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RESEARCH ARTICLE

PREVALENCE OF CANDIDA SPECIES AND THEIR DRUG RESISTANCE PATTERN IN PATIENTS ADMITTED IN ICU AT TERTIARY CARE HOSPITAL OF WESTERN RAJASTHAN

Sharmila Choudhary[1], Dr. Jahnvi Sharma[1], Dr. Pinky Bhagat[1,*] and Dr. P.K. Khatri[2]

[1]Post graduate student, Department of Microbiology, Dr. S.N. Medical College, Jodhpur
[2] Senior Professor, Department of Microbiology, Dr. S.N. Medical College, Jodhpur

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***Corresponding author:**
Dr. Pinky Bhagat

ABSTRACT

Introduction: Fungal infections are a major burden of mortality and morbidity in the critical care setting and are one of the leading causes of nosocomial infections despite recognition of risk factors and improvement in infection prevention. The mortality rate associated with candidemia worldwide is also high ranging from 10% to 49%. In India, the picture is not very clear due to lack of multicentre studies. ***Objectives:*** This study was done to determine prevalence and drug resistance pattern of candida isolates from patients admitted in ICU. ***Methods:*** This is a hospital based cross sectional study done in ICU of a tertiary care hospital from period of January 2022 to December 2022. In total 130 immunocompromised patients with clinical suspicion of having fungal infections were included in the study and samples were processed using standard microbiological methods and antifungal susceptibility testing was done as per CLSI 2022 guidelines. ***Result:*** Out of 130 samples, 36 samples (27.69%) were positive for *Candida* infection whereas 94 samples (72.30%) were found to be negative for *Candida* infection. (p=0.0001). It was observed that nonalbicans *Candida* species (75%) had predominance over *C. albicans* (25%). Among the non-albicans *Candida* spp., *Candida tropicalis* was the most common isolate seen in 15 (41.67%) isolates followed by *Candida parapsilosis* in 6 (16.67%), *Candida krusei* in 4 (11.11%) and *Candida glabrata* in 2 (5.55%) isolates. Among 9 *Candida albicans*, Nystatin, Amphotericin B and Miconazole showed 100% sensitivity followed by Ketoconazole (88.88%), Itraconazole (88.88%) and Fluconazole (88.88%). *Candida tropicalis* showed 100% sensitivity to Ketoconazole, Nystatin, Voriconazole, Amphotericin B and Miconazole followed by It raconazole (93.33%) and resistance to Fluconazole (73.33%). ***Conclusion:*** In our study non albicans candida were more prevalent than candida albicans with Antifungal susceptibility testing for *Candida* spp by Disk diffusion method showed resistance to Voriconazole in *C.albicans* and among NAC, resistance to Fluconazole. Increasing rate of resistance among *C.albicans* and NAC may be due to frequent use of antifungal prophylaxis in immunocompromised patients especially in ICU setup, this emphasizes the need of antifungal susceptibility testing in ICU which can help clinician to avoid over use of antifungal prophylaxis and start appropriate antifungal agents as per culture sensitivity report. This can help in reduction of multidrug resistance in fungal isolates.

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INTRODUCTION

The history of the discovery and naming of *Candida* extends from the ancient Greeks to modern day researchers. (1) The name *Candida* was proposed by Berkhout. It is from the Latin word *toga candida*, referring to the white toga (robe) worn by candidates for the Senate of the ancient Roman republic. (2) *Candida* species is a normal commensal flora of the oral cavity, gastrointestinal tract and vagina of a healthy human and colonizes the mucus membranes of 30-60% of humans.(3) Fungus are now considered as a primary cause of morbidity and mortality in severely ill and immunocompromised patients. Ranging from mucocutaneous overgrowth to bloodstream infections, they are responsible for various clinical manifestations. (4) There are more than 17 different *Candida* species that are known to be the aetiological agents of human infection and majority of the invasive infections are caused by *Candida albicans, Candida glabrata, Candida parapsilosis, Candida tropicalis,* and *Candida krusei.*(5,6) More worryingly, *C. auris* is being increasingly recognized as an emerging, multidrug-resistant (MDR) species was just discovered in 2009, causing invasive candidiasis. C. *auris* is becoming an important cause of nosocomial blood stream infections (BSIs) in Asia, Africa, America and Europe.(7) The infection caused by *Candida* spp. is among the top three infections commonly taking place in the intensive care units (ICUs) worldwide (8,9), accounting for 18% of all infections.(10)

In recent decades, several countries around the world have witnessed a change in the epidemiology of *Candida* infections, characterized by a progressive shift from a predominance of *C. albicans* to NAC species. (11) Some of the *candida* non-albicans are highly virulent and associated with treatment failure due to reduced susceptibility to antifungal agents. The drug resistance scenario has been increasing due to excessive use of random antifungal agents in the last decade.(12) Studies have shown that episodes of invasive candidiasis occur 5-10 times more often in the ICU compared to other wards and that two thirds of candidemia occur in the ICU or in surgical wards.(13) Candidiasis is responsible for the dilemma in both diagnosis and treatment. Therefore, the purpose of the study is to see various species of *Candida* and to determine the resistance pattern of different drugs. The findings will provide a generalized data of correlation of various species and their resistance pattern of particular drugs.

MATERIAL AND METHODS

This is a hospital based cross sectional study done in ICU of a tertiary care hospital from period of January 2022 to December 2022.

STUDY POPULATION: TOTAL-130 Samples of patient in ICU with clinical suspicion of fungal infection were received in study time period.

Inclusion criteria:

- Patients admitted in ICU at tertiary care centre irrespective of age and gender were included.
- Patients admitted in ICU from Jan 2022 to Dec 2022 were included.

Patients were enrolled in the study only after obtaining informed written consent. All patients satisfying the inclusion criteria were only once documented, and were assigned study serial numbers. Patients were interviewed by structured questionnaire and their hospital records were used to know about the previous episodes of invasive Candidiasis, use of any antifungal agents and past medical conditions.

Exclusion criteria

•Patients already on any Antimycotic drugs were excluded.

During the study (1 year: January 2022 to December 2022), samples (urine, sputum, blood, tracheal aspirate, urinary catheter) were collected from ICU patients and evaluated. Microscopy, culture, and antifungal susceptibility testing were performed as per standard laboratory protocol. Demographic details and risk factors were noted.

Antifungal agents used for Antimycotic sensitivity test is mentioned in the table no 10.

RESULTS

Total 130 samples received in study time period. Out of 130 samples 36 were positive for candida isolates. Out of 36, 12 were males and 24 females. In blood culture, C. tropicalis (33.33%) and C. albicans (33.33%) were commonly reported followed by C. parapsilosis (16.66%) and C. glabrata (16.66%).

In BAL, C. parapsilosis (50%) and C. glabrata (50%) were isolated. In endotracheal, C. tropicalis (42.85%) were most commonly isolated species followed by C. albicans (28.57%) and C. krusei (28.57%). TABLE 8: In the below table, Antifungal susceptibility testing of *Candida albicans* showed highest sensitivity to Nystatin (100%), Amphotericin B (100%) and Miconazole (100%) followed by Ketoconazole (88.88%), Itraconazole (88.88%) and Fluconazole (88.88%). *Candida tropicalis* showed 100% sensitivity to Ketoconazole, Nystatin, Voriconazole, Amphotericin B and Miconazole followed by Itraconazole (93.33%) and resistance to Fluconazole (73.33%). *Candida parapsilosis* showed highest sensitivity to Ketoconazole (100%), Nystatin (100%), Voriconazole (100%) and Miconazole (100%) followed by Amphotericin B (83.33%), Itraconazole (83.33%) and Fluconazole (83.33%). *Candida krusei* showed highly sensitivity to Amphotericin B (100%) followed by Miconazole (25%) and intrinsically resistant to Ketoconazole, Voriconazole, Itraconazole and Fluconazole. *Candida glabrata* showed highest sensitivity to Nystatin (100%) and Amphotericin B (100%) followed by Ketoconazole (50%) and Miconazole (50%) and 100% resistant to Voriconazole, Fluconazole and Itraconazole.

DISCUSSION

Out of 130 samples, 36 samples (27.69%) were positive for *Candida* infection whereas 94 samples (72.30%) were found to be negative for *Candida* infection. (p=0.0001). The maximum no. of patients were in the age group of >61 years (25%) followed by the age group of <10 years (22.22%). (p=0.081) This correlated with the study of Raval et.al. Higher rate of *Candida* colonization in 0–9 years could be understood as they are more susceptible to infections due to various reasons including weak immune systems and in the > 60 years age group this could correlate with prevalence of debilitating conditions, decreased immune status and aging (14). There was a female predominance accounting for 66.66% in our study (p=0.001). Similar findings have been recorded by Luiza et.al showed that 53.2% of the patients were females.(15) In contrast, Dutta et.al,(16), reported the male predominance in their study.

We observed that nonalbicans *Candida* species (75%) had predominance over *C. albicans* (25%), which is consistent with the published report from different parts of the world. *C. tropicalis* was the most common isolate in all samples, followed by *C. albicans*. A relatively greater proportion of *C. tropicalis* isolates in our study is concordant with study of Pahwa et.al (17). In study conducted by Naushaba et.al., most common pathogen isolated was *Candida albicans* (10), followed by *Candida parapsilosis* (1), which was found to be higher than the present study.(18). Among the 27 non-albicans *Candida* spp., *Candida tropicalis* was the most common isolate seen in 15 (41.67%) isolates followed by *Candida parapsilosis* in 6 (16.67%), *Candida krusei* in 4 (11.11%) and *Candida glabrata* in 2 (5.55%) isolates. This is correlated with the study of Ravinder et.al. (19) showed high rate of isolation of *Candida tropicalis* (41.1%) in intensive care unit patients. In contrast, study done by Roy et al.(20) among non-albicans *Candida*, *C. glabrata* was 32% followed by *C. tropicalis* 30% which were isolated. Majority of patients of IFI presented with

Table 1. Distribution of candida isolates among icu patients

Antifungal Agent	Code	Disc potency (mcg)	Interpretative Criteria		
			Sensitive (mm or more)	Intermediate (mm)	Resistant (mm or less)
Amphotericin B	Ap	10	≥15	10-14	≤10
Nystatin	NS	50	≥15	10-14	≤10
Fluconazole	Fu	25	≥19	15-18	≤14
Voriconazole	Vrc	1	≥17	14-16	≤13
Itraconazole	It	10	≥23	14-22	≤13
Miconazole	Mic	10	≥20	12-19	≤11
Ketoconazole	Kt	15	≥28	21-27	≤20

TOTAL SAMPLES	POSITIVE	NEGATIVE
130	36	94
100%	27.69	72.30

Table 2. The majority of positive confirmed cases of *Candida* positive belonged to the age group of >61 (30.55%) followed by age group < 10 (22.22%) as shown in graph below

AGE GROUP	TOTAL NO. OF CASES (n=130)		TOTAL POSITIVE CASES (n=36)	
	N	%	N	%
< 10	19	14.61	8	22.22
11-20	14	10.76	1	2.80
21-30	32	24.61	7	19.44
31-40	10	7.69	3	8.33
41-50	15	11.53	3	8.33
51-60	14	10.80	3	8.33
>61	26	20	11	30.55

[x^2=11.23; d.f.= 6, p =0.081]

Table 3. The following table shows that Non-albicans were the most frequently isolated species accounting for 77.78% and the remaining were Candida albicans accounting for 22.22%

ORGANISM ISOLATES	NO. OF ISOLATES	PERCENTAGE (%)
Candida albicans	9	25.00
Non albicans Candida (NAC)	27	75.00
Total	36	100

Comparison of proportion

Difference	50.0%
95% CI	12.7% to 71.4%
Chi-squared	7.000
DF	1
Significance level	P = 0.0082

Table 4. Among the non- albican *Candida* spp, *Candida tropicalis* was the most common species isolated followed by *C. parapsilosis, C. krusei,* and *C. glabrata* as shown in table below.

Species	Total no	Percentage (%)
Candida tropicalis	15	41.67
Candida albicans	9	25.00
Candida parapsilosis	6	16.67
Candida krusei	4	11.11
Candida glabrata	2	5.55
Candida auris	Not isolated	0
Total	36	100

Table 5. Among 130 patients in the study, 36 patients showed fungal growth. The majority of the growth was present in the urine sample (58.33%), followed by endotracheal (19.44%), blood (16.66%) and bronchoalveolar lavage (5.55%) as shown in table below

SAMPLES	GROWTH [n=36]	NO GROWTH [n=94]	TOTAL [n=130]	P value
URINE	21 (58.33%)	50 (53.19%)	71 (54.62%)	0.693
BLOOD	6 (16.66%)	13 (13.83%)	19 (14.62%)	0.874
BRONCHOALVEOLAR LAVAGE	2 (5.55%)	01 (1.06%)	03 (2.31%)	0.879
ENDOTRACHEAL	7 (19.44%)	30 (3.91%)	37 (28.46%)	0.148

Table 6. Below table shows that in urine sample, C. tropicalis (47.61%), C. albicans (23.80%) were reported commonly followed by C. parapsilosis (19.04%) and C. krusei (9.52%).

GENUS AND SPECIES	URINE (21)	BLOOD (6)	BRONCHOALVEOLAR LAVAGE (2)	ENDOTRACHEAL SECRETIONS (7)
Candida albicans	5 (23.80%)	2 (33.33%)	-	2 (28.57%)
Candida tropicalis	10 (47.61%)	2 (33.33%)	-	3 (42.85%)
Candida krusei	2 (9.52%)	-	-	2 (28.57%)
Candida parapsilosis	4 (19.04%)	1 (16.66%)	1 (50%)	-
Candida glabrata	-	1 (16.66%)	1 (50%)	-

Table 7. *C. albicans* were most commonly isolated species in renal failure patients (42.85%) followed by patients who were on prolonged antibiotic use (33.33%). *C. tropicalis* were most commonly isolated in patients who were on parenteral nutrition (100%) and malignancy (100%) as shown below in table

SPECIES	INDWELLING DEVICES	RENAL FAILURE	PROLONGED ANTIBIOTIC USE	PARENTRAL NUTRITION	MALIGNANCY	DIABETES MELLITUS	RESPIRATORY DISTRESS
C. albicans	1 (12.5%)	3 (42.85%)	2 (33.33%)	-	-	2 (25%)	1 (20%)
C. tropicalis	4 (50%)	2 (28.57%)	2 (33.33%)	2 (100%)	1 (100%)	4 (50%)	-
C. krusei	2 (25%)	-	1 (16.66%)	-	-	1 (12.5%)	-
C. parapsilosis	1 (12.5%)	1 (14.28%)	1 (16.66%)	-	-	1 (12.5%)	2 (40%)
C. glabrata	-	1 (14.28%)	-	-	-	-	2 (40%)

Table 8. In the below table, Antifungal susceptibility testing of *Candida albicans* showed highest sensitivity to Nystatin (100%), Amphotericin B (100%) and Miconazole (100%) followed by Ketoconazole (88.88%), Itraconazole (88.88%) and Fluconazole (88.88%)

Species	Ketoconazole			Nystatin			Voriconazole			Amphotericin B			Miconazole			Itraconazole			Fluconazole		
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
C.albicans (9)	8 (88.88%)	0	1(11.11%)	9(100%)	0	0	7 (77.77%)	0	2 (22.22%)	9 (100%)	0	0	9 (100%)	0	0	8 (88.88%)	0	1 (11.11%)	8 (88.88%)	0	1 (11.11%)
C.tropicalis (15)	15 (100%)	0	0	15 (100%)	0	0	15 (100%)	0	0	15 (100%)	0	0	15 (100%)	0	0	14 (93.33%)	0	1 (6.66%)	11 (73.33%)	0	4 (26.66%)
C.parapsilosis (6)	6 (100%)	0	0	6 (100%)	0	0	6 (100%)	0	0	5 (83.33%)	0	1 (16.66%)	6 (100%)	0	0	5 (83.33%)	0	1 (16.66%)	5 (83.33%)	0	1 (16.66%)
C.krusei (4)	0	0	4	4 (100%)	0	0	0	0	4	4 (100%)	0	0	2 (50%)	0	2 (50%)	0	0	4	0	0	4
C.glabrata (2)	1 (50%)	0	1 (50%)	2 (100%)	0	0	0	0	2	2(100%)	0	0	1(50%)	0	1(50%)	0	0	2	0	0	2

Table 9. In the below table, albicans showed maximum resistance to Voriconazole (22.22%) whereas NAC showed maximum resistance to Fluconazole (40.74%) followed by Itraconazole (29.62%).

ANTIFUNGAL	TOTAL NO. OF RESISTANT ISOLATES (%)		P value
	C. albicans	NAC isolates	
Ketoconazole	1 (11.1%)	5(18.51%)	0.870
Nystatin	0 (0%)	0 (0%)	00
Voriconazole	2 (22.22%)	6(22.22%)	0.999
Amphotericin B	0 (0%)	1 (3.70%)	NA
Miconazole	0 (0%)	3 (11.11%)	NA
Itraconazole	1 (11.1%)	8 (29.62%)	0.712
Fluconazole	1 (11.1%)	11 (40.74%)	0.576

Table 10. Antifungal agents used for Antimycotic sensitivity test

Antifungal Agent	Code	Disc potency (mcg)
Amphotericin B	Ap	10
Nystatin	NS	50
Fluconazole	Fu	25
Voriconazole	Vrc	1
Itraconazole	It	10
Miconazole	Mic	10
Ketoconazole	Kt	15

symptoms of urinary tract infections, sepsis and respiratory infections Pagano et al (21) studied patients with IFI and reported most common system involved was respiratory tract. In contrast, Pahwa et al. 2014, (22) reported that maximum samples were blood followed by urine. Among 9 *Candida albicans*, Nystatin, Amphotericin B and Miconazole showed 100% sensitivity followed by Ketoconazole (88.88%), Itraconazole (88.88%) and Fluconazole (88.88%). This is correlated with the study of Ravinder et al.(19) where *Candida* isolates demonstrated sensitivity to Amphotericin B. In contrast, in the study done by Bhattacharjee et al. where all the *Candida* isolates were sensitive to Fluconazole (23). *Candida tropicalis* showed 100% sensitivity to Ketoconazole, Nystatin, Voriconazole, Amphotericin B and Miconazole followed by Itraconazole (93.33%) and resistance to Fluconazole (73.33%). *Candida parapsilosis* showed highest sensitivity to Ketoconazole (100%), Nystatin (100%), Voriconazole (100%) and Miconazole (100%) followed by Amphotericin B (83.33%), Itraconazole (83.33%) and Fluconazole (83.33%). *Candida krusei* showed highest sensitivity to Amphotericin B (100%) followed by Miconazole (25%) and intrinsically resistant to Ketoconazole, Voriconazole, Itraconazole and Fluconazole. *Candida glabrata* showed highest sensitivity to Nystatin (100%) and Amphotericin B (100%) followed by Ketoconazole (50%) and Miconazole (50%) and 100% resistant to Voriconazole, Fluconazole and Itraconazole. Rajeevan et.al also reported the similar findings showed highest sensitivity to Nystatin (100%) and Amphotericin B (100%). Extensive fluconazole use is one of the possible causes, for the increased resistance to the drug as well as for the progressive substitution of albicans species with non-albicans drug resistant strains as principal etiologic agent of infection.

CONCLUSION

In present study non-candida albicans found to be more prevalent than candida albicans in immunocompromised patients with increase in antifungal resistance pattern which emphasis the need of astute use of antifungal prophylaxis in ICU setups. Antifungal susceptibility pattern will help clinicians in early detection and identification of the causal agent, so that appropriate treatment can be initiated as soon as possible in immunocompromised patients. This is crucial for monitoring the development of resistance and for assisting health professionals in delineating guidelines for appropriate use of these medicines.

ABBREVIATIONS

AFS- Antifungal Susceptibility Test
CLSI- Clinical Laboratory Standard Institute
ICU- Intensive Care Unit
NAC- Non Albicans Candida

CONFLICT OF INTEREST: Nil

SOURCE OF FUNDING: Nil

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