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FUNGAL PERITONITIS -CURRENT STATUS 1998

Wai-Kei Lo, Tak-Mao Chan, Sing-Leung Lui, Fu-Keung Li, Ignatius K.-P. Cheng

Division of Nephrology, Department of Medicine, Queen Mary and Tung Wah Hospitals, The University of Hong Kong

Fungal peritonitis (FP) is an uncommon but important complication of peritoneal dialysis. It is associated with high morbidity and mortality. Removal of Tenckhoff catheter and failure to continue peritoneal dialysis because of peritoneal adhesion or loss of ultrafiltration not uncommonly follows FP. The reported incidence varies from 2.7% -15% of all peritonitis complicating continuous ambulatory peritoneal dialysis (CAPD), with most reported series between 3% and 7%. Table 1 summarizes the incidence ofFP in major reported series in the last 10 years (1-10). Its occurrence rate basically follows the peritonitis rate, and the incidence (percentage of all peritonitis episodes) does not seem to vary among different connection systems (6).

Over 90% of FP cases are caused by yeast organisms, mainly candida species (more than 75%). *Candida albicans* and C. *parapsilosis* are the most common organisms. Other candida species include C. *tropicalis*, C. *guilliermondii*, C. *pseudotropicalis*, C. *lipolytica*, C. *famata*, C. *kusei*, and others. Other yeast organisms included *Torulopsis glabrata*, *Rhodotorula rubra*, *Geotrichum candidum.* Sporadic cases of filamentous fungi peritonitis are seen.

ETIOLOG

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Prior antibiotic exposure, particularly for treatment of bacterial peritonitis, is the most commonly identified predisposing factor. The incidence of such exposure before FP is summarized in Table 2 (2-12). Broad-spectrum antibiotic therapy can lead to gastrointestinal candida colonization (13), and isolation of candida from fecal flora following antimicrobial therapy in CAPD patients has been reported (14). But how intestinal candida colonization leads to FP is somewhat dubious.

Although transmural migration of intestinal organisms after peritoneal irrigation has been documented in dogs (15), such a route of spread in human beings is still largely speculative. The spread may be as equally likely to occur through the Tenckhoff catheter from environmental contamination as by consequence of intestinal colonization. Strangely, oral candidiasis following antimicrobial therapy has never been reported specifically as predisposing to FP. Aerosol spread from the oral cavity is a possibility that should not be neglected.

The fact that most patients have received antibiotic therapy for bacterial peritonitis rather than for other causes before the onset of FP indicates that a host factor, probably impaired peritoneal defense after peritonitis, is required. Patients with FP were reported to have a higher bacterial peritonitis rate, and FP is actually the last event ofa series of repeated peritonitis episodes in many patients (2,3,10). Patients who are on immunosuppressives and or who are positive for the human immunodeficiency virus (HIV) are also at risk for FP (6,10,16). Other host factors -including age, sex, duration of dialysis, and underlying renal disease, including diabetes mellitus -were not significant risk factors (6,10).

It has to be noted that a substantial number ofFP episodes are not preceded by antibiotic therapy. The lowest incidence of such exposure is found in Spain (34%) and Hong Kong (37% in 1983 1987 and 43% in 1990 1994), indicating the presence of other portals of entry for the causative organisms. In Hong Kong, FP occurs mainly in the hot and humid summer months (8). In Spain, it occurs more often in the hot and dry summer, and it correlates with the average temperature rather than with the humidity (4). It seems that hot climate rather than humidity favors the occurrence of FP. Environmental contamination by pigeon guano leading to an epidemic of C. *parapsilosis* peritonitis in 12 CAPD patients was reported in England (17). Other possible sources of infection

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Correspondence to: W.K. Lo, Department of Medicine, Tung Wah Hospital, 12 Po Yan Street, Hong Kong, P.R. China.

TABLE 1
Incidence of Fungal Peritonitis per 100 Peritonitis Episodes Complicating CAPD — Major Reports in the Last Ten Years

Author and Reference	Location	Period	Cases	Incidence (%)
Rubin *et al.* (1)	U.S.A. (MS)	1979–1983	17	7
Cheng *et al.* (2)	Hong Kong	1983–1988	27	7.1
Nagappan *et al.* (3)	New Zealand	1979–1991	38	3.2
Bordes *et al.* (4)	Spain	1981–1992	35	5.7
Amici *et al.* (5)	Italy	1980–1992	6	2.8
Michel *et al.* (6)	France	1984–1992	20	3.5
Montenegro *et al.* (7)	Spain	1989–1993	10	9
Chan *et al.* (8)	Hong Kong	1990–1993	21	6.3
Wadhwa *et al.* (9)	U.S.A. (NY)	1991–1993	15	14
Goldie *et al.* (10)	U.S.A. (CT)	1984–1994	55	3.2

TABLE 2
Incidence of Antibiotic Exposure Within 1 Month Before Onset of Fungal Peritonitis

Author and Reference	Cases	Percentage with antibiotic exposure
Bordes *et al.* (4)	35	34 (23% for peritonitis)
Cheng *et al.* (2)	27	37
Chan *et al.* (8)	21	43
Struijk *et al.* (11)	9	56
Montenegro *et al.* (7)	10	60
Goldie *et al.* (10)	55	65 (74% within 3 months)
Eisenberg *et al.* (12)	55	69
Nagappan *et al.* (3)	33	70
Wadhwa *et al.* (9)	15	80
Michel *et al.* (6)	20	95 (80% for peritonitis)
Amici *et al.* (5)	6	100 (within 2 months)

included fingernail, skin, and vaginal fungal infection (2,3), bowel perforation, diverticulitis, and direct contamination of the connection system (1). Contamination through colonization of C. *tropicalis* in the water bath used to warm dialysate has also been reported in Hong Kong, and therefore such practice of dialysate warming should be discouraged (18).

TREATMENT AND OUTCOME

Therapy for FP basically comprises antifungal agents with or without early catheter removal. Catheter removal alone had once been advocated as a successful treatment of FP. Nagappan *et al* reported a 76% success rate with catheter removal alone in patients with mild FP (3). However, a high failure rate was seen in many other reports (Table 3) (1,3,5,6). It seems that this option is applicable only to mild cases, and the catheter should not be reinserted in the same setting, as the recurrence rate is very high with early reimplantation (2).

Before the availability of fluconazole, antifungal therapy usually consisted of one or more of the following combinations: amphotericin B (intravenously or intraperitoneally), miconazole (orally or intraperitoneally), ketoconazole (orally), and 5-flucytosine (orally, intravenously, or intraperitoneally). No one combination showed clear superiority over the others. The overall cure rate without catheter removal was only around 10%. A literature review by Cheng *et al* showed that only 45% of cases could return to peritoneal dialysis and that the mortality was 19.3% (2).

Fluconazole is highly potent towards yeast-like organisms. In 1989, Levine *et al* reported two cases of FP successfully returned to CAPD after treatment with fluconazole and catheter removal (19). Isolated case reports also exist describing successful treatment with fluconazole alone without catheter removal (20,21). However, the overall cure rate without catheter removal in other, larger series was still very low (8%, Table 4) (3,6,8,10,17,22,23). Only around 50% of patients could continue CAPD with or without catheter removal, similar to the 45% success rate achieved with other antifungal agent combinations according to the review of Cheng *et al.*

Candida colonization of the Tenckhoff catheter is common, with the organism embedded in an amorphous matrix on the surface of the catheter (24). Therefore, it is not surprising to see that catheter removal is ultimately required in most cases of FP treated with fluconazole or other antifungal agents. No study has evaluated the right timing for catheter reinsertion, but most nephrologists would reinsert between 2 weeks and 8 weeks after subsidence of clinical signs and symptoms of peritonitis.

There was also an anecdotal report on successful treatment with intracatheter amphotericin instillation alongside fluconazole or 5-flucytosine without catheter removal (25), but this practice has not gained great popularity.

TABLE 3
Outcome of Fungal Peritonitis Treated with Immediate Catheter Removal

Author and Reference	Cases	Antifungal drugs	Clinical outcome CAPD	Hemodialysis	Death
Nagappan *et al.* (3)	21	Nil (mild cases)	16 (76%)	3 (14%)	2 (10%)
Nagappan *et al.* (3)	11	Yes	7 (64%)	2 (18%)	2 (18%)
Rubin *et al.* (1)	15	Yes	2 (13%)	7 (47%)	6 (40%)
Michel *et al.* (6)	8	Yes	2 (25%)	5 (62.5%)	1 (12.5%)
Amici *et al.* (5)	3	Yes	—	1	2
Overall	58		27 (47%)	18 (31%)	13 (22%)

TABLE 4
Outcome of Fungal Peritonitis Treated with Fluconazole (Excluding Single Case Report)

Author and Reference	Cases	Fluconazole dosage	Other[a]	Clinical outcome Cure[b]	CAPD[c]	Hemodialysis	Death
Hoch *et al.* (22)	5	200 mg/400 mg + 50 mg – 200 mg daily	Nil	0	—	3	2
Montenegro *et al.* (7)	9	200 mg + 100 mg daily	Nil	1	3	5	0
Chan *et al.* (8)	21	200 mg + 100 mg every other day	Nil	2	13	3	3
Levine *et al.* (19)	2	200 mg + 100 mg daily	Nil	—	2	—	—
Venning *et al.* (23)	3	200 mg + 100 mg daily	Nil	—	2	1	—
Michel *et al.* (6)	7	100 mg daily	5–FC	1	1	2	3
Nagappan *et al.* (3)	3	Not stated	Ampho	—	—	2	1
Overall	50			4 (8%)	21 (42%)	16 (32%)	9 (18%)

5-FC = 5-flucytosine; Ampho = amphotericin B.
[a] Other antifungal drugs.
[b] Cure without catheter removal.
[c] CAPD after catheter reinsertion.

Amphotericin given intravenously has variable penetration into peritoneal fluid (26), and when given intraperitoneally often results in severe pain and chemical peritonitis (12,27). This drug is now mainly used for cases refractory to fluconazole therapy and for filamentous fungal infection. 5-Flucytosine has very good oral bioavailability and peritoneal penetration, yet single therapy often resulted in rapid development offungal resistance (28). It is not recommended for single-agent therapy. Ketoconazole also penetrates poorly into peritoneal fluid. Fluconazole, a triazole with high oral and intraperitoneal bioavailability (87% for oral and 88% for intraperitoneal), has very good penetration into peritoneal fluid with a peritoneal level 60% that of serum (18). It is predominately excreted in the kidney, and its half-life is prolonged to between 72 hours and 85 hours in end-stage renal failure (29). Debruyne *et al* showed that the peritoneal fluid fluconazole level ofo. 7 ± 0.12 mg/L 48 hours after a single oral dose of lOO mg was significantly higher than the minimum inhibitory concentration (MIC) of 0.4 -0.5 mg/L for *Candida albicans*, but may not be enough for other candida species with more variable MICs (29). The dosage commonly used in CAPD patients is 200 -400 mg loading, with lOO mg daily or alternate-day maintenance. There was no obvious difference in clinical outcome with various fluconazole dosages (Table 4).

The current recommendation for treating FP caused by candida or other yeast-like organisms is oral fluconazole, plus oral or intraperitoneal 5-flucytosine (30). The catheter should be removed within 3 to 5 days if no satisfactory response is obtained. Antifungal treatment should be continued for at least 10 days after removal of the catheter or for 4 6 weeks without catheter removal. Whether a combination of fluconazole and 5-flucytosine is superior to fluconazole alone still requires proof, but the result of such a combination reported by Michel *et al* was no better than others (Table 4) (6).

PREVENTION

With such a high morbidity and mortality, prevention ofFP is essential, though its occurrence is infrequent. Zaruba *et al* reported a significant reduction, over a 6-year period, in the incidence of candida peritonitis with the concomitant use of any antibiotic prescription plus oral nystatin at a dose of

500000 units three times per day, when compared with the 4-year period before the policy was commenced (31). The four cases ofFP that occurred during the period were related to noncompliance. However, a marked concomitant decrease in incidence of bacterial peritonitis also occurred (from 4.4 patientmonths to 16.6 patient-months per episode), and compliance was not monitored, leaving room for argument concerning the effectiveness of nystatin prophylaxis for antibiotic-related FP.

We subsequently confirmed the effectiveness of nystatin prophylaxis in our two-year prospective randomized study (32). With a dose of nystatin at 500000 units four times per day with every antibiotic prescription, we found that the overall incidence of candida peritonitis was reduced from 12 episodes (6.4%) in the control group to 4 episodes (1.9%) in the nystatin group, and the incidence of antibiotic-related candida peritonitis was reduced from 6 episodes (3.2%) to 3 episodes (1.4%) respectively. The indication for antibiotic therapy was peritonitis in almost all cases of antibiotic-related FP. We have adopted routine nystatin prophylaxis with antibiotic therapy for peritonitis or severe sepsis (excluding exit site infection) for the last three years; the incidence ofFP in 1996 1997 was just 3.4%, much lower than the earlier incidence of 6% -7%. Among the eight cases of FP occurring in this period, two did not receive nystatin because their sepsis was treated in other hospitals. If they are excluded, the incidence was only 2.6%.

Oral nystatin is safe and cheap, and such a nystatin prophylaxis policy is highly cost-effective. Wadhwa *et al* also reported successful reduction in the incidence of FP from 14% to 4% after adopting a fluconazole prophylaxis policy with a dosage of 200 mg loading and DO mg alternate-day (9). The costeffectiveness of this expensive policy still requires documentation, and there is worry about the emergence of fluconazole resistance with widespread use of the drug. However, it has to be noted that nystatin reduces the incidence of antibiotic-related FP by only around 50%, and there are still a substantial number ofFP cases that are not antibiotic-related. Reductions in the incidence of bacterial peritonitis and early detection of possible environmental contamination in both the dialysis center and the home are also important in preventing this serious complication of peritoneal dialysis.

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