-Positive	Culture-Negative	
Male patients	42 (43.3)	52 (42.3)	.88
Mean age, y	53.4 ± 18.9	55.0 ± 16.6	.52
Cloudy dialysis solution	78 (30.2)	96 (33.1)	.48
Fibrin clots in dialysis solution	52 (20.1)	71 (24.5)	.28
Abdominal pain	110 (42.6)	121 (41.7)	.84
Nausea	33 (12.8)	45 (41.3)	.35
Vomiting	33 (12.8)	24 (8.3)	.12
Diarrhea	16 (6.2)	10 (3.4)	.18
Constipation	9 (3.5)	13 (4.5)	.49
Fever sensation	27 (10.5)	32 (11.0)	.84
Chills	29 (11.2)	23 (7.9)	.22
Abdominal tenderness	53 (20.5)	51 (17.6)	.40
Rebound tenderness	27 (10.5)	26 (9.0)	.60
Weakness	41 (15.9)	38 (13.1)	.40
Oral temperature $\geq 37.8^\circ\text{C}$	18 (7.0)	10 (3.4)	.07
Mean leukocyte count, $\times 10^9/L$	3.20 ± 5.32	1.8 ± 3.88	.07

*Symptoms and signs were studied in 391 peritonitis episodes, occurred in 220 patients. Values in parentheses are percents.

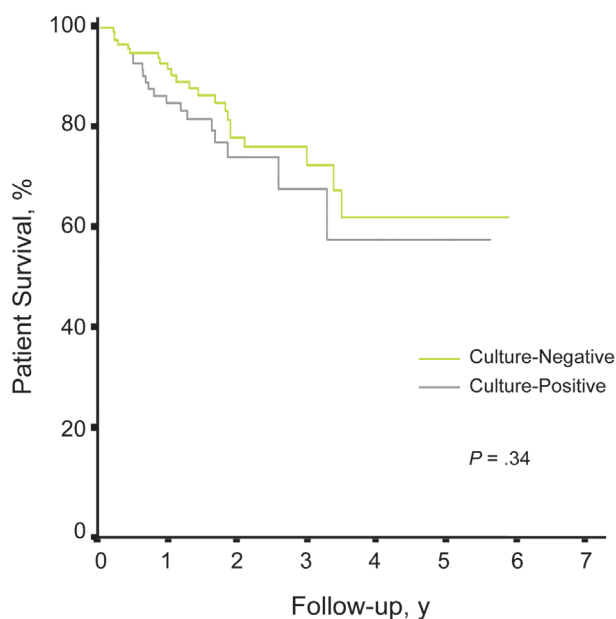


Figure 1. Comparison of patient survival in patients with culture-positive and culture-negative peritonitis.

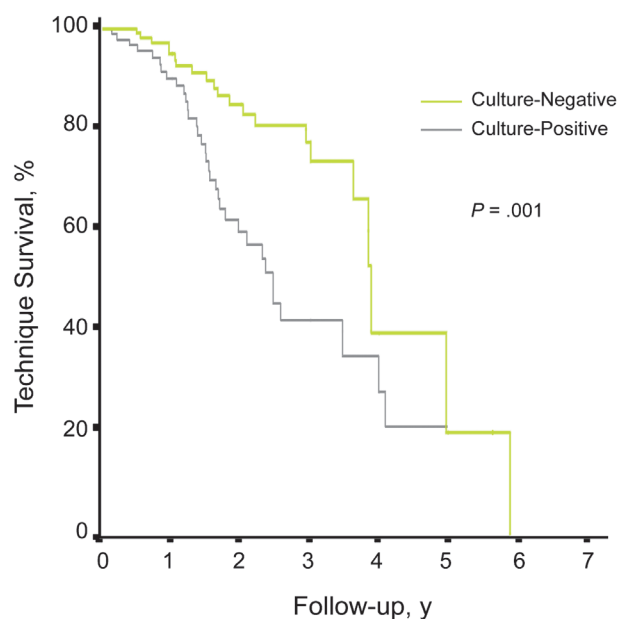


Figure 2. Comparison of technique survival in patients with culture-positive and culture-negative peritonitis.

survival rates were 90%, 57%, 42%, and 27% in the patients with culture-positive peritonitis, and 95%, 85%, 74%, and 40% in the patients with culture-negative peritonitis, respectively ($P = .001$; Figure 2).

There were higher rates of active PD patients (33.3% versus 19.6%), lower rates of PD dropouts (20.3% versus 40.2%), and higher rates of kidney transplantation (18.7% versus 7.2%) in patients with culture-negative peritonitis compared to those with culture-positive peritonitis ($P = .001$). Table 2 shows the current status of the patients with a history of culture-positive and culture-negative peritonitis. The overall mortality rates were similar between the two groups (30.9% versus 26.8%, $P = .55$). The ratio of PD-related death to PD-unrelated death was the same in the two groups (5/25 [0.2] versus 3/30 [0.1]; $P = .46$).

DISCUSSION

Culture-negative peritonitis may occur in approximately 20% of all peritonitis episodes in CAPD patients. In centers with rates higher than that, the culture methods should be reviewed and improved.¹⁰ However, the reported rate of culture negativity is quite variable between different centers and with different culture methods. The Network 9 study from Indiana reported an overall culture negative rate of 14% with different methods reported from various centers.¹⁰ In the study in the University of Manitoba, it was shown that the rate of culture-negative peritonitis decreased from 31.7% in 1991 to 15.7% in 1997.¹² This center practiced the International Society for Peritoneal Dialysis (ISPD) recommendations on culture method as standard.⁷ Two different centers from

Table 2. Current Status of Patients With History of Culture-Positive and Culture-Negative Peritonitis*

Current Status	Patients With Peritonitis (%)		Total (%)
	Culture-Positive	Culture-Negative	
On peritoneal dialysis	19 (19.6)	41 (33.3)	60 (27.3)
Switched to hemodialysis	39 (40.2)	25 (20.3)	64 (29.1)
Transplanted	7 (7.2)	23 (18.7)	30 (13.6)
Deceased	30 (30.9)	33 (26.8)	63 (28.6)
Kidney function recovered	1 (1.0)	1 (0.8)	2 (0.9)
Unknown	1 (1.0)	0	1 (0.5)
Total	97 (100)	123 (100)	220 (100)

* $P = .001$ (Fisher exact test).

Hong Kong have reported different values; the rate of culture-negative peritonitis has been 18.4% in Prince of Whales Hospital, using BacTAlert blood culture bottles versus 35.6% in Queen Marry Hospital using aerobic and anaerobic culture plates and thioglycollate enrichment broth.^{11,14} Culture negativity rates between 50% and 60% have been reported from King Khalid University Hospital, Riyadh, and Haseki Hospital, Istanbul, the former using aerobic and anaerobic blood culture bottles.^{15,16}

In our registry, we have had a high culture-negative peritonitis rate of 55.9%. Most of our PD centers have reported to perform standard ISPD culture method, ie, direct injection of 10 mL of effluent in blood culture bottles.⁷ However, the rate of culture negativity is very high compared to the ISPD recommendations, and we believe that despite the attempt of our centers to follow the guidelines of the ISPD for culture method, there have been serious actual pitfalls in culture performance. This necessitates a meeting between head nephrologists of our centers and the microbiology teams to elucidate these pitfalls and urgent decision making for serious improvement in our culture methods and possibly types of culture media. Also, the possibility of prior antibiotic use should be always considered and re-education of PD nurses and patients regarding “culture before antibiotic,” together with providing the patients with culture media in case they should start antibiotics at home is recommended.

Culture negativity has many reasons, the most important of which have been shown to be nonexpert personnel and previous antibiotic use.¹¹ Other causes of culture-negative peritonitis may be inadequate sample collection, poor culture techniques, low bacterial count in the sample, specific bacterial characteristics that make them difficult to grow in conventional culture media, and contamination of dialysate with endotoxin or acetaldehyde.¹⁷ Various unusual and fastidious microorganisms, including unusual bacteria, mycobacteria, fungi, viruses, and parasites, may cause peritonitis and remain not revealed in standard culture media, necessitating the use of specific media based on clinical suspicion.¹⁸ However, the similarity between demographic characteristics, the presenting symptoms and signs, patient survival, and the ratio of PD-related to PD-unrelated death between the two groups, together with a better technique survival in patients with culture-negative peritonitis, indicates good response

to conventional empiric therapy and low probability of existence of unusual microorganism, which would have caused high morbidity and mortality.

The course of culture-negative peritonitis has generally been reported benign. Szeto and colleagues showed a similar rate of catheter removal between patients with culture-negative and culture-positive peritonitis,¹¹ and Bunke and colleagues reported a lower catheter removal rate by 50% in patients with culture-negative peritonitis.¹⁰ Chen and colleagues showed an overall cure rate of greater than 80% in patients with culture-negative peritonitis with older age, abdominal pain, and the need for salvage therapy associated with an increased risk for relapse and treatment failure.¹⁹ Our study showed a significantly higher technique survival in patients with culture-negative peritonitis. This may have been due to administration of multiple and/or broad-spectrum antibiotics for a longer duration to eradicate the unknown microorganisms by some centers or to lower microorganism counts in PD effluent of patients with culture-negative peritonitis, as suggested by Ozturk and colleagues.¹⁶ Their study showed a significantly higher leukocyte count in PD effluent of patients with culture-positive peritonitis versus culture-negative peritonitis, suggesting the possible higher count of microorganisms in culture-positive peritonitis cases. We could also show a higher leukocyte count in culture-positive peritonitis compared with culture-negative peritonitis.

We should acknowledge limitations of the present study when interpreting our results, including practical nonuniformity of culture methods, together with lack of information about the detailed steps of culturing from all PD centers and lack of information from types of antibiotic coverage and the course of the disease that we hope to overcome through meetings with the directors of our PD centers.

CONCLUSIONS

This multicenter study which presents the 12-year data of the Iranian CAPD Registry is the first comprehensive report about the epidemiology and clinical course of our cases of peritonitis. We showed a high rate of culture-negative peritonitis. Culture negativity did not have any negative impact on clinical course, and technique survival was higher in patients with culture-negative peritonitis. However, to prevent inadvertent long-term use of

broad-spectrum antibiotics with their possible side effects and development of antibiotic resistances, a more rigorous program for re-education of our staff and culture methods, improvement of culture media by the laboratories, and supervision on taking the cultures before starting any antibiotics is necessary.

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CONFLICT OF INTEREST

None declared.

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