

The Outcome and Return to Peritoneal Dialysis Following Fungal Peritonitis: A 9-Year Experience at Uttaradit Hospital, Thailand

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Background: Fungal peritonitis (FP) treatments are successful in patients undergoing continuous ambulatory peritoneal dialysis (CAPD). There were few studies that reported the success and outcome of reinitiated CAPD.

Objective: To characterize the clinical characteristics and outcomes of patients who developed FP after reinitiating CAPD.

Materials and Methods: A retrospective study was undertaken in the peritoneal dialysis center at Uttaradit Hospital in Uttaradit, Thailand. Between November 2008 and November 2018, all FP-related CAPD patients had their medical records examined.

Results: Five hundred eighteen CAPD patients were enrolled. Twenty-eight bouts of FP occurred in 28 patients, with nine caused by *Candida* species and 19 caused by filamentous fungi. FP was responsible for 6.5% of all peritonitis occurrences. Sixteen of the 28 patients successfully resumed peritoneal dialysis, while 12 did not. Three patients died, one dropped out, two experienced technical failure, and six were switched to hemodialysis. All patients who resumed peritoneal dialysis had a 94 percent 1-year technical survival rate.

Conclusion: In regions where CAPD patients have trouble obtaining hemodialysis maintenance, more than half (57%) of FP patients can resume peritoneal dialysis under carefully selected social and physical conditions.

Keywords: CAPD; Fungal peritonitis

Received 30 October 2023 | Revised 17 September 2025 | Accepted 22 September 2025

J Med Assoc Thai 2025;108(11):863-9

Website: <http://www.jmatonline.com>

Since the first peritoneal dialysis (PD) policy was implemented in Thailand in 2007, continuous ambulatory peritoneal dialysis (CAPD) has gained widespread adoption due to government funding. There were people who previously could not afford long-term renal replacement therapy. PD-related infections, particularly peritonitis, are a major cause of CAPD failure. Previous investigations found 16% to 53% morbidity and mortality, respectively, and associated with the increased occurrence of unusual forms of fungal-related peritonitis⁽¹⁻⁸⁾.

When compared to bacterial peritonitis, fungal peritonitis (FP) is more likely to result

in hospitalization, catheter removal, transfer to hemodialysis, and death. The primary reason physicians are hesitant to restart CAPD is irreversible peritoneal adhesion. However, in locations where these categories of patients have limited access to hemodialysis, it is unclear if resuming PD in patients who had undergone FP is still conceivable.

The objective of the present study was to report the number of FP episodes at Uttaradit Hospital in Uttaradit Province, Thailand, between November 2008 and November 2018. The authors presented the results of FP patients and peritoneal equilibration test (PET) in which PD was restarted.

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How to cite this article:

Natejumnong C, Jitthorn K, Naka P, Noithachang W. The Outcome and Return to Peritoneal Dialysis Following Fungal Peritonitis: A 9-Year Experience at Uttaradit Hospital, Thailand. J Med Assoc Thai 2025;108: 863-9.
DOI: 10.35755/jmedassocthai.2025.11.863-869-00499

Materials and Methods

The present study was a retrospective study conducted in the PD center of Uttaradit Hospital in Uttaradit Province, Thailand. All of the PD-related FP occurrences were recorded between November 2008 and November 2018.

FP was defined as the presence of any two of the following, 1) symptoms and signs of peritoneal inflammation, 2) turbid dialysate with a white cell count of more than 100 cells/mm³ and a differential

cell count of more than 50% polymorphonuclear cells, or 3) identification of fungus by macroscopic and microscopic characteristics.

Any abnormal plaque lining in the peritoneal tube (Figure 1A) was taken out to perform a potassium hydroxide (KOH) smear for a prompt diagnosis (Figure 1B). The specimens were collected by adding 10 milliliter (mL) of peritoneal dialysate to Bact/Alert 3D blood culture bottles. The positive culture colonies (Figure 1C) were sub-cultured in Mac Conkey, Blood, and Chocolate agars. The plates were incubated at 35°C for at least 24 hours. A portion of the sample was examined further by gram stain under a microscope to look for fungal hyphae or yeast presence. If they were fungal hyphae, all isolates were cultivated on Sabouraud dextrose agar (SGA) and incubated until excellent sporulation occurred. They were then transferred to the National Institute of Health's Microbiology Laboratory Section. Each isolate was examined macroscopically, including the color of the surface and reverse colonies, texture, and growth rate. The conidiogenous process was analyzed using microscopic inspection and slide culture preparation. If they were yeast, they were examined under a microscope. The authors choose a single colony and streak it onto a fresh chromogenic agar plate and differentiated *Candida* species based on colony color. The biochemical tests and antifungal susceptibility tests were not performed due to the facility's limitations.

Data collection

All data was obtained from the Uttaradit Hospital's PD unit outpatient charts and outpatient program computer. Demographic characteristics of the study included age, gender, cause of end-stage renal disease, duration of PD, fungal species, evident fungal plaques in the peritoneal catheter, and a history of bacterial peritonitis within the past three months. The clinical signs and laboratory results were fever, abdominal discomfort, turbid dialysate, peritoneal white blood cell count, and neutrophil count. Data from PET on patients who had their PD re-initiated were also obtained.

Definitions

Death was considered by FP when both events occurred during the period of hospitalization. Primary FP was defined as the first episode of peritonitis caused by fungus, which was not related to the previous antibiotic administration.

PET was conducted by standard four-hour

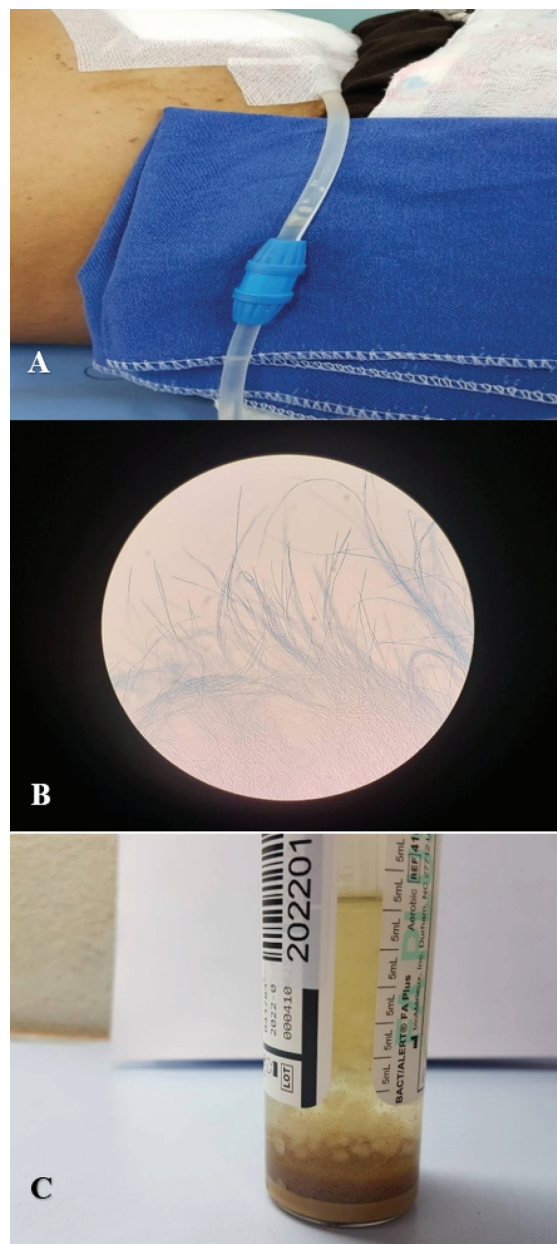


Figure 1. (A) The peritoneal tube is lined with many white plaques. (B) Microscopy revealed aseptate, non-pigmented hyphae in the KOH smear. (C) The fungal colony has a smooth, shiny surface and thick, creamy growth.

procedure by measuring the ratio of dialysate creatinine and glucose levels at 0, 2, and 4 hours of dwell, and serum levels of creatinine and glucose at any time during the test.

PET are classified as high transporter, low transporter, and average transport.

High transporter and high-average transporter have equilibration of creatinine, typically with a

D/Pcreat greater than 0.8 and 0.65 to 0.80 after four hours, respectively.

Low-average transporter and low transporter have equilibration of creatinine, typically with a D/Pcreat of less than 0.55 to 0.64 and less than 0.55 after four hours, respectively.

A baseline PET was done 12 months before the FP episode.

A PET after FP was desired to be performed three months after infection. Except it can be postponed if patients have two distinct peritonitis events in that period.

Data analysis

This section presented statistics as numbers and percentages for categorical variables, mean $\pm$ standard deviation for normally distributed continuous variables, and median and interquartile range for non-normally distributed continuous variables.

Fisher's exact test was used for categorical data, and the independent t-test was used for normally distributed variables to compare the dialysate white blood cell counts and polymorphonuclear cell counts between the *Candida* peritonitis group and the filamentous peritonitis group. The statistical analysis was performed using Stata/MP 16.0. Statistical significance was defined as a p-value of less than 0.05.

Ethical approval

The present study was approved by the Ethics Committee of Naresuan University (document number 005/66). All documents were kept in locked storage. Every computer file processed on the user's laptop required a password to be opened. In the transcript, none of the patients' names were stated.

Results

Between November 2009 and November 2018, there were 518 CAPD patients. Over a 1,156-patient-year follow-up period, twenty-eight episodes of FP were identified in 28 patients, including peritonitis. FPs accounted for 6.5% of total peritonitis episodes, with one per 495 patient months.

Table 1 shows the study's demographic characteristics. The study population's average age at the time of FP was 56.57 ± 11.3 years, with 28 patients including 13 men and 15 women. The median PD duration was 1.4 years (range of 0.4 to 5.1). Diabetes nephropathy was the primary cause of end-stage renal disease in eight patients (30%), hypertensive

Table 1. Demographic characteristics of 28 cases with fungal peritonitis in CAPD patients

Variable	
Age (years); mean $\pm$ SD	56.57 $\pm$ 11.3
Sex (male:female); n	13:15
Duration of CAPD (year); median (IQR)	1.4 (0.4 to 5.1)
Underlying renal disease; n (%)	
Diabetes nephropathy	8 (30)
Obstructive nephropathy	4 (28)
Hypertensive nephropathy	7 (25)
ADPKD	1 (4)
SLE	1 (4)
Unknown	6 (22)
Organisms; n (%)	
<i>Candida</i> species	9 (32)
• <i>Candida albicans</i>	2 (27)
• <i>Candida non albicans</i>	7 (25)
Filamentous	19 (68)
• <i>Aspergillus flavus</i>	3 (10)
• <i>Fusarium solani</i>	4 (14)
• <i>Paecilomyces lilacinus</i>	2 (7)
• <i>Phialophora repens</i>	1 (4)
• <i>Acremonium</i> species	1 (4)
• <i>Scyladidium dimidiatum</i>	1 (4)
• Non-sporulating mold	1 (4)
• Unidentified mold	6 (21)
Previous 3 months of bacterial peritonitis; n (%)	9 (32)
Primary fungal peritonitis; n (%)	11 (39)
Antifungal therapy; n (%)	
Amphotericin B alone	15 (54)
Fluconazole alone	3 (10)
Amphotericin B plus fluconazole	10 (36)
Duration of catheter removal (day); median (IQR)	6 (1 to 23)
Duration of treatment (day); median (IQR)	14 (3 to 28)

SD=standard deviation; IQR=interquartile range; CAPD=continuous ambulatory peritoneal dialysis; ADPKD=adult polycystic kidney disease; SLE=systemic lupus erythematosus

nephropathy in seven patients (25%), obstructive nephropathy in four patients (15%), autosomal dominant polycystic kidney disease (ADPKD) in one patient (4%), systemic lupus erythematosus (SLE) in one patient (4%), and unknown in six patients (22%). Nine patients (32%) previously had bacterial peritonitis.

The first episode of FP with no prior bacterial peritonitis occurred in 20 individuals (68%). Therapeutic antifungal regimens administered in the present study consisted of the following: 1) intravenous amphotericin B at a dosage of 0.5 to 0.7 mg/kg/day as monotherapy, which was given to 15 patients (54%), 2) oral fluconazole at 200 mg/day

Table 2. Clinical manifestation, peritoneal dialysate characteristics and outcomes of 28 cases with fungal peritonitis in CAPD patients

Parameters	Candida species (n=9)	Filamentous (n=19)	p-value
Symptoms and sign; n (%)			
Fever	4 (44)	3 (16)	0.12
Cloudy dialysate	9 (100)	19 (100)	1.00
Abdominal pain	5 (55)	13 (68)	0.40
Visible catheter particle	1 (12)	8 (42)	0.11
Lab values; median (IQR)			
Dialysate WBC (cell/mm ³)	990 (350 to 11,480)	660 (133 to 6,200)	0.80
Dialysate PMN (%)	80 (60 to 100)	73 (13 to 100)	0.80
Result; n (%)			
Dropped out	0 (0)	1 (5)	0.69
Transfer to hemodialysis	0 (0)	7 (37)	0.04
Return to PD	8 (88)	8 (42)	0.02
Death	1 (12)	3 (16)	0.61

IQR=interquartile range; WBC=white blood cell; PMN=polymorphonuclear neutrophil; PD=peritoneal dialysis

alone, administered to three patients (10%), and 3) a sequential regimen comprising intravenous amphotericin B at 0.5 to 0.7 mg/kg/day following 200 mg of oral fluconazole, prescribed in 10 patients (36%). The median time of peritoneal catheter removal was six days (range of 1 to 23) and antifungal treatment was 14 days (range of 3 to 28).

Filamentous fungi were the most commonly isolated fungal species in the present study center in 68% of the cases (19 patients). *Aspergillus flavus* was found in three patients (10%), *Fusarium solani* in four patients (14%), *Paecilomyces lilacinus* in two patients (7%), *Acremonium* species in one patient (4%), *Scybalidium dimidiatum* in one patient (4%), *Penicillium citrinum* in one patient (4%), non-sporulated mold in one patient (4%), and unidentified mold in six patients (21%). Nine patients (32%) were caused by *Candida* species, with *Candida albicans* in two patients (9%), and non-*albicans* *Candida* in seven patients (23%).

Table 2 shows the clinical symptoms, dialysate analysis, and results. Fever was reported in four out of nine patients in the *Candida* group and in three out of 19 patients in the filamentous group, at 44% versus 16% ($p=0.12$). Cloudy effluent was observed in all patients in both groups. Abdominal pain was present in 13 out of 19 patients in the *Candida* group and in five out of nine patients in the filamentous group, which was not statistically significant at 68% versus 55% ($p=0.40$). In addition, the authors found either white or black plaque lining in peritoneal tubes in both groups with 42% versus 12% ($p=0.112$). The median peritoneal dialysate white blood cell count was not different, at 990 versus 660 cell/mm³

($p=0.80$). Three of the 22 patients with FP died, one in the *Candida* group and two in the filamentous group, accounting for a 14% death rate. Seven patients (37%) in the filamentous group were permanently switched to hemodialysis, but none in the *Candida* group. Sixteen out of 22 patients (57%) in both groups were able to resume PD, with eight (88%) in the *Candida* group and eight (42%) in the filamentous group. One patient from the filamentous group dropped out of the present study program.

PET could be done before and after FP in eleven of the sixteen patients whose PD was reinitiated, as shown in Table 3. There was no change in transport status among eight patients with one for high, four for high-average, and three for low-average. Three patients had their PETs changed with one from high-average to high transport, one from high transport to high-average, and one from low to low-average status. Eight patients experienced FP for the first time, two had one previous episode of bacterial peritonitis, and one had three previous episodes of bacterial peritonitis.

Discussion

Although an increasing number of patients are eligible for CAPD through government funding, accumulative patients with refractory peritonitis or FP may be denied the opportunity to restart PD due to a variety of restrictions, including fear of extensive peritoneal adhesion. In the authors' institute, two-thirds of FP patients were caused by filamentous species, and one-third by *Candida* species, which differed from earlier research⁽¹⁻¹²⁾. Unsurprisingly, the previous three months of bacterial peritonitis

Table 3. Peritoneal equilibration test in 11 patients who could be performed PET before and after fungal peritonitis

Patient number	Organism	Episode number of peritonitis	Transport category (D/P Cr)	
			Baseline PET	PET after fungal peritonitis
1	<i>Candida</i> , non-albicans	1	HA	HA
2	<i>Candida</i> , non-albicans	1	HA	HA
3	<i>Acromonium</i> species	4	LA	LA
4	<i>Paecilomyces lilacinus</i>	1	HA	HA
5	<i>Candida ciferrii</i>	1	HA	H
6	<i>Candida parasilopsis</i>	1	HA	HA
7	<i>Aspergillus flavus</i>	1	LA	LA
8	<i>Candida parasilopsis</i>	1	LA	LA
9	<i>Candida grabata</i>	2	H	H
10	Mold (not identified)	2	H	HA
11	Mold (not identified)	1	Low	LA

PET=peritoneal equilibration test; D/PCr=dialysate/plasma creatinine ratio; H=high transporter; HA=high-average transporter; LA=low-average transporter

were associated with the *Candida* group more than the filamentous group in the present study (data not shown). Antibiotics will alter the fecal flora, they disrupt the beneficial bacteria and help promote *Candida* growth. Overgrowth of *Candida*, normally present in small amounts in the intestine, therefore possibly transmural migration into the peritoneal cavity. In CAPD patients, low immunological status in general and comorbidities are additional considerations. Similar to other research^(9,13,14), it was found that filamentous FP did not require antibiotic pressure. A variety of filamentous fungi are often isolated from soil and decomposing materials. Filamentous fungi typically enter the body via the intraluminal or through structural flaws in the catheter material. Home visits were conducted in an attempt to determine the cause of filamentous groupings. The authors found that certain household items were mold contaminated. A fungal culture utilizing cotton swabs contaminated by one patient indicated the presence of *Aspergillus* species. Thus, the aseptic technique, handwashing, and the significance of using clean equipment and surroundings thereafter would be stressed to all patients with peritonitis during their retraining. Many clinicians have prescribed antifungal prophylaxis to limit the incidence of FP. The results of observational data on antifungal prophylaxis during any course of antibiotic therapy, whether for non-bacterial peritonitis or not, were imprecise⁽¹⁵⁻¹⁹⁾. Restrepo et al.⁽²⁰⁾ conducted a small randomized controlled trial to assess the use of 200 mg of fluconazole every 48 hours after patients received antibiotics and found that it decreased the occurrence of secondary FP over the next 150 days. There is presently no guideline for routine antifungal

prophylaxis during bacterial peritonitis due to the lack of a large-scale prospective randomized controlled trial. It might, however, be taken into consideration for use in a center with a high FP rate of more than 10%.

The authors found that catheter removal had a significant impact on survival rate, even though the length of antifungal medication was less than recommended⁽²¹⁾. A high number of study patients survived with simultaneous empirical antifungal and peritoneal catheter removal, according to the International Society for Peritoneal Dialysis (ISPD) guidelines 2022⁽²²⁾. When a fungal susceptibility test cannot be done, the peritoneal catheter should be promptly removed. The study groups received empirical intravenous amphotericin B, oral fluconazole, or an initial intravenous amphotericin B followed by oral fluconazole without flucytosine. Four out of 28 patients died. One patient had acquired septic shock and multiple organ failure. Another patient with SLE who had previously taken a moderate dose of corticosteroid for autoimmune hemolytic anemia developed uncontrolled status epilepticus. The third patient, who had penicillin-resistant streptococcus viridian peritonitis, developed *Candida albicans* infection and died one day later after experiencing another bout of cloudy effusion. The final case, whose peritonitis fluid culture report was positive for *Bacillus* species, had a delayed diagnosis of FP and died despite Tenckhoff catheter removal and receiving antifungals.

In the authors' institute, the decision to restart PD was informed by group discussions of staff, patients, and their care providers. Prior to 2017, abdominal ultrasonography was utilized to detect intraabdominal

collections or compartmentalized ascites in some patients. Up until 2017, computed tomography (CT) peritoneography, was used to assess peritoneal adhesion. The authors' PD team discussion focuses on the probability of significant peritoneal adhesion by assessing abdominal pain severity during peritonitis, abdominal ultrasound findings, frequency of episodes of peritonitis, and personal hygiene. According to the patients' opinions, some of the barriers they had in accessing hemodialysis centers included distance from home, dependent status, working lifestyle, and transportation costs. In this regard, it turned out that there were more FP-related patients in the filamentous group permanently switched to hemodialysis without regard for the particular type of fungus.

Studies have documented a change in transport status after resuming PD following severe or refractory bacterial peritonitis^(23,24). Currently, no study has reported this concern from FP-experienced patients, which could be due to small numbers. The authors noticed a change in the results of the present study. That is, five patients had a baseline high average transport status. As a result, it is difficult to determine how much inflammation impacted their peritoneum, especially since four patients' transport status remained unchanged. Two individuals with low baseline average transport appeared to have the same transport status following peritonitis. Even though high transporters were not observed to perform well with CAPD, theorized causes such as fluid overload and increased protein losses led to malnutrition. A meta-analysis of 20 observational studies, published in 2006, found that patients with low transport status had an elevated mortality risk of 22%, 46%, and 77% compared to low-average, high-average, and high transporters, respectively⁽²⁵⁾. In contrast, the following studies found that patient survival in CAPD receiving automated peritoneal dialysis (APD) or icodextrin was unaffected by membrane transport status⁽²⁶⁻²⁸⁾. These therapeutic prescriptions can now be considered because the government covered the costs.

More than half of the authors' FP patients (57%) were able to resume their PD, which was equivalent to or higher than previously reported rates of 8.5% to 50%^(21,29). The authors agree with the government's PD policy of selecting patients to stay on PD if they had barriers to maintaining hemodialysis. However, returning to CAPD in the authors' institute has been discussed under the policy. First, the authors are not excluding such FP patients from undergoing PD, which may limit the potential candidate's

ability to continue on PD and have limited access to hemodialysis services. The one-year technical survival rate in patients who reinitiated PD in the present center was 94%, and therapy was tailored and constantly monitored based on their quality of life.

The present study is limited by its retrospective nature. The biological and antifungal susceptibility tests were not performed. Even though the authors indicated that the one-year follow-up survival rate was high in individuals resuming PD, long-term follow-up is beyond the study scope. The authors desire to demonstrate that PD can serve as a bridge therapy for up to a year for people who are not sufficiently prepared for hemodialysis.

Conclusion

In conclusion, in regions where CAPD patients have difficulties obtaining hemodialysis maintenance, FP patients are able to resume PD under carefully selected social and physical conditions.

What is already known about this topic?

Peritonitis is a common consequence of PD. FP accounts for 1% to 12% of all peritonitis in dialysis patients and has been associated with major complications such as technique failure and high mortality. Early catheter removal may improve outcomes marginally, according to observational studies.

What does this study add?

There is limited data published on whether individuals with FP can resume PD. This study observed that more than half of well-selected patients may continue PD with a high 1-year survival rate.

Acknowledgment

The authors would like to thank Ms. Nanthawan Mekla for her assistance with microbiology investigation and thanks to the Mycology Laboratory Section, National Institute of Health, Department of Medical Sciences, Thailand.

Conflicts of interest

The authors declare no conflict of interest.

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