J Microbiol Immunol Infect
2004;37:115-120

# Fungal peritonitis in peritoneal dialysis patients: effect of fluconazole treatment and use of the twin-bag disconnect system

**Chih-Ming Chen, Mao-Wang Ho, Wen-Liang Yu, Jen-Hsien Wang**

*Division of Infectious Disease, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan, ROC*

Received: May 17, 2003 Revised: July 17, 2003 Accepted: August 14, 2003

Fungal peritonitis is an uncommon but potentially life-threatening complication for patients undergoing continuous ambulatory peritoneal dialysis. This retrospective study evaluated the efficacy of fluconazole in fungal peritonitis treatment and the incidence of fungal peritonitis in different peritoneal dialysis disconnect systems. Fungal peritonitis was caused by *Candida* species in 67% of episodes. The most common pathogen in this series was *Candida parapsilosis* (29%), followed by *Candida albicans* (14%). One patient (5%) died within 1 month after admission for treatment of fungal peritonitis. Only 1 patient (5%) in this series could resume peritoneal dialysis. Treatment with fluconazole alone has an effect comparable to intraperitoneal (IP) amphotericin B alone or IP amphotericin B combined with oral or intravenous fluconazole. The incidence of fungal peritonitis in patients who used the spike, Y-set, and UV antiseptic systems was 5.69, 6.20, and 2.93 times, respectively, as frequent as that of fungal peritonitis in patients who used the twin-bag disconnect system.

**Key words:** Dialysis instrumentation, fluconazole, peritoneal dialysis, peritonitis

Despite technical improvements in peritoneal dialysis treatment, peritonitis remains one of the most frequent complications of long-term peritoneal dialysis. Fungal infection causes 3 to 6% of all cases of peritonitis in peritoneal dialysis patients [1-3]. Although fungal peritonitis is relatively rare, it is associated with serious complications. The mortality of fungal peritonitis is approximately 5 to 25% [4-6]. More than 50% of patients who develop fungal peritonitis must drop out from peritoneal dialysis [3,7]. Identification of risk factors and improved treatment strategies for fungal peritonitis may avoid development of these serious complications.

Fluconazole was reported as the first successful treatment for fungal peritonitis in 1989 [8]. In comparison with intraperitoneal (IP) amphotericin B, fluconazole has the advantages of high bioavailability, excellent peritoneal penetration, rare adverse reactions, and can be used in outpatients [9,10]. Some resistant *Candida* species have emerged and non-albicans *Candida* species have increased since the introduction of fluconazole. There is no consensus on the optimal treatment regimen for fungal peritonitis and further evaluation of the efficacy of fluconazole in fungal peritonitis treatment is needed.

Previous studies have shown that the incidence of bacterial peritonitis was significantly decreased after the introduction of the Y-set disconnect system and twin-bag disconnect system [11,12]. However, the effectiveness of these new dialysis systems in fungal peritonitis is not well established. A previous study found that the main risk factors for fungal peritonitis were a recent episode of bacterial peritonitis and recent exposure to antibiotics [13].

This study was designed to evaluate the efficacy of fluconazole in fungal peritonitis treatment and the incidence of fungal peritonitis in different dialysis disconnect systems.

## Patients and Methods

Between June 1988 and December 2002, a total of 813 patients with end-stage renal failure underwent chronic ambulatory peritoneal dialysis (CAPD) treatment in our dialysis unit. All patients had implanted double-cuffed silastic Tenckhoff catheters (Baxter Healthcare Co, Mountain Home, AR, USA). Patients were trained to perform peritoneal dialysis using contemporary available exchange systems including the conventional spike

*Corresponding author: Dr. Jen-Hsien Wang, Division of Infectious Disease, Department of Internal Medicine, China Medical University Hospital, No. 2, Yuh Der Road, Taichung, Taiwan 404, ROC.*
*E-mail: jenhsien@www.cmuh.org.tw*

system, the Y set system (“ O” set, UltraSet, Baxter), the twin-bag system (UltraBag, Baxter), and the ultraviolet antiseptic system (UVXD, UV FLASH, Baxter).

The medical records of all patients with fungal peritonitis were reviewed to retrieve information on factors that could affect the outcome of fungal peritonitis. Diagnosis of fungal peritonitis was made if there was an effluent cell count of 100/mL or greater, with a differential cell count showing more than 50% polymorphonuclear cells and a culture positive for fungi on 1 or more occasions. The clinical and demographic characteristics of patients including age, gender, cause of end-stage renal disease, and education were recorded. Data on total white cell and differential cell counts in the peritoneal effluent were collected. Information retrieved and analyzed included the presence of fever, abdominal pain, antibiotic use within 1 month before the onset of fungal peritonitis, time of catheter removal, days of hospital stay, species of fungus causing peritonitis, and antifungal agents administered.

## Data analysis and statistics

Data are expressed as mean ± standard deviation unless otherwise specified. The incidence of fungal peritonitis was calculated as the number of fungal peritonitis episodes divided by the total peritoneal dialysis duration of all patients and presented as episodes per 100 patient-months. The incidence density ratio for patients using different dialysis disconnect systems was calculated. Poisson distribution test was used to compare the incidence of fungal peritonitis for patients treated with different dialysis systems. Two-tailed Student’s *t* test was used to compare the duration of hospital stay and

**Table 1.** Clinical characteristics of 20 cases of fungal peritonitis in peritoneal dialysis patients

| Patient no. | Age/ gender | Duration of CAPD (months) | Recent bacterial peritonitis | Recent antibiotic therapy | PD fluid WBC | | Therapy | Outcome |
|---|---|---|---|---|---|---|---|---|
| | | | | | Count (cells/mL) | PMN (%) | | |
| 1 | 62/F | 39 | No | No | 450 | 86 | AmB ip then PC removal | PD |
| 2 | 52/M | 24 | Yes | Yes | 1800 | 97 | Fluconazole po then PC removal | Died[a] |
| 3 | 41/M | 48 | No | No | NA | NA | AmB ip then PC removal | HD |
| 4 | 14/F | 1 | No | No | NA | NA | Fluconazole po, AmB ip then PC removal | HD |
| 5 | 31/F | 11 | No | No | NA | NA | Fluconazole po, AmB ip then PC removal | HD |
| 6 | 54/M | 1 | No | No | 1980 | 85 | Fluconazole po then PC removal | HD |
| 7 | 57/M | 7 | Yes | Yes | 14200 | 91 | Fluconazole po then PC removal | Died[b] |
| 8 | 52/F | 26 | No | Yes | 5000 | 20 | Fluconazole po then PC removal | Died[b] |
| 9 | 45/F | 16 | Yes | Yes | 1140 | 20 | PC removal | HD |
| 10 | 41/M | 14 | No | Yes | 800 | 90 | Fluconazole po, AmB ip then PC removal | Died[c] |
| 11 | 60/M | 2 | No | Yes | 620 | 70 | Fluconazole po, AmB ip then PC removal | HD |
| 12 | 59/F | 25 | No | No | 2890 | 27 | Fluconazole po then PC removal | HD |
| 13 | 61/F | 19 | No | No | 590 | 85 | Fluconazole po then PC removal | HD |
| 14 | 64/F | 28 | Yes | Yes | 150 | 90 | Fluconazole po then PC removal | HD |
| 15 | 55/M | 30 | No | Yes | 2280 | 48 | AmB iv then PC removal | HD |
| 16 | 61/F | 29 | No | Yes | 590 | 14 | Fluconazole iv then PC removal | HD |
| 17 | 38/M | 6 | Yes | Yes | NA | NA | Fluconazole iv then PC removal | HD |
| 18 | 42/F | 13 | No | Yes | 180 | 95 | Fluconazole iv then PC removal | HD |
| 19 | 34/M | 26 | No | No | 800 | 70 | Fluconazole po then PC removal | HD |
| 20 | 20/M | 24 | No | No | 2390 | 70 | Fluconazole po then PC removal | HD |

Abbreviations: CAPD = continuous ambulatory peritoneal dialysis; PD = peritoneal dialysis; HD = hemodialysis; WBC = white blood cells; PMN = polymorphonuclear leukocytes; AmB = amphotericin B; iv = intravenous; ip = intraperitoneal; po = by mouth; PC = peritoneal catheter; NA = not available

[a]Died of gastrointestinal bleeding.

[b]Died of respiratory failure with nosocomial infection.

[c]Died of fungal peritonitis.

days between admission and peritoneal catheter removal for patients receiving different antifungal treatments. A *p* value of less than 0.05 was considered statistically significant.

## Results

A total of 24 episodes of fungal peritonitis was recorded between June 1988 and December 2002; however, only 20 of these cases had detailed records available. The overall incidence of fungal peritonitis was 0.12 episodes per 100 patient-months.

### Demographic and clinical characteristics

The demographics data of the patients and clinical characteristics of the 20 fungal peritonitis episodes are shown in Table 1. The mean age of patients was 47.2 ± 14.3 years. There were 10 males and 10 females. The cause of renal failure was diabetic nephropathy in 10 patients (50%), chronic glomerulonephritis in 5 patients (25%), hypertension in 3 patients (15%), transitional cell carcinoma in 1 patient (5%) and unknown cause in 1 patient (5%). Eleven episodes of fungal peritonitis (55%) occurred within 1 month of antibiotic use. Five episodes of fungal peritonitis (25%) occurred in patients with recent bacterial peritonitis. The mean duration from the start of peritoneal dialysis to the development of fungal peritonitis was 19.45 ± 12.78 months (range, 1 to 48 months). The clinical symptoms and signs of fungal peritonitis included cloudy dialysate effluent (100%), abdominal pain (70%), and fever (15%). The average white cell count in effluent was 2241 ± 3431/μL, and the mean percentage of neutrophils was 66.3 ± 30.0%.

**Table 2.** Causative fungi in 20 cases of fungal peritonitis in CAPD patients

| Causative fungi | No. of episodes (%) |
|---|---|
| *Candida* species | |
| *C. parapsilosis* | 6 (29) |
| *C. albicans* | 3 (14) |
| *C. glabrata* | 2 (10) |
| Other *Candida* species[a] | 3 (14) |
| *Trichosporin* species | 2 (10) |
| *Madurella mycetomatis* | 2 (10) |
| *Rhodotorula mucilaginosa* | 1 (5) |
| Others (unidentified) | 2 (10) |

Abbreviation: CAPD = continuous ambulatory peritoneal dialysis
[a]*Candida tropicalis* in 1 episode, *Candida famata* in 1, and *Candida haemuloniia* in 1.

### Microbiology

Table 2 shows the causative organisms for the 20 cases of fungal peritonitis. *Candida* species were the most common pathogens, accounting for 67% (14 episodes) of fungal peritonitis episodes, among which 14% (3 episodes) were *Candida albicans* and 52% (11 episodes) were non-albicans *Candida* species. Among the non-albicans species, *Candida parapsilosis* was the most frequent, accounting for 55% (6 episodes) of the fungal peritonitis episodes in our CAPD population. Other fungal organisms isolated included *Trichosporin asahii* in 1 episode, *Trichosporin cutaneum* in 1, *Madurella mycetomatis* in 2, and *Rhodotorula mucilaginosa* in 1.

### Disconnect system and fungal peritonitis incidence

The incidence of fungal peritonitis in patients using the different disconnect systems is shown in Table 3. Among the 24 patients, the Y-set disconnect system was used in 11 (45.8%), twin-bag disconnect system in 8 (33.3%), spike system in 3 (12.5%), and ultraviolet aseptic system in 2 (8.3%). The incidence of fungal peritonitis was 0.36 episodes per 100 patient-months during Y-set disconnect system use, 0.33 episodes per 100 patient-months in the spike system, 0.17 episodes per 100 patient-months in the ultraviolet aseptic system, and 0.058 episodes per 100 patient-months in the twin-bag

**Table 3.** Incidence of fungal peritonitis in patients using different peritoneal disconnect systems

| Dialysis system | No. of patients (%) | Patient-months for all patients | Incidence[a] | Incidence density ratio[b] | *p* |
|---|---|---|---|---|---|
| Spike | 3 (12.5) | 915.7 | 0.33 | 5.69 | <0.001 |
| Y-set | 11 (45.8) | 3045.6 | 0.36 | 6.20 | <0.001 |
| Ultraviolet antiseptic | 2 (8.3) | 1198.9 | 0.17 | 2.93 | 0.04 |
| Twin-bag | 8 (33.3) | 13800.9 | 0.058 | 1.00 | <0.001 |
| Total | 24 (100) | 18961 | 0.12 | | |

[a]Incidence of episodes per 100 patient-months.
[b]The incidence density ratio represents the ratio of incidence for patients using the disconnect system compared with the incidence for patients using the twin-bag disconnect system.

disconnect system. The incidence of fungal peritonitis in the spike system, Y-set disconnect system, and the ultraviolet aseptic system was 5.69-, 6.20-, and 2.93-fold, respectively, the incidence for the twin-bag disconnect system.

### Treatment and outcome

Among the 20 patients with fungal peritonitis episodes for which detailed medical records were available, 19 had undergone antifungal treatment and peritoneal catheter removal, and the remaining 1 patient underwent peritoneal catheter removal only. Two patients with mold infection were treated with IP amphotericin B. One patient with *Candida glabrata* infection was treated with intravenous amphotericin B. Four patients with *Candida* infection were treated with IP amphotericin B and oral fluconazole. Twelve patients received oral or intravenous fluconazole 100 to 200 mg per day. The mean duration of admission before catheter removal was 12 ± 7.17 days (range, 2 to 25 days). The mean duration of hospital stay was 39.1 ± 31.43 days (range, 12 to 130 days). Data from the 20 patients with medical records available showed that only 1 patient died from fungal peritonitis. Two of these patients died from respiratory failure as a complication of nosocomial infection, and 1 died from gastrointestinal bleeding. Among the surviving 16 patients, only 1 could resume peritoneal dialysis after complete treatment, and the others had to be switched to hemodialysis.

The 16 surviving patients were divided into 2 groups based on the use of amphotericin B or not. The duration of hospitalization until catheter removal and discharge from the hospital were compared between these 2 groups. Six patients received treatment with either amphotericin B alone or amphotericin B combined with fluconazole. In this group, the duration from admission to catheter removal was 13.5 ± 8.82 days, and the hospital stay was 26.67 ± 10.01 days. Ten patients received fluconazole only as antifungal treatment. Among the patients who did not receive amphotericin B, the duration from admission to catheter removal was 11.11 ± 5.84 days and the hospital stay was 28.33 ± 13.47 days. There was no significant difference in these durations between the 2 groups.

## Discussion

In this study, fluconazole had efficacy comparable to amphotericin B alone or amphotericin B plus fluconazole in the treatment of fungal peritonitis due to yeast infection in peritoneal dialysis patients. Patients using the twin-bag disconnect system had a significantly lower incidence of fungal peritonitis.

Fungal peritonitis is an uncommon but potentially life-threatening complication of CAPD. The incidence of fungal peritonitis in our CAPD population averaged approximately 6% of all peritonitis cases per year and was similar to previous reports [1,14,15]. Similar to previous reports, *Candida* species was the most common pathogen in this series, accounting for 67% of fungal peritonitis episodes [1,2,4]. Fifty two percent of the episodes of fungal peritonitis were caused by *Candida* species other than *C. albicans*, and 29% of the episodes were caused by *C. parapsilosis*. *C. albicans* was previously the most commonly reported pathogen of fungal peritonitis [5,14,15]. However, a shift towards non-albicans *Candida*, particularly *Candida parapsilosis*, has been observed during the past 2 decades [1,2,16]. *C. parapsilosis* is a common skin and subungual colonizer which has the ability to adhere easily to synthetic material [17]. *C. parapsilosis* infection is highly associated with catheter implantation and its high prevalence as a cause of fungal peritonitis in peritoneal dialysis patients is thus not surprising.

Previous studies have consistently showed that prior antibiotic use is an important risk factor predisposing to the development of fungal peritonitis [1-3]. Treatment with antibiotics has been suggested to suppress the normal bacterial flora of the intestine inducing an overgrowth of intestinal fungi, which in turn invades across the intestinal mucosal barrier and reaches the peritoneal cavity, causing fungal peritonitis if dialysate is present [5,14]. In this series, 11 patients (55%) had prior use of antibiotics, a slightly lower rate than in previous reports [4].

Li et al [11] found that patients using the Y-set disconnect and twin-bag disconnect system had a lower incidence rate (more patient-months per episode) of bacterial peritonitis than those using the conventional spike system. A lower incidence of infection in patients using the twin-bag system than the Y-set system was also reported by Kiernan et al [18]. However, the association of fungal peritonitis and peritoneal dialysis system is not well established. This is the first report of significantly lower incidence of fungal peritonitis in patients using the twin-bag disconnect system. Because all of the components of the twin-bag disconnect system are preassembled and the whole system is sterilized as a single unit, a lower rate of infection is expected.

Current treatment recommendations for fungal peritonitis from the International Society of Peritoneal Dialysis include administration of successful antifungal chemotherapy for 4 to 6 weeks and catheter removal if there is no clinical improvement after 4 to 7 days. If the catheter is removed, antifungal agents should be used for an additional 10 days [19]. However, there is still no consensus about the best time for catheter removal and the best antifungal regimen.

Administration of IP amphotericin B has the side effect of local irritation [5]. Fluconazole, a water-soluble triazole derivative with good tissue penetration and oral bioavailability, has been used since 1990. Pharmacokinetic studies in CAPD patients showed good dialysate drug concentrations against common *Candida* species with oral fluconazole [9,10]. Some previous reports also suggested that oral fluconazole with catheter removal was an effective treatment for fungal peritonitis and was comparable in efficacy to fluconazole plus 5-fluorocytosine [8,20]. The prevalence of non-albicans strains has been increasing and 5-fluorocytosine is not available in many hospitals. This situation led us to evaluate the efficacy of fluconazole in fungal peritonitis treatment. In this series, 10 patients were treated with oral or intravenous fluconazole alone plus catheter removal. Only 1 patient (10%) died in the fluconazole treatment group, a mortality rate comparable with a previous study [5]. There was no significant difference in the duration of hospital stay and days of hospitalization until catheter removal between the amphotericin B and fluconazole treatment group. Our results indicate that fluconazole was effective in the treatment of fungal peritonitis in CAPD patients, even when not combined with 5-fluorocytosine.

In conclusion, this study found that oral or intravenous fluconazole had comparable effect in the treatment of *Candida* peritonitis. As fluconazole is associated with fewer complications, a high bioavailability, and is orally active, it should be the drug of choice of for the treatment of fungal peritonitis due to yeast. This study also showed that the twin-bag disconnect system not only reduced the incidence of bacterial peritonitis but also that of fungal peritonitis. Fungal peritonitis has a high morbidity and mortality rate and few patients can resume peritoneal dialysis after its resolution. As certain risk factors for fungal peritonitis cannot be removed or effectively prevented, such as previous antibiotic use or recent bacterial peritonitis, use of or switching to the twin-bag system may be beneficial for all peritoneal dialysis patients.

## References


1. Goldie SJ, Kiernan-Troidle L, Torres C, Gorban-Brennan N, Dunne D, Kliger AS, et al. Fungal peritonitis in a large chronic peritoneal dialysis population: a report of 55 episodes. Am J Kidney Dis 1996;28:86-91.
2. Wang AY, Yu AW, Li PK, Lam PK, Leung CB, Lai KN, et al. Factors predicting outcomes of fungal peritonitis in peritoneal dialysis: analysis of a 9-year experience of fungal peritonitis in a single center. Am J Kidney Dis 2000;36:1183-92.
3. Bren A. Fungal peritonitis in patients on continuous ambulatory peritoneal dialysis. Eur J Clin Microbiol Infect Dis 1998;17: 839-43.
4. Cheng IK, Fang GX, Chan TM, Chan PC, Chan MK. Fungal peritonitis complicating peritoneal dialysis: Report of 27 cases and review of treatment. Q J Med 1989;265:407-16.
5. Eisenberg ES, Leviton I, Soeiro R. Fungal peritonitis in patients receiving peritoneal dialysis: Experience with 11 patients and review of the literature. Rev Infect Dis 1986;8:309-21.
6. Nagappan R, Collins JF, Lee WT. Fungal peritonitis in continuous ambulatory peritoneal dialysis—the Auckland experience. Am J Kidney Dis 1992;20:492-6.
7. Johnson RJ, Ramsey PG, Gallagher N, Ahmad S. Fungal peritonitis in patients on peritoneal dialysis: Incidence, clinical features and prognosis. Am J Nephrol 1985;5:169-75.
8. Levine J, Bernard DB, Idelson BA, Farnham H, Saunders C, Sugar AM. Fungal peritonitis complicating continuous ambulatory peritoneal dialysis: Successful treatment with fluconazole, a new orally active antifungal agent. Am J Med 1989;86:825-7.
9. Debruyne D, Ryckelynck JP, Moulin M, Hurault de Ligny B, Levaltier B, Bigot MC. Pharmacokinetics of fluconazole in patients undergoing continuous ambulatory peritoneal dialysis. Clin Pharmacokinet 1990;18:491-8.
10. Debruyne D, Ryckelynck JP. Fluconazole serum, urine, and dialysate level in CAPD patients. Perit Dial Int 1992;12: 328-9.
11. Li PK, Chan TH, So WY, Wang AY, Leung CB, Lai KN. Comparisons of Y-set disconnect system (Ultraset) versus conventional spike system in uremic patients on CAPD: outcome and cost analysis. Perit Dial Int 1996;16(Suppl 1): S368-70.
12. Li PK, Szeto CC, Law MC, Chau KF, Fung KS, Leung CB, et al. Comparison of double-bag and Y-set disconnect systems in continuous ambulatory peritoneal dialysis: A randomized prospective multicenter study. Am J Kidney Dis 1999;33: 535-40.
13. Michel C, Courdavault L, Al Khayat R, Viron B, Roux P, Mignon F. Fungal peritonitis in patients on peritoneal dialysis. Am J Nephrol 1994;14:113-20.
14. Huang JW, Hung KY, Wu KD, Peng YS, Tsai TJ, Hsieh BS.

Clinical features of and risk factors for fungal peritonitis in peritoneal dialysis patients. J Formos Med Assoc 2000;99: 544-8.
15. Zaruba K, Peters J, Jungbluth H. Successful prophylaxis for fungal peritonitis in patients on continuous ambulatory peritoneal dialysis: six years' experience. Am J Kidney Dis 1991;17:43-6.
16. Montenegro J, Aguirre R, Gonzalez O, Martinze I, Saracho R. Fluconazole treatment of Candida peritonitis with delayed removal of the peritoneal dialysis catheter. Clin Nephrol 1995; 44:60-3.
17. Weem JJ Jr. *Candida parapsilosis*: Epidemiology, pathogenicity, clinical manifestations, and antimicrobial susceptibility. Clin Infect Dis 1992;14:756-66.
18. Kiernan L, Kliger A, Gorban-Brennan N, Juergensen P, Tesin D, Vonesh E, et al. Comparison of continuous ambulatory peritoneal dialysis-related infections with different "Y-tubing" exchange systems. J Am Soc Nephrol 1995;5:1835-8.
19. Keane WF, Bailie GR, Boeschoten E, Gokal R, Golper TA, Holmes CJ, et al. Adult peritoneal dialysis-related peritonitis treatment recommendations: 2000 update. Perit Dial Int 2000; 20:396-411.
20. Chan TM, Chan CY, Cheng SW, Lo WK, Lo CY, Cheng IK. Treatment of fungal peritonitis complicating continuous ambulatory peritoneal dialysis with oral fluconazole: A series of 21 patients. Nephrol Dial Transplant 1994;9:539-42.