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Original Research Article

Candida Parapsilosis: An Emerging Pathogen, Its Distribution and Antifungal Susceptibility to Fluconazole and Amphotericin B

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ABSTRACT

Candida is one of the leading causes of fungal infections mainly in immunocompromised patients. *Candida parapsilosis* infection has been on rise from past few years. Though C. *parapsilosis usually* susceptible to fluconazole, recent repot suggest resistance. In view of this, a study was carried to know the distribution and antifungal susceptibility of C. *parapsilosis* to Fluconazole and Amphotericin B.

Out of 293 candida species isolated, 43(14.7%) were C. *parapsilosis*. It accounts for 30(20.8%) cases of Candidemia followed by other infections. Vascular catheterization, Use of antibiotics is common associated risk factors and majority of C. parapsilosis were isolated from Intensive Care unit (ICU). In our study, all isolates were sensitive to Amphotericin B. 39.5% isolates of C. *parapsilosis* were resistant and 23.3% were susceptible dose dependent to Fluconazole as per latest CLSI 2012 M27-S4 document.

Key words: *Candida parapsilosis*, antifungal susceptibility

INTRODUCTION

Mycotic infections have been increased significantly due to the widespread usage of aggressive medical practices like chemotherapy for malignancies, immunosuppressive therapy, invasive surgeries, transplantations, increased intensive care unit frequency and extensive use of broad spectrum antibiotics. [1,2] Candida is one of the leading causes of fungal infections in such immunocompromised states. It is the most common cause of invasive fungal infections mainly nosocomial bloodstream infections. [3]

80% cases of human candidiasis were caused previously by Candida *albicans*. There has been a significant shift from Candida albicans to Non-albicans Candida (NAC) species like Candida *tropicalis*, Candida *parapsilosis* and C. *glabrata* in last two decades. [4,5] Incidence of C. *parapsilosis* has dramatically increased over the past few years. It is a skin commensal which can be carried by the hands of health care workers. [6] Due to its ability to form biofilms on intravascular devices and catheters, it is closely associated with candidemia. [7,8]

There exists a marked variation in candidial species distribution and antifungal susceptibility patterns not only in different parts of the world but also within different regions of a country. [9] NAC species have varying antifungal susceptibility patterns with some exhibiting resistance to antifungal agents. [10]

Amphotericin B and fluconazole are the most widely used antifungals for systemic fungal infection. C. *parapsilosis*

strains have usually been reported to be susceptible to azoles. [11,12] However, an emerging resistance and decreased susceptibility to fluconazole has lately been observed. [13,14] Due to the emergence of C. *parapsilosis* as one of the leading cause of candidemia in our set up, the present study was conducted to know its distribution and antifungal susceptibility pattern against the commonly used antifungal agents i.e. Amphotericin B and Fluconazole.

MATERIALS AND METHODS

A prospective observational study was carried after institutional review board approval for a period of one year from January 2015 to December 2015.All specimens received in the mycology division were processed as per standard protocol. *Candida* isolates were identified and speciated by Germ tube test, urease test, fermentation and assimilation tests, Dalmau plate culture on Corn meal agar for microscopic morphology and pigment production on CHROM agar.

Antifungal susceptibility testing was done using broth Macrodilution method (BMD) as per standard Clinical Laboratory Standards Institute (CLSI) guidelines, document M27-A3. [15] Sterile, disposable, 96 well microdilution plates were used for susceptibility testing of fluconazole and Amphotericin B. RPMI 1640 was used as the broth medium. The endpoint readings were taken. Grading of turbidity was done from 0 to 4. Optically clear well was assigned grade 0 and grade 4 was assigned to turbidity equal to or more than that of control well without the drug. Endpoint for Amphotericin B was defined as the minimum concentration inhibiting visual growth. For azoles, endpoint was the concentration where there was a decrement of almost half of original in turbidity. Minimum inhibitory concentration (MIC) values for two antifungal agents were determined at 24 and 48 hr. Criteria used for fluconazole according to CLSI supplement M27-S3 (2008) [16] AND CLSI supplement M27-S4 (2012) [17] was as follows.

CLSI M27-S3(2008)			CLSI M27-S4(2012)		
S (≤8 µg/ml)	SDD (16-32 µg/ml)	R (≥64 µg/ml)	S (≤2 µg/ml)	SDD (4 µg/ml)	R (≥8 µg/ml)

(S- susceptible, SDD-Susceptible dose dependent and R –Resistant)

Susceptibility reference for Amphotericin B was used as defined by Yang et al [18] with MIC ≤ 1 µg/ml considered susceptible and MIC ≥ 2 µg/ml as resistant. C. *parapsilosis* ATCC 22019, *C albicans* ATCC- 90028 and *C krusei* ATCC- 6258 were used for performing quality control.

Statistical analysis:

Statistical analysis was done using SPSS software version 20.0 with Chi square test and odds ratio used to analyze the association with various factors. P value of ≤0.05 was considered as significant.

OBSERVATION AND RESULTS

A total of 293 Candida were isolated from 2152 specimens received in mycology division during one year study period. The mean age of the patients was 46 years with a male to female ratio of 1.98:1.

Table 1: Distribution of clinical isolates of candida species.

	C. albicans (n=68, 33.2%)	Non-albicans Candida (n=225, 76.8%)							Total
		C. tropicalis	C. parapsilosis	C. glabrata	C. kefyr	C. krusei	C. gullermondii	C. lusitaniae	
Blood	22	49	30	39	3	2	3	0	**148**
Fluid	3	2	1	2	1	0	0	0	**9**
Tissue	2	6	2	3	0	0	0	0	**13**
Urine	32	32	2	7	2	0	0	2	**77**
Nail	0	10	6	0	0	2	0	0	**18**
Bile	1	2	0	1	0	0	0	0	**4**
Pus	8	12	2	2	0	0	0	0	**24**
Total	**68(23.2%)**	**113(38.6%)**	**43(14.7%)**	**54(18.4%)**	**6(2.04%**	**4(1.4)**	**3(1.02%)**	**2(0.64%)**	**293**

Non-albicans Candida accounted for 76.8% of isolates as compared to 33.2% isolates of C. *albicans*. Candida species isolated were C. *tropicalis* (n=113, 38.6%), C. *albicans* (n= 68, 23.2%), C. *glabrata* (n=54, 18.4%), C. *parapsilosis* (n=43, 14.7%), C. *kefyr* (n=6, 2.04%), C. *krusei* (n= 4, 1.4%), C. *guilliermondii* (n= 3, 1.02%) and C. *lusitaniae* (n=2, 0.64%).

Out of 68 isolates of C. *albicans*, 32(47.1%) were isolated from urine followed by 22(32.3%) from blood while majority of Non-albicans Candida were isolated from blood (n= 126, 50.3%). Among 148 blood isolates, C. *tropicalis* was predominant 49 (33.1%) followed by C. *glabrata* 39 (26.3%), and C. *parapsilosis* 30 (20.8%). Among the Candida *parapsilosis*, 30 were isolated from blood, 6from nail, 2 each from urine, pus & tissue and 1 isolate from fluid.

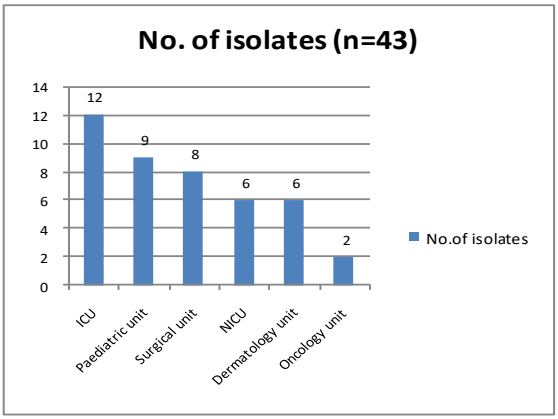

Table / Fig 3: Isolation of C. *parapsilosis* from hospitalization units

Isolation of C. *parapsilosis* in order of frequency from different hospitalization units are Intensive care unit (ICU) 12(27.9%), paediatric 9(20.9%), surgery 8(18.6%), Neonatal Intensive Care Unit (NICU) 6(14%), dermatology unit 6(14%) and oncology 2(4.6%).

Table 2/ Fig 2: Demographic characteristics of 43 patients with mycosis caused by C. *parapsilosis*

Gender	
Male	29 (67.4%)
Female	14 (32.6%)
M/F Ratio	2.07
Age group	
Neonates	6 (13.9%)
Children	9 (20.9%)
Adults	16 (37.2%)
Elderly	12 (28%)
Mean age of the patient (range)	38.6 years (1 month-79 years)

Mean age of patient with C. *parapsilosis* infection was 38.6 years with male to female ratio of 2.07:1. No significant difference found in distribution of cases among paediatric, adult and elderly age group (Table 2)

Table/Fig 4: Risk factors associated with C. *parapsilosis* infection

Underlying conditions	Number of cases
Vascular catheterization	34 (79.1%)
Broad spectrum antibiotics	29 (67.4%)
Parenteral nutrition	24 (55.8%)
Major Surgery	6 (13.9%)
Premature birth	4 (9.3%)
Malignancy	2 (4.7%)

Table 4 shows the risk factors associated with C. *parapsilosis* infection. The presence of an indwelling vascular catheter (79.1%) was the most frequent predisposing factor associated followed by use of broad spectrum antibiotics (67.4%), parenteral nutrition (55.8%), major surgery (13.9%), prematurity (9.3%) and malignancy (4.7%).

Table/Fig 5: Comparative susceptibility of C. *parapsilosis* to fluconazole according to the breakpoints (µg/ml) from M27-S3(2008) and M27-S4(2012) guidelines

	CLSI M27-S3(2008)			CLSI M27-S4(2012)		
C. parapsilosis (43)	S (≤8)	SDD (16-32)	R (≥64)	S (≤2)	SDD (4)	R (≥8)
	26 (60.5%)	17 (39.5%)	0	16 (37.2%)	10 (23.3%)	17 (39.5%)

(S- susceptible, SDD- Susceptible dose dependent and R –Resistant)

MIC testing of 43 *C. parapsilosis* isolates was done by BMD method for fluconazole and Amphotericin B (Table 5).

All 43 isolates were susceptible to Amphotericin B having MIC ≤ 1 µg/ml.

When the susceptibility of *C. parapsilosis* was evaluated based on 2008 CLSI M27-S3 guidelines, 26 (60.5%) isolates were susceptible, 17 (39.5%) susceptible dose dependent and no isolate was resistant.

As per2012 CLSI M27-S4 guidelines, 16 (37.2%) *C. parapsilosis* isolates were susceptible to fluconazole while 10 (23.3%) showed susceptible dose dependence and 17 (39.5%) showed resistance.

DISCUSSION

The spectrum of candida infections has changed in recent times with the emergence of Non-albicans Candida species and occurrence of resistance to commonly used antifungal agents. Epidemiology of candidemia is different in various parts of the world with C. *albicans* as the predominantly isolated pathogen in USA, northern and central Europe. In contrary, non-albicans species are the major pathogens in Asia, South America and South Europe. [19] In our study Non-albicans Candida species (76.8%) outnumbered *Candida albicans* (33.2%) with C. *tropicalis* (38.6%) being the most common isolate, followed by C. *glabrata* and C. *parapsilosis*. Various studies have also shown the same pattern of distribution with prevalence of C. tropicalis as high as 67-90%. [20-22]

The incidence of C. *parapsilosis* has risen in the recent years. In our study C. parapsilosis accounted for 30(20.8%) cases of Candidemia, thus emphasizing the emergence of C. *parapsilosis* as etiological agent. Many studies reported C. *parapsilosis* as the most common or the second common etiological agent of Candidemia. [23,24]

In the present study, out of 18 cases of onychomycosis, C. *parapsilosis* is the etiological agent in 6 cases (30%). Segal et al [25] have isolated a higher frequency of C. *parapsilosis* isolates (39.5% in toenails, 36.7% in fingernails) in onychomycosis.

We have seen an isolation of 27.9% of C. *parapsilosis* isolates from patients admitted in ICU and 14% from NICU. Other studies also reported an increased isolation of C. *parapsilosis* from critically ill patients admitted in ICU. It is associated with nosocomial blood stream infections and neonatal Candidemia in intensive care units. [26,27]

Though skin commensal, C. *parapsilosis* has capability to grow in hyperalimentation solutions and capability to form biofilm on intravascular devices. [28] Predisposing factors commonly associated in our study are vascular catheterization (79.1%), broad spectrum antibiotics (67.4%), parenteral nutrition (55.8%). Almirante et al [23] in a study of 72 patients with C. *parapsilosis* infection elucidated vascular catheterization (97%), antibiotic use (91%), hyperalimentation (54%), surgical procedure (46%), immunosuppressive therapy (38%), malignancy (27%), organ transplant (16%), neutropenia (12%) and colonization (11%) as risk factors. In a study conducted by Canton et al, [14] various underlying conditions included catheterization (65.2%), major surgery (40.3%), burns (5.8%), premature birth (5.5%), neutropenia (5.2%) and HIV (1.5%). The association of predisposing factors with C. *parapsilosis* infection in our study was statistically significant ($P<0.05$).

The most frequently administered antifungal for candidal infections is Fluconazole. Amphotericin B though available, has limitations owing to its nephrotoxicity and poor aqueous solubility. Fluconazole is the drug of choice for candidal infection because of its better bioavailability, easy route of administration and minimal side effects. [29,30]

Acquired resistance to azoles can be seen after prolonged usage, as is observed in cases of antifungal prophylaxis. The overuse of common antifungal agents has led to the selection of candida species with inducible resistance like C. *glabrata* and C. *tropicalis* or those exhibiting intrinsic resistance like C. *krusei*. [31,32] Some studies have shown that fluconazole at subinhibitory concentrations causes resistance in C. *albicans*. [33]

Initially, C. *parapsilosis* strains rarely showed resistance to azoles but change of susceptibility pattern with

resistance has been recently observed. [13,14,34]

In our study, 39.5% isolates of C. *parapsilosis* were resistant and 23.3% were susceptible dose dependent to Fluconazole as per latest CLSI 2012 M27-S4 document. All isolates were sensitive to Amphotericin B. Oberoi et al [35] also reported 100% susceptibility of C. *parapsilosis* isolates to Amphotericin B but an increased resistance of 33.9% to fluconazole in their retrospective review study. There was different fluconazole resistance pattern observed in different regions of the world with <5% resistance seen in North and Latin America, Europe, Asia-Pacific region, and 15% resistance seen in Africa/Middle east countries. [36]

National Committee for Clinical Laboratory Standards developed standard guidelines for susceptibility testing of Candida species to antifungal agents. European Committee on Antibiotic Susceptibility Testing (EUCAST) also has devised antifungal susceptibility guidelines for Candida sp. [37] However, both CLSI and EUCAST have defined different break points to define antifungal resistance or susceptibility. The new breakpoints as defined by CLSI M27-S4 guidelines are in harmony with EUCAST guidelines and are more sensitive in detection of emerging resistance among Candida species. [37]

Comparative susceptibility of C. *parapsilosis* to fluconazole in our study showed 60.5% susceptible, 39.5% susceptible dose dependent and No resistant to Fluconazole as per CLSI 2008 M27-S3 document while there was decreased susceptible (37.2%) and increased resistant to 39.5% as per CLSI 2008 M27-S4 document. This might be due to new clinical break points (CBPs) for Fluconazole which are lowered in CLSI 2012 M27-S4 document as compared to CLSI 2008 M27-S3 document. Studies have reported increased resistance among C. *parapsilosis* isolates based on these new clinical break points (CBPs) when compared to previous guidelines. Woon et al [38] and Fothergill et al [39] observed increased resistance to fluconazole when compared resistance rates determined by previous and recent CLSI antifungal breakpoints. In a study conducted by Santos et al, [40] 7.1% isolates were categorized as fluconazole non susceptible based on the revised CLSI M 27-S4 CBPs when compared to none resistant defined by original CBPs. Similar findings were also reported in our study with39.5 of C. *parapsilosis* isolates were resistant based on new CLSI guidelines as compared to none as per previous CLSI guidelines.

The emergence of Fluconazole resistance in C. *parapsilosis* might be attributed to continued fluconazole exposure over prolonged time. This may lead to isolates become less susceptible which are susceptible initially. [13] Similarly Use of fluconazole prophylactically has led to emergence of resistant subclones of C. *parapsilosis.* [41] Occurrence of cross resistance to voriconazole after fluconazole exposure has been also observed. [13]

CONCLUSION

The emergence of Fluconazole resistance in C. *parapsilosis* embarks the importance of surveillance for species distribution of candida and their drug susceptibility patterns.

Conflict of interest: Nil

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