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Peritoneal Dialysis Related *Candida* Peritonitis: A 16-year Single-Centre Experience

Abstract

Background: Fungal peritonitis represents one of the most serious complications in patients on Continuous Ambulatory Peritoneal Dialysis therapy. In the present study we have analyzed peritoneal dialysis patients who have developed *Candida* peritonitis.

Methods & Findings: In between January 2000 to August 2015, in our retrospective study we identified 65 episodes of peritoneal dialysis associated with fungal peritonitis, and examined their demographic features, predictors, incidence of *Candida* species and their outcome.

Among 65 fungal episodes 89.3% were *Candida* species, 1.5% yeast and 9.2% were dimorphic fungi. *Non-albicans Candida* species outnumbered the *Candida albicans*. Significant association was found between predictors and pathogens. Previous bacterial peritonitis episode was strongest predictor amongst the all.

On analyzing the outcome data obtained from all 65 patients through Chi test, we inferred that *non-albicans Candida* species were the major cause of death in majority of the patients. The similar trend was found in almost all the primary causes of End Stage renal disease test set, however the sample size (in others) was less than the minimum number of cases to be inferred statistically sound. The Loss of life parameters was found to be more than 3 fold higher in cases of *non-albicans Candida* species.

Conclusion: This study emphasizes that *non-albicans Candida* species appeared to be the significant pathogen in cases of Peritoneal Dialysis associated with fungal peritonitis. Hence, the study concludes that to reduce morbidity we need to start empirical antifungal coverage by taking into account their local epidemiological prevalence and their intrinsic behavior to antifungal drugs. Therefore to reduce mortality and chances of treatment failure we have to ensure rapid fungal species identification and risk assessment.

Keywords: Fungal peritonitis; End stage renal disease; Continuous Ambulatory Peritoneal Dialysis (CAPD); Predictors; *Candida albicans; Non-albicans Candida* species; Dimorphic fungi

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Introduction

Peritonitis is a common complication of Peritoneal Dialysis (PD) and Fungal Peritonitis (FP) is almost 3-30% of all peritonitis [1-5]. The majority of patients could not resume PD [1,2], and the patients FP-related mortality was very high [4,5]. Predictors for developing FP could not be clearly determined. Numerous

situations were listed which play an important role in the appearance of the mycotic infection. The strongest predictors for FP in PD patients were previous bacterial peritonitis, prolonged use of antibiotics, prolonged time in the dialysis program, prolonged time with the peritoneal catheter inserted, use of immunosuppressive agents, hospitalization and co-existence of an extra peritoneal fungal infection [6].

Most FP cases were caused by yeasts with *Candida* species, accounting for 70%-90% in adults and 80%-100% in the paediatric population. Filamentous fungi (moulds) such as *Aspergillus*, *Penicillium*, and the other yeasts were much less common, and together represent about 10% cases. In most centres, *C. albicans* were more predominant as a single pathogen; however, four other major *Candida* species-*C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei* became increasingly recognized cause of FP [7,8]. Thus the significance of the presence of *non-albicans Candida* species in the pathogenesis of PD associated peritonitis was required to be reconsidered. Therefore, this retrospective study was carried out to assess the frequency of Candida species as a single pathogen, its association with the predictors and its impact on the outcome of the patients.

Methods

It is a retrospective study involving patients undergoing Continuous Ambulatory Peritoneal Dialysis (CAPD) at our centre who developed peritonitis over a period of 16 years, from Jan 2000 to August 2015. Out of 402 patients, 65 End Stage Renal Disease (ESRD) patients developed fungal peritonitis. Aerobic, Anaerobic, mycobacterium and polymicrobial peritonitis were excluded from the analysis due to their different outcomes.

As per the peritoneal dialysis related infection recommendations published by ISPD in 2010 [9], the patient's exchange bags, containing effluent dialysate were received in the microbiology laboratory for macro level examination, microscopic examination and culturing simultaneously. From these bags, 100 ml of fluid was withdrawn with a sterile needle and syringe under aseptic conditions. The fluid was centrifuged in sterile tubes at a rate of 3000 g for 15 minutes and supernatant was discarded, leaving 0.5 ml. In the centrifuged deposit, 10 ml of sterile distilled water was added together and the mixture was shaken vigorously on vortex for 30 sec. This mixture was then divided into 4 parts of 1 ml, 3 ml, 3 ml and 3 ml each. 1 ml was further divided for staining characteristic like gram stain, Z.N. stain, and lacto phenol cotton blue film, while 3 ml in FA bottle for isolation of aerobes and fungi, 3 ml in FN bottle and remaining 3 ml in MP bottle for the isolation of anaerobes and mycobacterium respectively. These three inoculated bottles were further incubated in BactAlert 3D system following standard protocols. The isolated fungi were reexamined microscopically to ensure the staining and morphologic characteristic. Each positive specimen was inoculated on Sabouraud Dextrose agar (M286) and Sabouraud Cycloheximide Chloramphenicol agar (M664).

Cultures were routinely incubated at 25°C and 37°C and examined daily for a long period of four weeks. The identification of individual fungi was based on standard methods such as microscopy, morphology, colonial characterization, pigment production, rate of growth while yeast identification was done by Vitek-2 (Biomeurix, France). Here it is important to note that what took a long time in the above process, it took comparatively very short spell of time for the same e.g. microscopy became available within 3 to 5 hrs and identification along with antibiogram of *Candida* species and yeast was made available within 48 hrs dimorphic fungi was identified within 4-6 days after the clinical diagnosis was made.

The definitions used in the article are as follows. Predictors have been defined as predictors for developing FP. Previous bacterial peritonitis episode suggests that fungal peritonitis appears after the episodes of bacterial peritonitis. Prior antibiotic use means the use of antibiotic for a suspected infectious disease in a period of 30 days, 3 months, or 6 months prior to the development of FP. Prolonged time in the dialysis program means prolonged use of catheter for several years. Prolonged time with the peritoneal catheter inserted means maintaining the catheter after detecting the fungal infection. Use of immunosuppressive agents referred to steroid or immunosuppressive use for at least 2 weeks prior to the diagnosis of FP. Hospitalization means a risk when an infection of nosocomial origin occurs in the 30 days, 3 months, or 6 months prior to development of FP. Co-existence of an extra peritoneal fungal infection illustrates when a patient is suffering from extra peritoneal fungal infection which causes a fungal peritonitis through a haematogenic pathway [6]. De novo means those cases of FP which occur due to direct contamination of dialysis during the exchange procedure, underlying intestinal pathology such as diverticulosis in the host and environmental contaminations [10,11].

Statistical analysis was performed using chi square test and contingency coefficient. Data were expressed as mean \pm standard deviation. Statistical significance was defined at a p value of 0.05

Results

During the period from Jan 2000 to June 2015, 402 ESRD patients were initially on CAPD. The total no of episodes of fungal peritonitis during the entire period was 65. The average rate of fungus peritonitis was 2.6 episodes/CAPD year. Their base line and demographic data were described as follows. Out of total FP population males were 89.2% and females were 10.8%. The mean age of the study population was 58.29 ± 8.845 and the mean duration on CAPD before development of fungal infection was 18.26 ± 8.080 months. Predominant cause of ESRD in this group was diabetic nephropathy (52.3%), glomerulonephritis (32.3%), hypertension (13.9%) and others (1.5%).

In our case series fungal peritonitis was presented with abdominal pain, sub-acute intestinal obstruction, nausea, vomiting, occasional fever and cloudy dialysate.

Microscopic examination of 65 episodes of FP of the dialysate pellet with lacto phenol cotton blue film revealed conidia, blastoconidia, pseudohyphae and in few cases occasional mycelia like structures and culture examination revealed 89.3% *Candida* species, 1.5% yeast and 9.2% dimorphic fungi. On analyzing the data of *Candida* species 78.5% were *non-albicans* and10.8% were *C. albicans*. Among *non-albicans Candida* species *C. tropicalis* (13.8%) was the most frequent fungi isolated. It is worth mentioning here that it is for the first time when thirteen species of *Candida* were isolated from the cases of PD associated peritonitis. The spectrum of *Candida* and its species is depicted in **(Figure 1)**.

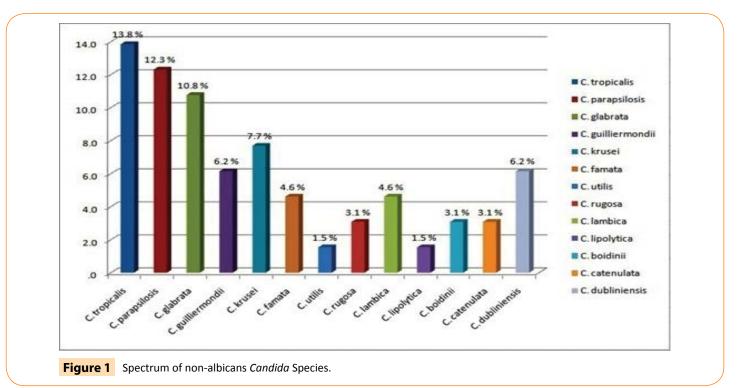
Association between predictors and pathogen reveals 30.8% de novo episodes and remaining 60.2% episodes of FP predisposed by different predictors. Among de novo *non-albicans* were 23.1 %. The strongest predictor to predispose the fungal infection was previous bacterial peritonitis episode (16.9%) as shown in **Figure 2**. It was first time when analysis was done between predictors and pathogen and was found significant at 0.05 levels **(Table 1)**.

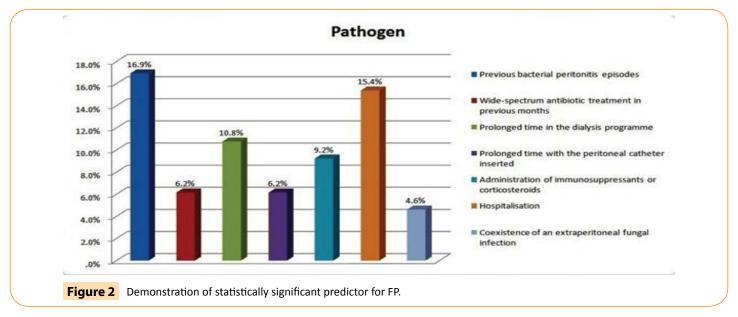
Association among primary cause of ESRD, pathogens and outcome showed that catheter removal (32.4%) and loss of life (14.7%) was significantly more frequent in patients suffered with peritonitis due to *non-albicans Candida* species while in glomerulonephritis, patient required maximum hospitalization (28.6%) due to *non-albicans Candida* species for resolution of

peritonitis. Cure rate (55.6%) was more significant in patients with hypertension. It is also noticed that de novo fungal infection was more frequent with glomerulonephritis group **(Table 2)**. On analyzing the outcome data obtained from all 65 patients through Chi test, we inferred that *non-albicans* were the major cause of death in majority of patients. The similar trend was found in almost all the primary causes of End Stage renal disease test set as depicted in **Figure 3**, however the sample size (others) was less than the minimum number of cases to be inferred statistically sound. The Loss of life parameters was found to be more than 3 fold higher in case of *non-albicans Candida* species pathogen.

Discussion

Fungi are widely found in human environment, being part of the





2016

Vol. 7 No. 2: 10

Table 1 Association between predictors and pathogens.

	Fungi						Pearson	Contingonau
Predictors	Candida albicans	Non albicans	Yeast	Di morphic fungi	Total	df	Chi-square	Contingency Coefficient
Previous bacterial peritonitis episodes	0 0.0%	7 10.8%	1 1.5%	3 4.6%	11 16.9%		1 51.990*	0.667
Wide-spectrum antibiotic treatment in previous months	0 0.0%	3 4.6%	0 0.0%	1 1.5%	4 6.2%	21		
Prolonged time in the dialysis programme	0 0.0%	7 10.8%	0 0.0%	0 0.0%	7 10.8%			
Prolonged time with the peritoneal catheter inserted	4 6.2%	0 0.0%	0 0.0%	0 0.0%	4 6.2%			
Administration of immune suppressants or corticosteroids	0 0.0%	6 9.2%	0 0.0%	0 0.0%	6 9.2%			
Hospitalisation	0 0.0%	10 15.4%	0 0.0%	0 0.0%	10 15.4%			
Coexistence of an extra peritoneal fungal infection	0 0.0%	3 4.6%	0 0.0%	0 0.0%	3 4.6%			
De novo	3 4.6%	15 23.1%	0 0.0%	2 3.1%	20 30.8%			
Total	7 10.8%	51 78.5%	1 1.5%	6 9.2%	65 100.0%			

* Significant at p value 0.05.

 Table 2 Association among primary cause of ESRD, pathogens and outcome.

Primary Diagnosis	Pathogens	Outcomes						
		Loss of Life	Loss of Catheter	Hospita-lization	Change of Modality	Cure	Total	
Diabetes	Non albicans	5 14.7%	11 32.4%	6 17.6%	1 2.9%	4 11.8%	27 79.4%	
	Yeast	0 0.0%	1 2.9%	0 0.0%	0 0.0%	0 0.0%	1 2.9%	
	Dimorphic Fungi	2 5.9%	4 11.8%	0 0.0%	0 0.0%	0 0.0%	6 17.6%	
	Total	7 20.6%	16 47.1%	6 17.6%	1 2.9%	4 11.8%	34 100.0%	
Hypertension	Non albicans	1 11.1%	1 11.1%	2 22.2%		5 55.6%	9 100.0%	
	Total	1 11.1%	1 11.1%	2 22.2%		5 55.6%	9 100.0%	
Glomerulo- nephritis	Candida albicans	0 0.0%	0 0.0%	0 0.0%		6 28.6%	6 28.6%	
	Non albicans	2 9.5%	5 23.8%	6 28.6%		2 9.5%	15 71.4%	
	Total	2 9.5%	5 23.8%	6 28.6%		8 38.1%	21 100.0	
Unknown	Candida albicans					1 100.0%	1 100.0%	
	Total					1 100.0%	1 100.0%	

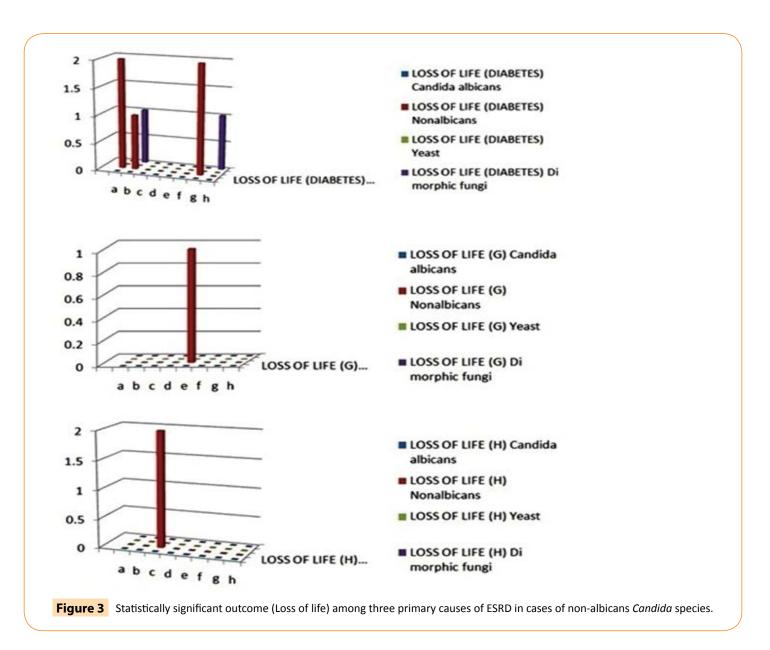
normal flora of the skin and mucosa, but in certain conditions, they become pathogenic. The lethality, although variable, remains very high [12] because the fungi form a biofilm on the surface of the silastic catheters that reduces the penetration of antifungal agents [13]. It penetrates the peritoneal cavity through intraluminal or periluminal pathways and cross the intestinal mucosa, or enters through the hematogenic pathway due to a distant fungal infection [6].

In our case series *Candida* species were isolated in 89.3% cases, yeast in 1.5% cases and dimorphic fungi were isolated in 9.2% cases. On analyzing the data of *Candida* species 78.5% *non-albicans* and 10.8% *C. albicans* were found. Among *non-albicans*

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C. tropicalis (13.8%), C. parapsilosis (12.3%), C. glabrata (10.8%), C. quilliermondii (6.2%), C. cruzi (7.7%), C. famata (4.6%), C. utilis (1.5%), C. rugosa (3.1%), C. lambica (4.6%), C. lipolytica (1.5%), C. boidinii (3.1%), C. catenulata (3.2%) and C. dubliniensis (6.2%) were isolated in 48 to 50 hours. Hence, here in for the first time in the world we are reporting isolation of 13 species of non-albicans from dialysate pellet which is unique in itself. This had been made possible because of the prompt identification of the isolated colonies done by Vitek -2.

Association among primary cause of ESRD, pathogens and outcome showed that non-albicans species of Candida were more complicated to treat as compared to *albicans*. As data revealed, due to non-albicans species of Candida, catheter removal (32.4%) and loss of life (14.7%) were significantly more frequent in diabetics while in glomerulonephritis, patient required maximum hospitalization (28.6%) for resolution of peritonitis. Cure rate (55.6%) was more significant in patients with hypertension. It was also noticed that de novo infections were more frequent with glomerulonephritis group. Statistical analysis had been calculated separately and was found significant in case of glomerulonepritis at p value of 0.05. On analyzing the outcome data obtained from all 65 patients through Chi test, we inferred that non-albicans Candida species were the major cause of death in majority of patients. The similar trend was found in almost all the primary causes of End Stage renal disease test set, however the sample size (others) was less than the minimum number of cases to be inferred statistically sound. The Loss of life parameters was found to be more than 3 fold higher in cases of non-albicans Candida species.

In Australia [3] and Turkey [14] Candida albicans predominated but in Hong Kong [5] and in USA [1] Candida parapsilosis were found to be the dominant strain. However Candida tropicalis was the most common species in Taiwan [15]. While more than 90% of FPs were caused by Candida species in a report from the United Kingdom [16], most of the reports from Eastern countries and South American countries had described the presence of non-Candida FPs, including Aspergillus and Penicillium species [3,14,17-19]. Tropical climate may increase the likelihood of non*Candida* species with reports from Australia describing up to 32% of *non-Candida* FPs. Seasonal variation was also reported [3,19]. An Indian study reported *Candida albicans* 65%, *non-albicans Candida* 25%, *Rhizopus* species 5% and *Alternaria* 5% [20]. According to Levallois all nine 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 again one by *C. glabrata* [21].

The incidence rate for other *non-albicans Candida* species was not well-established because the species were not identified in many cases and listed as *Candida* species only. Over the last decade, the number of *non-albicans Candida* species had been growing and their involvement had become associated with increased mortality and were intrinsically resistant to the usual antifungal used in the treatment [1,5,22-24].

Although larger series of FP in PD had already been published, antifungal susceptibility testing of isolates had been reported in two series. The first series was from Mexico and reported antifungal susceptibilities to triazoles only. Ten *Candida* isolates were identified resistant with various triazoles [25]. The second series was from Greece, which reported 46 episodes of fungal peritonitis and was tested for susceptibility to Amphotericin B and various triazoles [13].

Fluconazole resistance was predictable with *C. krusei, itraconazole* and *voriconazole* were resistant with *C. glabrata* isolate. Resistance to specific triazoles had 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 was the first published report of in vitro resistance of *Candida* species isolates to amphotericin B in a PD population [21].

In recent years it is confirmed that appearance of *Candida* species were resistant to fluconazole (*C. krusei, C. ciferrii, C. norvegensis, C. glabrata, C. famata, C. lusitaniae, C. guilliermondii* and *C. tropicalis*), which indicates that it is not convenient to use fluconazole in monotherapy for certain peritonitis episodes, and that its effectiveness must be evaluated for some yeast species [6].

From the results obtained in the forging paragraph, identification of species had become necessary and essential to start empirical therapy on the basis of microscopy as few species of *non-albicans* exhibited resistance towards triazoles which consequently increase morbidity and drug resistant.

This study has limitations. Because of the relative rarity of FP, our total number of episodes remains quite small, despite a long follow-up time. Furthermore, the analysis between predictors and pathogens and analysis among disease, pathogen and outcome were more limited due to small sample size. Despite these limitations, we believe that this study is important considering its unique description of *Candida* species in FP.

Thus current study concludes that in PD associated FP *non-albicans* species of Candida predominates in comparison to *Candida albicans*. Therefore, initial empirical antifungal therapy should be based on the local epidemiology and their intrinsic behavior to different antifungal agents. Further early assessment of predictors, rapid species identification and optimum antifungal coverage can lead to reduce morbidity, allowing shorter stay in the hospital and thereby preventing further nosocomial infection, antifungal resistance and chances of treatment failure.

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