Ten-year experience with fungal peritonitis in peritoneal dialysis patients: antifungal susceptibility patterns in a North-American center

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SUMMARY

Objective: To describe the clinical and microbiological features associated with fungal peritonitis in peritoneal dialysis (PD) patients at Hôpital Maisonneuve-Rosemont, from August 1996 to July 2006. Methods: Cases were retrieved from the microbiology laboratory culture registry. Antifungal susceptibility was determined by the Clinical and Laboratory Standards Institute M27-A3 method. Results: Among 288 PD patients (total follow-up of 7258 patient-months), nine were found with fungal peritonitis. Candida spp were identified in all of them, with a majority of non-albicans Candida species. Resistance to fluconazole, itraconazole, or voriconazole was as frequent as potential resistance to amphotericin B. No isolate was resistant to caspofungin and one was resistant to micafungin. Prior bacterial peritonitis was frequent (67%). All patients had their PD catheter removed and all of them survived.

Conclusions: In our institution, fungal peritonitis in PD patients is rare. All cases were caused by Candida species. Variable susceptibility patterns were observed, which may influence the initial empirical antifungal therapy and underscore the importance of individual speciation and susceptibility testing of invasive Candida isolates.

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1. Introduction

Fungal peritonitis (FP) is a rare but serious complication of peritoneal dialysis (PD).1 It is associated with temporary and frequently permanent cessation of PD. The lethality, although variable, remains very high.2 The majority of these infections are caused by Candida species. In recent reports, non-albicans Candida species were more prevalent than Candida albicans in PD patients with FP.2,3 These non-albicans Candida species, such as Candida glabrata and Candida krusei, frequently exhibit resistance to triazole antifungals. Only two studies on FP in PD patients have reported antifungal susceptibility to triazoles4,5 and none have reported susceptibility to echinocandins. We reviewed our 10-year experience with fungal peritonitis in our PD population with an emphasis on in vitro susceptibility of the isolates to different antifungal antibiotics, including echinocandins.

2. Materials and methods

Hôpital Maisonneuve-Rosemont is a tertiary-care university hospital. Its PD population lives in an urban environment located in the eastern part of Montreal (Canada). All FP cases were retrieved through a systematic review of all peritoneal fluid cultures sent to our microbiology laboratory from August 1996 to July 2006. During this 10-year period, 288 adult patients were treated by PD in our hospital, for a total experience of 7258 patient-months. During the same period, 289 episodes of peritonitis were recorded for a global incidence of 1 episode per 25 patient-months (0.48 episodes per patient-year). The diagnosis of peritonitis was based on the positivity of two out of three criteria: abdominal pain, peritoneal fluid cell count of >0.1 leukocytes/μL, or positive peritoneal fluid culture. The medical records of all PD patients with a peritoneal fluid culture positive for a fungus were reviewed for demographics, duration of prior experience with PD, presence of potential risk factors for FP (diabetes, immunosuppressive therapy, recent antibacterial therapy, recent episode of bacterial peritonitis, or bowel perforation), confirmation of a peritonitis episode, nature and duration of the antifungal therapy, and evolution (days of hospitalization, survival, catheter removal, delay between diagnosis of FP and catheter removal, and definitive or temporary transfer to hemodialysis).

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Speciation and antifungal susceptibility testing of the recovered isolates were performed with germ tubes, chlamydospore formation, Vitek YBC identification system (BioMérieux, St-Laurent, QC, Canada), and the Clinical and Laboratory Standards Institute (CLSI) broth microdilution susceptibility testing method. Standard antifungal powders were used: amphotericin B, itraconazole (Ortho-Janssen), fluconazole, voriconazole (Pfizer), micafungin (Astellas-Pharma), and caspofungin (Merck). Serial two-fold dilutions were made in RPMI 1640 medium (Gibco BRL) buffered to pH 7.0 with 0.165 M morpholino-propanesulfonic acid (MOPS) buffer (Sigma) for all antibiotics. The final concentrations of the antifungal agents were: 0.008 to 16 mg/l for amphotericin B, itraconazole, voriconazole, micafungin, and caspofungin, and 0.25 to 256 mg/l for fluconazole. Drug-free and yeasts-free controls were included. Trays were incubated in air at 35 °C, and minimum inhibitory concentration (MIC) endpoints were visually read after 48 h of incubation. The MICs of amphotericin B were defined as the lowest concentration resulting in a complete inhibition of growth, while the MICs of all the other compounds were defined as the lowest concentration that resulted in a substantial reduction of growth (80% inhibition) compared to that of growth-control wells. Candida parapsilosis ATCC 22019 and C. krusei ATCC 6258 reference strains were used for quality control. In vitro susceptibilities were evaluated according to the currently established interpretation criteria of the CLSI. For fluconazole, strains are considered susceptible when the MIC is ≤8 mg/l, intermediate when the MIC is 16–32 mg/l, and resistant when the MIC is >64 mg/l. Corresponding criteria for itraconazole are ≤0.125, 0.25–0.5, and >1 mg/l. Resistance to voriconazole was defined as a MIC >4 mg/l. Non-susceptibility to echinocandins was defined as a MIC >2 mg/l. Since no established criteria exist for amphotericin B, strains with values >1 mg/l were considered resistant, as proposed by the CLSI.

### 3. Results

Between August 1996 and July 2006, among 288 patients on PD, nine cases of FP were identified in nine patients (seven men and two women) during their PD follow-up. The incidence of FP was 1 episode per 806 patient-months (1 episode per 67 patient-years), representing 3.1% of all peritonitis episodes that occurred in our PD population during the same period. The mean patient age was 62 years (range 35–78 years). Three patients were diabetics. None of our patients were positive for HIV or had been treated with immunosuppressive therapy. The mean PD experience prior to FP was 53 months (range 0–168 months). Six patients (67%) had been treated with antibiotics in the previous 3 months for bacterial peritonitis; none of them had received antifungal prophylaxis. One episode was associated with appendicitis. The mean dialysate white cell count was 7.74 × 10^3/l (range 0.06–39.3 × 10^3/l).

All episodes of FP were caused by Candida species. Only one episode was caused by C. albicans. Among the other eight episodes, three were caused by C. parapsilosis, three by Candida tropicalis, one by C. krusei, and one by C. glabrata (Table 1). Gram staining of the peritoneal fluid showed yeasts in seven patients; the mean time to culture positivity was 3.75 days.

### Table 1

<table>
<thead>
<tr>
<th>Year</th>
<th>Sex/age</th>
<th>Species</th>
<th>Amphotericin B</th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Voriconazole</th>
<th>Caspofungin</th>
<th>Micafungin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>F/56</td>
<td>C. tropicalis</td>
<td>0.25</td>
<td>0.5</td>
<td>0.12</td>
<td>0.03</td>
<td>0.03</td>
<td>0.25</td>
</tr>
<tr>
<td>1997</td>
<td>M/78</td>
<td>C. parapsilosis</td>
<td>0.5</td>
<td>1</td>
<td>0.12</td>
<td>0.016</td>
<td>1</td>
<td>16 R</td>
</tr>
<tr>
<td>1997</td>
<td>M/35</td>
<td>C. tropicalis</td>
<td>0.25</td>
<td>0.5</td>
<td>0.25</td>
<td>0.06</td>
<td>0.12</td>
<td>0.5</td>
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<tr>
<td>1997</td>
<td>M/75</td>
<td>C. albicans</td>
<td>0.5</td>
<td>1</td>
<td>0.12</td>
<td>0.12</td>
<td>0.12</td>
<td>0.25</td>
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<tr>
<td>1998</td>
<td>M/69</td>
<td>C. parapsilosis</td>
<td>0.125</td>
<td>2</td>
<td>0.06</td>
<td>0.008</td>
<td>0.25</td>
<td>2</td>
</tr>
<tr>
<td>1999</td>
<td>M/67</td>
<td>C. krusei</td>
<td>1</td>
<td>R^a</td>
<td>0.5</td>
<td>0.5</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2001</td>
<td>F/62</td>
<td>C. parapsilosis</td>
<td>2 R</td>
<td>0.25</td>
<td>0.06</td>
<td>0.016</td>
<td>0.5</td>
<td>0.06</td>
</tr>
<tr>
<td>2002</td>
<td>M/51</td>
<td>C. glabrata</td>
<td>2 R</td>
<td>16</td>
<td>32 R</td>
<td>32 R</td>
<td>0.5</td>
<td>0.06</td>
</tr>
<tr>
<td>2003</td>
<td>M/61</td>
<td>C. tropicalis</td>
<td>2 R</td>
<td>4</td>
<td>1 R</td>
<td>0.5</td>
<td>1</td>
<td>0.25</td>
</tr>
</tbody>
</table>

R, resistant; I, intermediate.

^a C. krusei are assumed to be intrinsically resistant to fluconazole.

Comparative in vitro susceptibilities are summarized in Table 1. Four of the nine isolates (two C. tropicalis, one C. albicans, and one C. parapsilosis) were sensitive to all three classes of antifungal, i.e., the polypene amphotericin B, triazoles, and the echinocandins. Three isolates were resistant to amphotericin B, i.e., MIC = 2 mg/l (C. tropicalis, C. parapsilosis, and C. glabrata). Of these three isolates, the C. tropicalis isolate was also resistant to itraconazole (MIC = 1 mg/l), and the C. glabrata isolate was resistant to both itraconazole (MIC = 32 mg/l) and voriconazole (MIC = 32 mg/l), and intermediate to fluconazole (MIC = 16 mg/l). The C. krusei isolate was considered intrinsically resistant to fluconazole. In general, compared to the other Candida spp, the caspofungin and micafungin MICs were higher with C. parapsilosis. One isolate was highly resistant to micafungin (MIC = 16 mg/l).

Initial empirical antifungal therapy was as follows: fluconazole in six episodes, amphotericin B in two episodes, and caspofungin in one episode. Resistance of the isolate to the initial antifungal agent was associated with a switch to another appropriate agent in three patients. All nine patients had the PD catheter surgically removed after the diagnosis of FP, with a mean lag time between diagnosis and removal of 7.6 days (range 2–13 days). The mean total duration of antifungal treatment was 23.4 days. All patients survived the episode, but only one patient resumed PD 12 months later. One patient developed sclerosing peritonitis during the initial hospitalization for FP and was treated successfully with mycophenolate and prednisone. She was transferred permanently to hemodialysis.

### 4. Discussion

Fungal peritonitis is a relatively rare complication in patients on PD. It represents only 3% to 6% of all episodes of peritonitis, but is associated with much greater morbidity and mortality than bacterial peritonitis. Initially empirical antifungal therapy has to take into account the frequency of different species of fungi based on the local epidemiology, and their susceptibilities to different antifungal agents.

Although larger series of FP in PD have already been published (Miles et al., 2009, 162 cases; Wang et al., 2000, 70 cases; Goldie et al., 1996, 55 cases; Nagappan et al., 1992, 38 cases; Prasad et al., 2004, 28 cases; Michel et al., 1994, 20 cases), antifungal susceptibility testing of isolates has been reported in only two series. The first series was from Mexico and reported antifungal susceptibilities to triazoles only. Ten Candida isolates were identified with various triazole resistance patterns. The other series, from Greece, reported 46 episodes of fungal peritonitis. Isolates were tested for susceptibility to amphotericin B and various triazoles. Amphotericin B was the only antifungal agent to which all recovered organisms were susceptible. No susceptibility
testing of the newer antifungal agents such as the echinocandins have been published for the PD population. Our study is also the first series of FP in PD patients reported from Canada.

All nine cases of FP reported in this study were caused by Candida species. This appears somewhat different from the literature where Candida species represent 68–90% of causative organisms. This may be explained by larger series and different geographical areas. In our series, only one case of peritonitis was caused by C. albicans. This is in accordance with the literature where the majority (from 50% to 80%) of Candida species isolated are non-albicans Candida species.3,8–12 As described in all other series, C. parapsilosis and C. tropicalis were the most frequent Candida species.

Variable in vitro susceptibility patterns were observed in our isolates. Low resistance rates to fluconazole, itraconazole, and voriconazole have been reported in our institute for Candida bloodstream infection isolates.13 Not surprisingly similar observations were noted with our peritoneal fluid Candida spp isolates. Fluconazole resistance was predictable with C. krusei, and resistance to itraconazole and voriconazole was not unexpected with our C. glabrata isolate. Resistance to specific triazoles has also been described in the literature with some isolates of C. albicans, C. parapsilosis, and C. tropicalis. Of concern was the amphotericin B MIC of 2 mg/l observed in one C. tropicalis, one C. parapsilosis, and one C. glabrata isolate. This is the first published report of in vitro resistance of Candida spp isolates to amphotericin B in a PD population. One C. parapsilosis was resistant to micafungin. Although all isolates appeared sensitive to caspofungin, the echinocandin MICs were in general higher against C. parapsilosis. The clinical significance of such observations remains to be determined.6,14 However, underscores the importance of individual speciation and susceptibility testing of invasive Candida isolates. Combination therapy with amphotericin B and fluconazole as initial empirical therapy may be appropriate until speciation of the Candida isolate in the peritoneal fluid is established.

Two-thirds of our patients had received antibiotics within the previous 3 months, a well-known risk factor for FP in PD patients.1,3,9,15 All patients survived in our study, in contrast to a reported lethality of FP of between 5% and 50%.2 The reason for this is probably multifactorial, including the relatively small number of cases in this study, the absence of fungus other than Candida in our series, and the fact that all patients had their catheter removed, which has been shown to reduce mortality in previous studies.2,3 Finally, access to antifungal susceptibility profiles may have helped to optimize the treatment and outcome of our patients (Table 2).

One of our patients presented a sclerosing peritonitis during the initial hospitalization. Sclerosing peritonitis is another rare and frequently lethal complication in patients on PD, characterized by fibrosis of the visceral and parietal peritoneum.16 This patient experienced a favorable outcome with cessation of PD and immunosuppressive therapy. Previous peritonitis, either bacterial or fungal, may predispose to sclerosing peritonitis.16,17

In conclusion, fungal peritonitis is a rare complication of PD that is associated with significant morbidity and mortality. In our center, during a 10-year period, nine cases of fungal peritonitis were found among 288 PD patients, and all cases were caused by Candida species, with a majority of non-albicans Candida species. Resistance to fluconazole was rare, and potential resistance to amphotericin B was observed in one-third of the isolates recovered in this small series. The echinocandins were less active in vitro against the C. parapsilosis isolates. These observations must be taken into consideration when choosing the most appropriate initial empirical antifungal therapy. Definitive treatment is based on susceptibility testing results and cost-effectiveness considerations.

Conflict of interest: No conflict of interest to declare.

Table 2
Antifungal treatment before and after antibiotic susceptibility testing

<table>
<thead>
<tr>
<th>Year</th>
<th>Sex/age</th>
<th>Species</th>
<th>Empirical treatment</th>
<th>Treatment after fungus identification</th>
</tr>
</thead>
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<tr>
<td>1997</td>
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<td>C. tropicalis</td>
<td>Fluconazole</td>
<td>Amphotericin B</td>
</tr>
<tr>
<td>1997</td>
<td>M/78</td>
<td>C. parapsilosis</td>
<td>Fluconazole</td>
<td>Amphotericin B</td>
</tr>
<tr>
<td>1997</td>
<td>M/35</td>
<td>C. tropicalis</td>
<td>Fluconazole</td>
<td>Fluconazole</td>
</tr>
<tr>
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<td>M/75</td>
<td>C. albicans</td>
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<td>Fluconazole</td>
</tr>
<tr>
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<td>Fluconazole</td>
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<td>M/67</td>
<td>C. krusei</td>
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<td>Amphotericin B</td>
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<tr>
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<td>F/62</td>
<td>C. parapsilosis</td>
<td>Amphotericin B</td>
<td>Fluconazole</td>
</tr>
<tr>
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<td>C. glabrata</td>
<td>Amphotericin B</td>
<td>Caspofungin</td>
</tr>
<tr>
<td>2003</td>
<td>M/61</td>
<td>C. tropicalis</td>
<td>Caspofungin</td>
<td>Fluconazole</td>
</tr>
</tbody>
</table>

References