

Exit-site fungal infections – experience of a Peritoneal Dialysis Unit

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ABSTRACT

Introduction: Exit-site infections are an important complication of peritoneal dialysis; however, very little is known about fungi-related exit-site infections. The literature is very sparse and there are virtually no studies that report it. **Objective:** To evaluate in retrospect the risk factors associated with exit-site fungal infection and its development. **Methods:** The study included all diagnosed episodes of exit-site fungal infections in patients undergoing peritoneal dialysis in a hospital unit between 2011 and 2014, analyzed in relation to demographic, clinical and analytical variables. **Results:** The studied group included 26 patients, 70% of which were female, with a median age of 54 years old; average length in PD treatment three years. The majority of patients (70%) were undergoing manual peritoneal dialysis. About 30 episodes of exit-site fungal infections were diagnosed during the follow-up period, which corresponded to 5.6% of total exit-site infections diagnosed. About 23% of patients suffered from diabetes *mellitus* and 13% had undergone immunosuppressive therapy in the six months previous to the episode. Two thirds of patients (n=20) had undergone antibiotherapy in the previous three months, the majority (65%) for the treatment of peritoneal dialysis-related infection and 46% of these patients underwent concomitant antifungal prophylaxis with fluconazole. The exit-site fungal infections were predominantly caused by *Candida parapsilosis* (67%). Eighty per cent of patients (n=24) improved with antifungal therapy (fluconazole or itraconazole), and the remaining patients underwent peritoneal catheter replacement (n=3) or removal (n=3) due to persistent infection. Exit-site fungal infections were the cause of technique failure in 2 of these patients. **Conclusion:** Exit-site fungal infections are an unusual but important complication of peritoneal dialysis. In this study, the most relevant risk factor associated with these infections was previous antibiotherapy and the majority of patients evolving favourably under medical treatment.

Key Words: Antibiotherapy; exit-site infections; fungal infection; peritoneal dialysis.

BACKGROUND

The success of the peritoneal dialysis (PD) technique rests on the permanent and safe access to the peritoneal cavity. Despite the recent evolution, mainly concerning exit-site care, the establishing of infection prophylaxis protocols and the development of PD technique, infection is still an important cause of morbidity and PD failure^{1,2}. Infections directly related to technique are,

for the most part, caused by bacterial agents; infections caused by fungal agents are considerably less common². Although fungal peritonitis is well documented in the literature³⁻¹¹, and there are international recommendations in place for its diagnosis and treatment¹, this is not the case for exit-site fungal infections (ESFI). The literature is very sparse and there are virtually no studies that report its incidence, its impact on morbidity and death rate and the appropriate therapeutic

regimen. On the whole, the agent responsible for the majority of fungal infections in humans is *Candida spp*¹². There are over 350 different species that colonize the skin, oropharynx, gastrointestinal tract and vagina. They may cause opportunist infection in the presence of normal flora disruption, in a breach of the skin and mucous membranes or in a defect of cellular immunity within the host¹³⁻¹⁵. At least 13 species of *Candida* are known to cause infection, the most common being *albicans*, *glabrata*, *krusei*, *parapsilosis* and *tropicalis*^{13,14}. The more benign forms of infection are mucocutaneous infections¹⁴ (where exit-site infections (ESI) can be placed) and these occasionally recur, without the identification of an obvious predisposition element¹². The main risk factors for fungal infection are widely known: immunosuppression; previous antibiotherapy, especially of long duration; malnutrition and the presence of other outbreaks of fungal infection, amongst others^{14,15}. It is known that in patients undergoing PD, especially in relation to fungal peritonitis, an ascertained risk factor is the occurrence of previous episodes of bacterial peritonitis, in which there is also overgrowth of the fungal agent in the gastrointestinal tract (due to a flora imbalance subsequent to the use of antibiotics) and a decline in the activity of the local immune system caused by peritonitis³. Although not proven, Gram negative infections seem to carry a greater risk³. It remains to be seen if the same mechanisms related to ESFI apply, in what way they should be considered and if they carry a greater risk of technique failure that imply the immediate application of early antifungal therapy or even peritoneal catheter removal.

■ METHODS AND STUDIED POPULATION

A retrospective and observational study was undertaken to analyze all ESFI episodes occurring in a population of prevalent peritoneal dialysis patients at the Peritoneal Dialysis Unit of the São João Hospital (Hospital de São João – Porto, Portugal) between January 2011 and December 2014. All patients had a swan neck, double-cuffed peritoneal catheter with a curved edge implanted via laparoscopy, minilaparotomy or Y-TEC® system in the paraumbilical region. All patients were submitted to antibiotic prophylaxis with 1 gram of intravenous cephazolin. On average, patients initiated treatment at least two weeks after catheter insertion. The training included exit-site care, which was based on the use of a povidone iodine solution in the initial healing phase and, afterwards, on daily cleaning with 0.9% sodium chloride and the prophylactic topical

application of mupirocin. The nasal search for *Staphylococcus aureus* colonization was undertaken in all patients, and those with a positive result were treated with nasal mupirocin, according to Unit protocol. All ESI episodes were obtained through a clinical archive where they are systematically registered. The data relative to ESFI were obtained from medical records for the following variables: demographic characteristics; comorbidities; aetiology of chronic kidney disease; previous episodes of ESI or peritonitis (in the preceding three months); isolated agents and whether or not prophylaxis of fungal peritonitis with fluconazole was undertaken; antibiotherapy in the preceding three months or immunosuppressive therapy in the preceding six months; characterization of PD technique (time, modality and adequacy parameters); analytical profile; characterization of ESFI episodes, mainly an isolated agent, the isolating of bacterial agents taking place within the episode, type and duration of medical treatment and clinical progression. The instances of ESFI where there was a previous ESI episode with a bacterial agent, in which the infection was resolved through the use of antibiotherapy, were considered as “previous ESI”; in the instances where the bacterial infection was not resolved, the ESFI was considered subsequent. ESI was diagnosed according to the recommendations of the International Society of Peritoneal Dialysis (ISPD)¹. In the cases of a clinically questionable orifice (in the absence of purulent exudates) observation was maintained and local treatment with topical antibiotic and/or silver nitrate was administered, and systemic antibiotherapy was initiated if there was no clinical improvement at the end of one week. In most cases, this was undertaken according to Unit protocol, with sulfamethoxazole-trimethoprim or ciprofloxacin. As soon as the microbial examination result was available, drug therapy was adjusted according to fungal susceptibility to antibiotics/antifungal agents. In the ESI episodes with no resolution under appropriate and prolonged medical treatment, the patient was submitted to a shaving of the external cuff (if tunnel infection was present), peritoneal catheter substitution under antifungal coverage and/or antibiotic in the cases of controlled infection, or peritoneal catheter removal in the cases of unsuccessfully controlled infection.

■ RESULTS

During the four years, 30 ESFI episodes were diagnosed occurring in 26 patients. In the same time period, there was a total register of 534 ESI episodes, resulting

in a proportion of ESFI corresponding to 5.6% of the total ESI. Twelve percent (3 patients) of patients had more than one ESFI episode.

■ Characterization of the population studied (tables I and II)

The median age at time of diagnosis was 54.2±11.6 years of age and 69% of the population was female. About 23% had diabetes *mellitus*. The average span of time undergoing PD was 32.8±22.9 months, with 80% of patients receiving treatment for over a year and 33% for over five years. No episode occurred before the start of PD; in other words, during the healing or training period. Of the studied population, 70% was undergoing continuous ambulatory peritoneal dialysis (CAPD) and 30% received automatic peritoneal dialysis (APD), where 90% showed a total Kt/V over 1.7, as recommended by international guidelines²⁹. In regards to the analytical profile, the average albumin was of 3.6g/dl (lower than 3.5g/dl in 70% of cases) and the average HbA1c was 5.7% (6.5% in patients with known cases of diabetes *mellitus*). The remaining ascertained parameters are presented in table 2. Two thirds of the patients (n=20) had undergone antibiotherapy in the previous three months; of these, over half (n=14) owing to PD-related infection: eight cases of ESI (all Gram positive) and six cases of peritonitis (four Gram negative). Of this patient group, 46% had undergone concomitant

Table I

Characterization of the patient population

Number of patients	26
Single ESI episodes (n%)	23 (88%)
Age (years)^b	54.2± 11.6 (38-78)
Gender female (n%)^a	18 (69%)
Comorbidities (n%)^a	
Diabetes <i>mellitus</i>	6 (23%)
Cardiovascular disease	9 (35%)
Other comorbidities	7 (27%)
Aetiology of chronic kidney disease (n%)^a	
Unknown	8 (31%)
Glomerulonephritis	5 (19%)
Diabetic nephropathy	4 (15%)
Hypertensive nephropathy	3 (12%)
Interstitial nephritis	3 (12%)
Obstructive uropathy	3 (12%)
Others	
Treatment duration (months)^b	32.8± 22.9 (5-103)
Infection before start of PD (n%)	0 (0%)

ESI: Exit-site infection; ESFI: Exit-site fungal infection; PD: Peritoneal dialysis; a: Values according to the sample of patient; b: Values relative to the sample of episodes.

Table II

Characterization of the patient population with ESFI

PD Modality (n%)	
CAPD	21 (70%)
APD	9 (30%)
Dialysis adequacy parameters	
Weekly Kt/V	2.3 ±0.56 (1.5-4.3)
Kt/V > 1.7	30 (90%)
Weekly creatinine clearance (L/week)	79.4 ± 36.8 (39-167)
Creatinine clearance > 45L/min (n%)	
Total renal clearance (ml/min)	28 (93%)
Total renal clearance < 1ml/min (n%)	3.1 ± 4.7 (0-21)
D/P Cr (mg/dl)	16 (53%)
High-transport (>0,81) (n%)	0.73 ±0.1 (0.5-0.9)
Medium-high/ medium low (0.80-0,50) (n%)	3 (10%)
Unknown (n%)	25 (83%)
	2 (7%)
Biochemical profile	
Haemoglobin (g/dl)	11.6 ±1.5 (8.8-14.7)
Leukocytes (n ^o x 10 ⁹ /μL)	6.5 ±2.0 (1.1-9.2)
Sedimentation rate (mm/h)	74 ±28.8 (5-140)
C-reactive protein (mg/L)	11.9 ±20.2 (0.8-100)
Albumin (g/dl)	
HbA1c (%)	3.6 ±0.4 (2.8-4.4)
pH	5.7 ± 0.6 (4.8-7.2)
Bicarbonate (mmol/L)	7.32 ±0.0 (7.2-7.4)
	29.5 ±3.3 (22-35)
Antibiotherapy in the previous 3 months (n%)	20 (67%)
ESI in the previous 3 months (n%)	8 (27%)
Peritonitis in the previous 3 months (n%)	6 (20%)
Fluconazole prophylaxis in previous ESI/peritonitis (n%)	6 (46%)
Immunosuppressive therapy in the previous 6 months (n%)	4 (13%)

ESI: Exit-site infection; ESFI: Exit-site fungal infection; CAPD: continuous ambulatory peritoneal dialysis; APD: automatic peritoneal dialysis. The values displayed are relative to the sample of episodes.

fungal peritonitis prophylaxis with fluconazole. There was no recent history of fungal infection in any of the cases (<3 months). Two patients corresponding to four ESFI episodes) had undergone immunosuppressive therapy in the six months prior to the ESFI episode. Of the nine cases not associated with any of the aforementioned conditions, diabetes *mellitus* was identified among six other risk factors of fungal infection.

■ Characterization and evolution of ESFI episodes (tables III and IV)

All ESFI episodes were caused by *Candida spp.* The most frequently isolated species was *Candida parapsilosis* (67%), followed by *Candida glabrata* (10%), *Candida famata* (7%) and *Candida zeylanoides* (7%). In two cases there was concomitant isolation of two fungal agents (*Candida parapsilosis/guilliermondii* and *Candida parapsilosis/albicans*). In 23% of the cases the isolation of

Table III

Characterization of ESFI episodes (n/%)

Agents of fungal infection	
<i>Candida parapsilosis</i>	20 (67%)
<i>Candida glabrata</i>	3 (10%)
<i>Candida zeylanoides</i>	2 (6.6%)
<i>Candida famata</i>	2 (6.6%)
<i>Candida tropicalis</i>	1 (3.3%)
≥ 2 agents	2 (6.6%)
Seasonality	
Warm months (June-September)	10 (33%)
Cold months (November-February)	9 (30%)

ESFI: Exit-site fungal infection.

Table IV

Treatment and progress (n/%)

Antifungal treatment	
Fluconazole as 1 st antifungal	30 (100%)
Use of 2 nd antifungal	3 (10%)
Duration (days)	64,4 ±34,4 (13-140)
Antibiotic treatment*	
Monotherapy	12 (43%)
Antibiotics used	
<i>Trimethoprim-sulfamethoxazole</i>	17 (56,7%)
<i>Ciprofloxacin</i>	13 (43.3%)
<i>Vancomycin</i>	12 (40,0%)
<i>Amoxicillin/ clavulanic acid</i>	4 (1,3%)
<i>Others</i>	10 (3,3%)
Tunnel infection	5 (17%)
Posterior isolation of bacterial agent	17 (57%)
External cuff shaving	5 (17%)
Catheter substitution	3 (10%)
Catheter removal	3 (10%)

IP: Intra-peritoneal

the fungal agent was concomitant (n=2) or posterior (n=5) to the isolation of bacterial agents, more commonly *Staphylococcus epidermidis* (44%), and an average of 47 days after bacterial isolation in these. No difference was ascertained in ESFI incidence according to season. Concomitant tunnel infection was observed in 17% of the episodes. All cases were initially treated with fluconazole (a dosage of 200mg/day), and in 10% of cases, due to poor clinical response, a second antifungal was associated (itraconazole). The average length of treatment was 64.4 (±33.9) days. In 93% (n=28) of episodes there was concomitant use of antibiotics, overall applied empirically at the moment of diagnosis. Eighty per cent of cases (n=24) progressed favourably with medical treatment. In the cases with evidence of tunnel infection and with inferior clinical response after prolonged therapy, a shaving of the external cuff was performed in 17% (n=5), in

an attempt to control the infection, succeeding in only two cases. In total, 20% (n=6) did not respond to appropriate and prolonged antifungal therapy, and were submitted to peritoneal catheter removal (n=3) or substitution (n=3), resolving the infectious process. There was one case in which two consecutive episodes of peritonitis showed the same agent (*Candida glabrata*), and the second episode occurred 52 days after the termination of antifungal therapy and resulted in peritoneal catheter removal. ESFI were the cause of technique failure in 2³ of 6.7% patients that required the removal of the peritoneal catheter.

■ DISCUSSION

ESFI are an uncommon complication of PD. Studies that discuss it are sparse and even international guidelines from the ISPD¹ say very little beyond suggesting treatment with fluconazole. In our experience, ESFI represent a small but not insignificant percentage of total ESI. Luzar *et al*¹⁶ report a ESFI incidence between 1 and 3% in patients undergoing CAPD, which is considerably lower than that observed in our population. Another recent study¹⁷ with the aim of identifying, in a low occurrence context, the targets in ESI and tunnel prevention, reports an even lower incidence of ESFI (0.9%). ESFI seem to mostly share the general characteristics of fungal infections, mainly the association to variable degrees of immunosuppression and prior prolonged antibiotherapy. In this study, the most important risk factor in ESFI seems to have been previous antibiotherapy. In regards to the prophylactic use of antifungals, some studies^{5-7,18} have shown a reduced occurrence of fungal peritonitis with the implementation of this therapy during prolonged treatment of bacterial peritonitis. However, we ascertained that of the ESFI patients with previous PD-related infection, almost half had undergone antifungal prophylaxis. It may signify that antifungal prophylaxis use is not effective in preventing ESFI or, alternatively, that in previously treated ESI there was already a non-identified fungus involved (for which the prophylactic dose of fluconazole was ineffective). A factor that was not addressed and which might have contributed to the development of ESFI is the prophylactic use of antibiotics in the ES, which may be linked to an increased risk of fungal infection¹⁹. Bernardini *et al*²⁰ showed that the prophylactic use of gentamicin in the ES, compared to mupirocin, is also associated to an important percentage (20%) of ESFI, even though it leads to a decrease in the number of ESI and peritonitis. On the other hand, Shan Shan Chen *et al*²¹ did not observe an increase in the

occurrence of ESFI with the use of gentamicin. In regards to infections previous to ESFI, we observed that, similarly to what occurs in the development of fungal peritonitis³, in the instances where bacterial peritonitis preceded ESFI, it was more commonly caused by Gram negatives, probably related to the fact that Gram-negative infections tend to be more serious and in need of prolonged antibiotic treatment. The same was not observed in cases where ESFI was preceded by bacterial ESI (probably because Gram-negative ESI is significantly less frequent). Concerning other risk factors, malnutrition may also have significantly contributed. Moreover, the presence of disease/immunosuppressive therapy was identified in a comparatively smaller percentage. In relation to diabetes *mellitus*, specifically, Rodríguez-Carmona *et al*²² showed a causal link between poor glycaemic control in diabetic patients in the early stages of PD and the subsequent development of ESI. In our study, this was not a contributing factor to the development of ESFI. There were four episodes (13%) in which no risk factor was identified and that progressed favourably, requiring a shorter span of antifungal therapy, raising the pertinent question of whether treatment is sometimes initiated in cases of local colonization, when clinically irrelevant changes at the orifice of the dialysis catheter adapter precipitated a diagnosis of infection when there was no infection. Furthermore, in 23% of total episodes and in 50% of those which required surgical treatment, the isolation of the fungus was concomitant or posterior to bacterial isolation, which casts doubt on the effective contribution of the fungal agent to the infection. Contrary to what is observed in most *Candida* infections, including peritonitis³, the most prevalent species was not the *albicans* but the *parapsilosis*. Although in relation to peritonitis, this agent is already predominant in certain series⁹⁻¹¹. The recommended treatment for mucocutaneous candidiasis rests fundamentally on antifungal therapy with topical or systemic azoles, according to guidelines by the Infectious Diseases Society of America^{12,13}. *Candida parapsilosis* is generally highly susceptible to most antifungal agents¹³, which might explain the favourable clinical progress of most ESFI in this study. Hsu WD *et al*²⁸ report the effective use of topical sulconazole for four weeks in the treatment of four cases of ESI to *Candida parapsilosis*. On the other hand, it is known that some species of *Candida*, especially *glabrata*, are resistant to azoles^{12,24} (the only therapy used in this study), which might have been an important factor in the instances of medical therapy failure. However, that was not analyzed. The sensitivity tests are especially useful in these cases of infection to *non-albicans Candida* species¹². The length of antifungal therapy was generally considerable, although it was substantially greater in the

patient group submitted to surgical therapy. Yamaguchi *et al*²⁵ compared the use of prolonged antibiotherapy with peritoneal catheter substitution in resistant ESI and concluded that early peritoneal catheter substitution (in the absence of internal cuff infection) seems to constitute a simple and effective method in the treatment of intractable ESI, allowing the patient to continue PD and avoid being transferred to haemodialysis, suggesting that the substitution is evaluated after two weeks of antibiotherapy with no infection resolution. In our study, the four cases of ESFI submitted to catheter substitution under antifungal therapy progressed favourably, effectively resolving the infection. External cuff shaving, however, was not an effective measure in the treatment of these infections. Just as with other aspects of ESFI, the most effective therapeutic approach is still to be ascertained. There are studies with divergent results^{26,27} in regards to the establishment of a consistent causal link between ESI and subsequent peritonitis, but it is believed that peritonitis occurred due to the persistence in colonization of the peritoneal catheter by the fungal agent. Nevertheless, in our experience, the majority of ESFI showed a favourable clinical evolution under medical treatment, although it is wise to consider removal or replacement of the catheter in the absence of response to prolonged antifungal therapy.

■ CONCLUSION

Although relatively uncommon, fungal infections represent a complication of PD with relevant prognostic implications. Concomitant infection with bacterial agents is still frequent; therefore the correct diagnosis and distinction between infection or colonization by fungi might be a challenge. The most relevant factor for the development of ESFI was previous systemic antibiotherapy. Shaving of the external cuff does not seem to be an effective therapeutic approach; therefore, peritoneal catheter removal or substitution must always be considered to control the infection. Additional studies that contribute to a more precise ESFI characterization are required, mainly in terms of clinical repercussions, progress and effective therapy and, above all, regarding patient morbidity and technique survival.

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