IDENTIFICATION OF CANDIDA SPECIES ISOLATED FROM DIFFERENT CLINICAL SAMPLES AND THEIR SUSCEPTIBILITY AGAINST COMMONLY USED ANTIFUNGAL DRUGS

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ABSTRACT

Background & Objectives: Antifungal resistance is becoming prevalent in Candida species globally and threating the human health. Aim of this study was to identify Candida to species levels isolated from different clinical samples and analyze their antifungal susceptibility patterns.

Methods: 70 Candida species isolated from 120 different clinical samples were identified and their antifungal susceptibility testing was carried out against azoles, polyenes, echinocandins and pyrimidine by using Vitek 2 Compact System.

Results: Candida species were identified in 58.3% of clinical isolates from different samples of patients. The most frequent strains found in female patients were of *C. albicans*, followed by *C. glabrata*, whereas in male patients *C. krusei* was the commonest. All of the isolated Candida species showed resistance to Fluconazole (100%), whereas 46% showed resistance to Itraconazole and 28% were resistant to Voriconazole. However, the majority of isolates were sensitive to polyenes (Amphotericin B 91%), echinocandins (Caspofungin 84%) and pyrimidine (Flucytosine 80%) respectively.

Conclusion: Identification of Candida species and antifungal susceptibility testing is necessary to help the physician in deciding on the suitable antifungal drug.

Keywords: Antifungal susceptibility, Candida species, Fluconazole resistance

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The antifungal resistance is becoming a global threat to human health wherefore fungal pathogens exhibit high resistance to drugs by employing multiple mechanisms which warrants their survival.[1] More than 150 million cases of severe fungal infections have been reported per annum globally that results in to 1.7 million deaths annually.[2] Out of these, invasive candidiasis affects more than 250,000 people globally every year and results in to 50,000 deaths approximately.[3] More than 90% of reported fungal-associated deaths result from severe fungal infections of species of three genera including Candida, Cryptococcus, and Aspergillus.[4] Most invasive fungal infections result from the suppression of immune system consequent to conditions such as AIDS or from treatments including chemotherapy for cancer, immunosuppressive therapy for organ transplantation, and corticosteroid therapy for inflammation.[5]

Invasive fungal diseases have been associated with prolonged hospitalization and higher financial costs for patients.[6] Antifungal drugs include four main classes: azoles (Fluconazole, Itraconazole, Voriconazole, and Posaconazole), polyenes (Amphotericin B), echinocandins (Caspofungin, Micafungin, Anidulafungin, and Aminocandin) and antimetabolites (5-Flourocytosine). Mechanistically, the azoles inhibit ergosterol biosynthesis, whereas polyenes form large pores by bind to ergosterol in the plasma membrane that disrupt cell function. The echinocandins are cell wall–active agents that inhibit b-1,3-Dglucan biosynthesis (major structural component of the fungal cell wall) and finally 5-Fluorocytosine inhibits metabolism of pyrimidine and synthesis of DNA.[5] The resistance to the azoles is predominant among the different classes of antifungals

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based on strong selective pressures employed on exposed populations.[5,8] The widespread use of antifungal drugs has been reported to be a factor that promotes drug resistance.[9] Fluconazole is the most widely prescribed antifungal agent especially in developing countries because of its high efficacy, low toxicity, and immunomodulatory capacity and it can be used orally and its resistance is becoming prevalent in Candida species in comparison to other azoles.[10] Fluconazole susceptibility is also highly variable between institutions, with some reporting no azole resistance while others have reported that fluconazole resistant isolates may be as high as 50% in intensive care units and more than 70% in chronic tuberculosis patients.[11] The frequency of invasive candidiasis continues to rise despite of new antifungal drug development.[12] The emergence of new species is demonstrating the resistance to multiple classes of antifungal agents (e.g., *C. auris*).[13]

Candida albicans is considered the most common opportunistic fungi and most common infection causing Candida species in human.[14] *Candida albicans* is a common fungus that can colonizes the oropharyngeal cavity, gastrointestinal and vaginal tract, and healthy skin. *C. albicans* is the normal microbiota but can manifest localized, superficial mucocutaneous disorders to invasive diseases involving multiple organ systems and threatens life.[15] Due to the differences in population at greater risk, species distribution, and infection management, prognostic factors associated with mortality varies according to the geographic region.[16] Continued clinical studies are required for evaluation of susceptibility studies of Candida spp., prognostic factors and molecular changes in fluconazole resistant genes to overcome the microbiologic and clinical failure in the setting of antifungal resistance.[17] Early isolation, speciation and antifungal susceptibility testing helps clinicians to choose the rationale-based therapeutics which may reduce morbidity and mortality. This study aims to identify Candida species in different clinical isolates and analyze their antifungal susceptibility patterns.

METHODS

For this descriptive cross-sectional study, 70 isolates of Candida species obtained from 120 different clinical samples were included. Those were collected from various tertiary care hospitals of Lahore city, including Mayo Hospital, Sir Ganga Ram Hospital, Services Hospital, Lahore General Hospital, Sheikh Zayed Hospital and Children Hospital. Using Non-probability convenient sampling technique isolates from urine, blood, pus, wound swabs, high vaginal swabs (HVS), ascetic fluids, central venous pressure (CVP) tips, throat swabs and endotracheal tube (ETT) aspirates were collected during the period from Jul 2023 to Jun 2024. Sample size was calculated using formula N = pqz2/e2.[18] Repeated samples from the same patients in the same course of illness were excluded. The isolates of C. krusei were also excluded due to intrinsically resistant to Fluconazole.

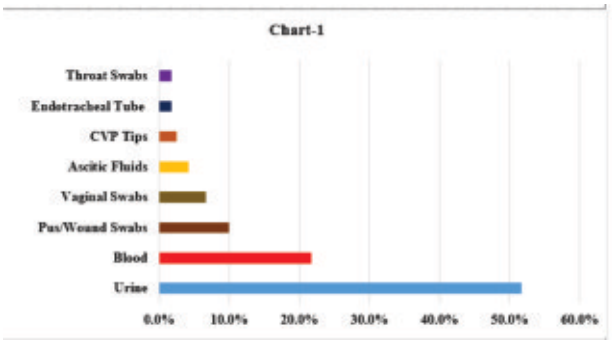
The samples were cultured on Sabouraud Dextrose agar culture plates (Biolife, Italiana) and incubated for 24 hours at 37 °C. Next day, the Sabouraud agar culture plates were examined for any growth and observations were noted. In case of insufficient growth or no growth, the plates were re-incubated for another 24 hours at 37 °C and the findings were observed on the next day. The Candida species were identified by their morphological colonial characteristics, Gram stain and microscopy. Antifungal susceptibility testing was carried out by Modified Kirby-Bauer disc diffusion method. The discs used were Fluconazole 25µg, Itraconazole 50µg, and Ketoconazole 10µg. The results were interpreted according to Clinical Laboratory Standard Institute, CLSI M44 guidelines and manufacturer recommendation for the control strain (ATCC 10231) and test isolates of Candida species[19]. VITEK 2 system (VITEK 2 Compact, USA) was used for speciation and antifungal susceptibility testing of the isolated Candida species. The AST-YS08 yeast cards were used for the selected 70 strains showing Fluconazole resistance on disc diffusion. The inoculum of various Candida species was made in a sterile polystyrene tube from 24 hours old culture. The polystyrene tubes were labelled with the laboratory sample numbers. The inoculum was prepared by dispensing 3.0 ml of sterile normal saline in the polystyrene tube and adding 2-3 morphologically similar colonies in the tube. The tube was vortexed to get uniform turbidity of the inocu-lum. The turbidity of the inoculum was set to 2.0 McFarland. Normal saline of 3.0 ml was taken in another polystyrene tube and 280 µl of the microorganism inoculum was transferred to second tube to make final dilution for VITEK AST testing. The polystyrene tube was placed into the cartridge. The VITEK 2 Identification card was taken out from the sealed pack and transferred into the cartridge by inserting its blue color-coded trans-fer tube in to the tube carefully by avoiding touching the walls of the tube. It was kept in mind that cards should be set up within half an hour of inoculum dilution. For quality control purpose, the control strain Candida albicans (ATCC 10231) was used. This study was carried out after getting ethical approval from Research

and Ethical Committees of PGMI, AMC, LGH Lahore vide Reference No.UHS/Education/126-23/1119 dated 27-2-23.

RESULTS

Of 120 specimens, 76 (63.3%) were collected from female patients and 44 (36.7%) from males. The female to male ratio was 1.72:1. The nature and frequency of different clinical specimens was: urine (51.7%), blood (21.7%), pus/wound swabs (10%), vaginal swabs (6.7%), ascetic fluids (4.2%), CVP tips (2.5%), endotracheal tube (1.7%) and throat swabs (1.7%) respectively (Chart-1).

Of 120 samples, Candida species were identified in 70 (58.3%). Out of 70 isolates, 44 (62.9%) belonged to females and remaining 26 (37.1%) belonged to males. All 70 Fluconazole-resistant isolates were run on



VITEK 2 system to find the type of Candida species and susceptibility patterns of antifungal drugs. The VITEK 2 system identified the following Candida species: Candida *albicans*=25 (35.7%), C. *glabrata* =19 (27.1%), C. *troplicalis*=11 (15.7%), C. *famata* =7 (10.0%), C. *krusei*=4 (5.7%), C. *intermedia*= 1(1.4%), C. *spherica* = 1 (1.4%), C. *parapsilosis*=1(1.4%) and C. *catenulata*=1 (1.4%) in clinical isolates as shown in Table-1. The most frequent infection by Candida in female patients was due to *C. albicans* (35.7%), followed by *C. glabrata* (27.1%) and *C. tropicalis* (15.7%). However, in male patients, *C. Krusei* was the most frequent species found (5.7%). Moreover, *C. spherica* (1.4%) and *C. parapsilosis* (1.4%) infections were exclusively found in male patients.

The antifungal sensitivity pattern was determined on the VITEK 2 AST system using antifungal drugs including Amphotericin B, Caspofungin, Flucytosine, Voriconazole and Itraconazole. Prior to that, disk diffusion for antifungal susceptibility testing was performed on all 70 Candida species clinical isolates. All (100%) were Fluconazole-resistant. The zone of inhibition around each disk was measured using a millimeter scale and interpreted according to the CLSI recommendations. A diameter of ≥ 15 mm was interpreted as susceptible dose dependent (S-DD) and ≤ 14 mm as resistant (R). As per disk diffusion susceptibility results, Candida species showed highest sensitivity to Amphotericin B (91% with range of MIC values: ≤ 0.25 - >16 µg/ml), Caspofungin 84% (with range of MIC values: ≤ 0.125 - >8 µg/ml) and Flucytosine 80% (with range of MIC values; ≤ 1- >64µg/ml) which was evaluated in urine samples only. Furthermore, Candida species showed lowest sensitivity to Itraconazole i.e., 54% (with range of MIC values; ≤ 0.125 - >8µg/ml) (Table-2).

Table 1: *Frequency of Candida species identified by VITEK 2 & their Gender-wise distribution*

Sr. No.	Candida spp. Identified by VITEK 2 System	Gender-wise Distribution		Total	Percent (%) Frequency
		M	F		
1	*C. albicans*	8	17	25	35.7
2	*C. glabrata*	6	13	19	27.1
3	*C. tropicalis*	5	6	11	15.7
4	*C. famata*	2	5	7	10.0
5	*C. krusei*	3	1	4	5.7
6	*C. intermedia*	0	1	1	1.43
7	*C. spherica*	1	0	1	1.43
8	*C. parapsilosis*	1	0	1	1.43
9	*C. catenulata*	0	1	1	1.43
Total		**26**	**44**	**70**	-

Table 2: *Antifungal drug sensitivity with MICs in Fluconazole-resistant Candida species*

Antifungal Drug	Sensitivity	MICs
Amphotericin B	91 %	≤0.25 >16 µg/ml
Caspofungin	84%	≤0.125- >8 µg/ml
Flucytosine	80%	≤1.0- >64µg/ml
Voriconazole	72%	≤0.125- >8µg/ml
Itraconazole	54%	≤0.125- >8µg/ml

DISCUSSIONS

This study has revealed the Fluconazole resistance of Candida species isolated from clinical samples of patients and susceptibility testing of those species against other antifungal drugs including amphotericin B, Caspofungin, Flucytosine, Voriconazole and Itraconazole. We detected highest frequency of Candida species isolated from the urine samples (51.7%). The results of our study are in agreement with two previous studies from South India which have shown the high

frequency of Candida isolation from urine samples as 60% and 46.9% respectively.[20, 21] Candida species were identified in 58.3% of clinical isolates of patients (n=70/120). Furthermore, infections caused by Candida species were predominantly higher i.e., 44 (62.9%) in female patients as compared to male patients (37.14%) in our settings. Several earlier studies have also reported that Candida infections are more common in females.[22] A study carried out by one of our authors at a tertiary healthcare facility in Kabul on patients with candiduria had shown that 61.9% were girls and 38.1% were boys.[23]

In this study, the most frequent Candida species found in female patients was *C. albicans* (35.7%), followed by *C. glabrata* (27.1%) and *C. tropicalis* (15.7%). On the other hand, *C. krusei* was the most frequent species found in male patients (5.7%), while *C. spherica* (1.43%) and *C. parapsilosis* (1.43%) infections were also exclusively found in male patients. Similar to our findings, a study conducted in our neighbor country has shown that *C. albicans* was the most common cause of candida infections in Iranian patients (59.7%).[24] Moreover, another study investigated the epidemiology of Candida species causing invasive candidiasis in Chinese patients and yet again *C. albicans* (45.3%) and *C. glabrat*a (30%), were reported to be the more frequent species involved in such infections.[25] *Candida glabrata* (38.0%) and *Candida albicans* (33.2%) were the two most common Candida species found in patients with candidaemia belonging to USA.[26]

Fluconazole is commonly used as first-line antifungal agent for systemic infection caused by Candida species.[27] Fluconazole is a highly selective inhibitor of fungal enzyme lanosterol 14-α-demethylase which is required for converting lanosterol to ergosterol.[28] In our study we have observed a differential pattern of resistance against the antifungal drugs. Candida species 100% resistant to Fluconazole also showed trends for resistance against other azoles including Itraconazole (46%) and Voriconazole (28%). Amazingly however, the clinical isolates showed highest sensitivity to other antifungal drugs including polyenes (amphotericin B: 91%), echinocandins (Caspofungin: 84%) and pyrimidine (Flucytosine: 80%). A study of Indian Candida species isolates has reported high drug resistance (70.6%) against Fluconazole.[29] Highly variable Fluconazole susceptibility between institutions has been reported, some reports have shown lower azole resistance while others have shown higher azole resistance (50%) in patients of intensive care units.[31,32] Contrary to our results, in a study conducted on Ethiopian clinical isolates, they had reported lower resistance to Fluconazole (10.5%) and very low resistance to Voriconazole (0.6%).[33] as compared to Voriconazole resistance of 28% in our study. The variation in Fluconazole susceptibility patterns in the clinical isolates of Candida albicans from different geographical regions has been reported previously and suggested to be influenced by underlying conditions of patients from the particular region.[34]

CONCLUSION

The frequency of infections caused by different Candida species is steadily increasing and posing difficulties for physicians to distinguish from colonization to true Candida infection due to unusual symptoms. The rise of non-albicans Candida is alarming and its recovery from clinical specimens must not be disregarded as a contaminant. Identification of Candida species and antifungal susceptibility testing is necessary in patients having such infection to help the physician in deciding on the suitable antifungal drug.

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Author's Contribution

Conceptualization study design	SM, TMT, ZT, WA
Data Acquisition	ZT, MCH, RS. FM
Data Analysis/ interpretation	WA, FM, TMT, WA, RS. MCH, TMT, SM
Manuscript drafting	SM, FM, RS, TMT, ZT, WA
Manuscript review	SM, MCH, TMT, RS

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