



# Experience in fungal peritonitis in a dialysis unit for 10 years

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## SUMMARY

*Fungal peritonitis is a rare cause of peritonitis, but it is associated to poorer prognosis and higher mortality than bacterial peritonitis. Until now, predisposing factors and treatment have not been well established. We retrospectively reviewed all the cases of fungal peritonitis diagnosed for ten years in 218 patients undergoing continuous ambulatory peritoneal dialysis. In all we detected 11 episodes of fungal peritonitis in 11 patients, that means the 4% of continuous ambulatory peritoneal dialysis peritonitis. All the cases of fungal peritonitis were caused by Candida species. As a result of fungal peritonitis 36% of the patients died, 55% had to change to long-term hemodialysis because of failure in peritoneal dialysis technique. Only one case (9%) managed to continue peritoneal dialysis. The factors associated with the development of fungal peritonitis were: the presence of antibiotic use within 1 month before fungal peritonitis, patient older than 70 years old, low levels in albumine plasmatic and long permanence in continuous ambulatory peritoneal dialysis. The treatment consisted in intraperitoneal fluconazol combined with oral 5-flucytosine for 4 to 6 weeks. In the two last cases we associated intravenous caspofungine too. Given that no improvement was seen within 72 hours of treatment, the catheter must be removed in all the cases.*

Key words: **Peritoneal dialysis. Fungal peritonitis.**

## EXPERIENCIA EN PERITONITIS FÚNGICA EN UNA UNIDAD DE DIÁLISIS DURANTE DIEZ AÑOS

## RESUMEN

*Las peritonitis fúngicas constituyen una causa poco frecuente de peritonitis en los pacientes en DP, pero presentan peor pronóstico y mayor mortalidad que las peritonitis bacterianas. Hasta el momento los factores predisponentes y su tratamiento no han sido establecidos. Revisamos retrospectivamente todos los casos de peritonitis fúngica aparecidos a lo largo de diez años en 218 pacientes en tra-*

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tamiento con diálisis peritoneal continua ambulatoria. Detectamos en total 11 episodios de peritonitis fúngica en 11 pacientes, constituyendo el 4% del total de peritonitis. Todos los casos de PF fueron producidos por *Candida species*. Como consecuencia de la peritonitis fúngica, el 36% de los pacientes fallecieron, el 55% presentaron fallo de técnica y tuvieron que cambiar a hemodiálisis periódica. Sólo un caso (9%) pudo permanecer en diálisis peritoneal. Los factores asociados con la aparición de peritonitis fúngica fueron: la presencia de antibioterapia el mes anterior al episodio de peritonitis, la edad mayor de 70 años, el descenso en los niveles plasmáticos de albúmina y una permanencia prolongada en diálisis peritoneal. El tratamiento consistió en fluconazol intraperitoneal combinado con 5-fluocitosina oral durante 4 a 6 semanas. En los últimos dos casos asociamos además caspofungina intravenosa. Dado que no existió mejoría a las 72 horas de iniciado el tratamiento, el catéter tuvo que ser retirado en todos los casos.

Palabras clave: **Diálisis peritoneal. Peritonitis fúngica.**

## INTRODUCTION

Peritonitis remains one of the most common complications of peritoneal dialysis (PD). Decrease in solutes transport and in ultrafiltration that may result from peritoneal damage represent one of the major reasons for technical failure and withdrawal from the program in these patients (5.8-16.4%).<sup>1-4</sup> Fungal peritonitis (FP) account for somewhat less than 10% of all peritonitis, but they have a poorer prognosis (40% of FP are associated with technical failure and switch to hemodialysis), and greater mortality (5.40%) than bacterial peritonitis<sup>5-9</sup>. *Candida sp.*, particularly *C. albicans* is the most frequently isolated organism. Clinically, FP is undistinguishable from bacterial peritonitis, so that diagnosis is based on Gram staining (sensitivity of about 20-30%<sup>6,7</sup>) and culture in specific media.

Risk factors of its onset and treatment are not well established. Previous antibiotic therapy, advanced age, the presence of diabetes mellitus or immunosuppression, or even high temperatures are among some of the proposed predicting conditions for its occurrence.<sup>5,7,10-15</sup> FP treatment is difficult since fungi create a biofilm on the catheter's surface that decreases penetration of antifungal agents. Although catheter removal is usually necessary, the most adequate timing is unknown. Current guidelines<sup>16</sup> recommend to start early with fluocytosine and fluconazol for 4 to 6 weeks and catheter removal if there is no improvement within 4-7 days from treatment onset. Some authors suggest early removal within the first 24 hours<sup>5</sup>. Others may even remove the catheter without associating any antifungal treatment<sup>9</sup>.

Prognostic factors of FP are not well established either. The occurrence of ileus and abdominal pain, and catheter maintenance seem to be associated to a greater mortality<sup>5</sup>. Usage of antibiotics within the 3 previous months to the episode and also ileus and abdominal pain may be predictors of technical failure<sup>5</sup>. The presence of particular organisms (*C. parapsilosis*) may also be a poor prognosis factor<sup>17</sup>.

The aim of this study was to determine the clinical and analytical features of all patients included in a PD unit that have presented some episode of FP, to describe their course, and to try to determine factors associated with its onset.

## PATIENTS AND METHODS

A retrospective study from January 1993 to November 2003 has been performed. Two hundred and eighteen patients with chronic renal failure (CRF) started on PD program in our Unit: 131 males and 87 females, with a mean age of 55.68 years (18-67 years). Average stay has been 25.73 months (1-102 months), with a cumulated experience of 5610 months.

Causes of CRF have been the usual ones: 45 patients had glomerulopathy (21%), in 41 (19%) the cause was unknown, 38 (17%) patients had diabetes, 37 (17%) patients with vascular disease, 34 (16%) with interstitial nephropathy, 11 with polycystic disease, and 12 with various causes.

During the 10-year follow-up study, 42 patients remain on PD. Of the 176 patients that ended up the

program, 69 were deceased, 50 received renal transplantation, 38 had technical failure and were switched to hemodialysis (18 of them after a peritonitis episode), five recovered their renal function, three terminated the treatment, and 11 withdrew from the program for several reasons.

During the 10 years of the study, all clinical, anthropometrical, analytical and dialysis data, as well as other incidences, from all patients were collected in a database. Our diagnostic criterion for fungal peritonitis was the presence in the peritoneal effluent or 100 or more leucocytes per microliter (with at least 50% polymorphonuclear) and fungi isolation with culture.

From January 1993 to November 2002, our treatment protocol for FP consisted of intraperitoneal fluconazol (200 mg/day) together with oral 5-fluocytosine (initial dose 2 g, followed by 1 g/24 h) for 4-6 weeks until resolution of the clinical condition. From December of 2002, the protocol also included intravenous caspofungin (initial dose 70 mg, followed by 50 mg/24 h). The dialysis catheter was removed if there was no clinical improvement within 48-72 hours from onset of treatment.

Patients' characteristics have been compared between those with some FP episode and those have had none. For comparison of the means Mann-Whitney U test has been used, and for percentages, the Chi-squared test.

## RESULTS

Among the 218 patients that received treatment in our Unit during the 10-year period, there were 263 peritonitis episodes, of which 11 were fungal (which accounts for 4.18% of all peritonitis episodes). Vital statistics and clinical features of these patients are summarized in Table I. The average annual peritonitis rate in these patients for the last 10 years was 0.52 episodes/patient/year for the group of patients without FP whereas it was 1.17 for patients with FP ( $p < 0.05$ ). Patients that developed FP were generally older (45% were older than 70 versus 23% in the group of patients without FP,  $p < 0.05$ ), and had been for longer on peritoneal dialysis program (mean stay 37.45 months vs. 24.95,  $p < 0.05$ ). We did not observe differences between groups by gender, renal failure etiology or cardiovascular co-morbidity.

Six out of 11 episodes occurred one month after antibiotic therapy (in five cases, the antibiotic was prescribed for a bacterial peritonitis). FP rates were similar all year round.

Among the analytical data that could predict the occurrence of a FP episode, the only that had a significance was plasma albumin. Patients that developed FP had a baseline albumin at PD onset of  $4.02 \pm 0.5$  g/dL, decreasing to  $3.32 \pm 0.47$  g/dL within the month prior to FP occurrence ( $p < 0.01$ ).

In all FP cases, *Candida* was the most frequently isolated mold. *Candida* sp. was found in seven cases,

**Table I.** Demographic characteristics of patients with and without FP episodes

Characteristics	Pacientes con PF (n = 11)	Paciente sin PF (n = 207)	p
Gender (males/females)	5/6	123/84	n.s.
Age (years)	60.64 (31-76)	55.57 (18-87)	n.s.
Age $\geq$ 70 years	5 (45%)	48 (23%)	$< 0.05$
Time on PD (months)	37.45 (2-85)	24.95 (1-102)	$< 0.05$
Peritonitis rate (num cases/patient/year)	1.17	0.52	$< 0.05$
Cause of renal failure			n.s.
Vascular	3	34	
Glomerulopathies	2	43	
Diabetes mellitus	1	39	
Tubulointerstitial nephropathy	1	32	
Polycystic disease	0	13	
Others	1	7	
Unknown	3	39	
Cardiovascular comorbidity			n.s.
Arrhythmia	1	21	
Ischemic heart disease	4	58	
Diabetes mellitus	1	49	
Cerebral vascular disease	1	7	
Peripheral vascular disease	1	14	

Abbreviations: PD = peritoneal dialysis. FP = fungal peritonitis.

*C. albicans* in two, and *C. parapsilosis* and *C. famata* in one. The 11 patients with FP had abdominal pain, general condition worsening and turbid effluent. All were hospital-admitted.

Nine patients received treatment with intraperitoneal fluconazol plus oral 5-fluocytosin, whereas the last two also received intravenous caspofungin. All patients required dialysis catheter removal because persistence of symptoms after 72 hours of treatment. The clinical course is shown in Table II. Four patients were *exitus letalis*, six had technical failure and were switched to hemodialysis, whereas only one could remain on PD after resolution of the condition and insertion of a new catheter.

## DISCUSSION

For the last 10 years, 4.18% of all peritonitis cases in our Unit were caused by fungi; a similar incidence than other groups, varying from 3.2% to 15%.<sup>5,8,12</sup> *Candida* sp. is the most frequently isolated mold. Contrary to other groups, we have had no case of FP caused by other fungal species.

Previous antibiotic therapy constitutes the most important predisposing factor for FP occurrence in patients on PD program, present in up to 64.8% of the cases according to different series.<sup>5,7,10,11,12,13</sup> Most of the times, antibiotics are given for a previous bacterial peritonitis. In our group of patients, 54% had antibiotic therapy within the previous month, in 83% of the cases prescribed for bacterial peritonitis. This association between FP occurrence and the use of antimicrobials may be due to fungal overgrowth after selective bacterial elimination and to peritoneum inflammation that would render it more prone to fungal invasion. Under these cir-

cumstances, prophylactic treatment with fluconazol or nistatin might be useful. Although not routinely recommended, prophylaxis should be considered in high-risk patients for infection (protracted antibiotic therapy, recurrent peritonitis, HIV, etc.) due to the good experience in some centers.<sup>18</sup>

Other factors associated to FP occurrence reported in the literature have been immunosuppression,<sup>7,12</sup> presence of diabetes mellitus,<sup>19</sup> a greater rate of previous peritonitis,<sup>12,15</sup> and advanced age.<sup>15</sup> We have only found a significant association with advanced age and with the presence of a greater rate of peritonitis (slightly over twice). That is to say, FP are usually not the first peritonitis episode in a patient on PD. Moreover, in our patients that have developed FP we have observed a longer average stay on PD and a decrease in albumin levels within the prior month to peritonitis occurrence. This latter association between hypoalbuminemia and FP occurrence has not been previously reported in the literature and may explained by several factors. In the first place, by hyponutrition and inflammation associated to renal failure. In the second place, by volume overload secondary to a real decrease in lean weight together with an ultrafiltration deficit in a peritonitis setting. Finally, it could be due to the increase in peritoneal protein loss that occurs in peritonitis. We have not found any relationship with other nutritional parameters such as prealbumin or transferrin, probably due to the limited number of cases in our series. We have not found a significant association either between peritoneal Kt/V or with residual renal function, or with  $\beta_2$ -microglobulin levels.

Signs and symptoms do not differ from those of bacterial peritonitis, being constant the abdominal pain, turbidity of peritoneal effluent and the drama-

**Table II.** Patients and treatment in 11 fungal peritonitis episodes

Patient Num.	Age	Gender	Antibiotics 1 mo prior	Previous peritonitis	Initial treatment	Catheter removal	Course
1	57	F	+	1	Flu+5-F	+	E
2	75	M	-	2	Flu+5-F	+	E
3	37	M	+	6	Flu+5-F	+	HD
4	77	F	+	7	Flu+5-F	+	E
5	72	M	-	1	Flu+5-F	+	E
6	70	F	+	2	Flu+S-F	+	HD
7	55	F	+	1	Flu+5-F	+	PD
8	66	M	+	4	Flu+5-F	+	HD
9	77	F	+	4	Flu+5-F	+	HD
10	33	F	+	1	Flu+5-F+Casp	+	HD
11	64	M	-	0	Flu+5-F+Casp	+	HD

Abbreviations: Casp = intravenous caspofungin. PD = peritoneal dialysis. E = exitus. Flu = oral fluconazol. %-F = 5-fluocytosin. HD = hemodialysis. F = female. M = male.

tic worsening of the general condition, which motivated hospital admission in all of our patients.

FP treatment is not well established. Guidelines are based on the results of small series of patients. The role of the diverse antifungal agents, the administration route, the dose and combinations are unknown. Our current protocol includes the combination of two antifungal agents, one intraperitoneally and the other systemically, and early removal although not immediate of the catheter. However, catheter removal was necessary in all of our patients due to persistence of the clinical condition within 72 hours after beginning of treatment. Since the catheter implies a site for microbial colonization, it seems logical to remove it early. Some group<sup>9</sup> even recommends immediate catheter removal with or without the association of antifungal agents, with similar results. However, the number of patients in that study is limited. Concerning reinsertion of a new intraperitoneal catheter, it is generally recommended to perform it at least two weeks after resolution of the episode. An immediate reinsertion of the catheter would mean a high risk for its colonization.<sup>12</sup> In our series, in just one case the peritoneal catheter was reinserted and this was done several weeks after FP healing.

The use of new and more potent antifungal agents, such as caspofungin and voriconazole, must be considered in the case of conventional therapy failure or patient's condition worsening.<sup>20</sup> For these reasons, two of our patients received treatment with caspofungin, being the results disappointing. Peritonitis resolved, but in both cases the catheter had to be removed and both patients were definitely switched to hemodialysis. There is a very limited experience with the use of these agents in patients on PD.<sup>21</sup>

The clinical course of our patients was similar to that in other groups. FP is an infrequent type of peritonitis but has a poorer prognosis (40% of FP present technical failure and switching to hemodialysis), and a greater mortality (5-40%<sup>5,6,7,8,9,12</sup>). In our series, the mortality rate was 36% and the technical failure rate was 55%.

We conclude that FP is an infrequent but severe type of peritonitis in patients on a PD program, associated to high morbidity and mortality rates and technical failure rates. Signs and symptoms are similar to those of other types of peritonitis. Many of these patients have previously received antibiotic therapy and have presented previous episodes of peritonitis. Other less well-established risk factors are immunosuppression conditions such as advanced age, hyponutrition and a prolonged stay on a PD program. Fungal infection is difficult to eradi-

cate and requires catheter removal in most of the cases. We believe that antibiotic therapy may be initially tried but if fluid does not become clear within 72 hours the catheter ought to be removed. Antifungal therapy must be prolonged (2-6 weeks), while keeping the patient on hemodialysis. Insertion of a new catheter may be considered, at least two weeks after early removal of the old catheter, and provided that the clinical course has been favorable.

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