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Antifungal Susceptibility of Candida Species Isolated from Urine Samples: A Laboratory-Based Analysis

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Abstract

Background: This study investigates the distribution and antifungal susceptibility patterns of various *Candida* species isolated from urine samples collected between December 2022 and March 2024. A total of 1,313 isolates were examined, with a gender distribution of 29.9% male and 71.1% female, across five distinct age groups. The aim was to provide a comprehensive analysis of species prevalence and their sensitivity to different antifungal agents.

Results: The most frequently isolated species was *Candida albicans*, comprising 63% of all cases, predominantly found in the 65+ age group. Other less common species included *Candida tropicalis* (36 cases), *Candida kefyr* (11 cases), *Candida glabrata* (8 cases), and *Candida spp.* (442 cases). The antifungal susceptibility analysis showed that *Candida albicans* exhibited high sensitivity to Fluconazole (834 sensitive cases) but intermediate sensitivity to Amphotericin in 243 cases. *Candida tropicalis* and *Candida kefyr* showed high sensitivity to all antifungals, while *Candida spp.* demonstrated considerable resistance to Fluconazole and Micafungin.

Conclusion: The findings highlight that while most *Candida* species are sensitive to commonly used antifungals, certain species like *Candida spp.* and *Candida albicans* show notable resistance to Amphotericin and Micafungin. The results emphasize the importance of performing susceptibility testing to guide effective treatment, especially in older patients who exhibit a higher prevalence of *Candida* infections. The data from this study provide valuable insights for clinicians managing fungal infections and tailoring antifungal therapy.

Keywords: Candida species, Antifungal susceptibility, Urine samples, Resistance patterns ,Fluconazole sensitivity

Introduction

Candida is one of the most omnipresent genera of yeasts that can be found as a commensal organism in the human's mucous membranes lining the genitourinary or the skin's surfaces (1). Though there are over 200 recognized species of Candida (2), only around 20 species tend to be sourced from humans, with Candida albicans being the most prominent (3). Nonetheless, non-albicans species of candida (NAC) such as Candida tropicalis, Candida glabrata, and Candida auris have emerged as turning out to be opportunistic pathogens (4) It is usually found that candida co-exists without causing harm to its host. Nevertheless, in imuno-compromised hosts, it is responsible for many types of infection.

It also serves as an important contributor to the pathogen of urinary tract-induced inflammation, pyelonephritis, cystitis and other variations of the inflammatory UTI(5) Certain conditions make one predisposed to candiduria, which is the presence of Candida in the urine. Examples of such

conditions include the female gender, age extremities, diabetes mellitus, steroids or antibiotic use, prolonged hospital care, ICU admission, and genitourinary surgeries(6). In candiduria, the broad prevalence rate of an estimated 27.4 in every 1000 (7) admissions is noticeable. Furthermore, summarized records show that 10% - 15% of the hospital-acquired UTIs are caused by candida. There has been an upsurge in reports on NAC infections which emotionally strengthens the notion that evolution plays an important role for the internal ecosystem of treatment-resistant biofilm infections. In Pakistan, a review article reported that from 2014 to 2016, about 35.6% to 38.6% of the total cases of candidiasis were isolated from urine samples. (8) Studies conducted in recent years indicate a relative increase in the number of infections due to non albicans candida (NAC) species as compared to the previous years (9)(10)(11).

Chronic systemic candidiasis is known to be one of the most life-threatening infections since it often leads to serious complications such as endocarditis, peritonitis, and hepatosplenic candidiasis with nearly 50 percent mortality rate (12)(13). The reason for this shift in trends has been attributed to various factors such as development of genetic mutations in the yeasts, biofilm formation, production of hydrolytic enzymes and empirical use of wide-spectrum antifungals This study intends to evaluate the epidemiology and antifungal susceptibility of Candida species in our area, thereby addressing a need for relevant data that will guide the development of evidence based management of candiduria and overall better patient management.

Methodology

Study Design and Setting

The current cross-sectional study was conducted from December 2022 to March 2024, at Islamabad Diagnostic Centre. Retrospective data collection was done. The ethical Permission was obtained from the coordinator of Islamabad Diagnostic Center for data collection in this study. The aim of the study was to isolate Candida species from urine samples and assess their antifungal susceptibility. The study population included patients across all age groups, ranging from neonates to individuals above 65 years of age.

Sampling

A total of 1,351 Candida isolates were collected from urine specimens obtained from patients under strict sample collection standards for microbiological specimens. The samples were transported to the laboratory in sterile containers and processed immediately.

Identification of Candida Species

The isolates were cultured on Sabouraud's Dextrose Agar (SDA) at 37°C for 48 hours. Colonies suspected as Candida based on their white to creamy appearance and morphology were further processed for identification. The identification of Candida species was performed using VITEK MS (Maldi-TOF) technology (bioMérieux, France), which allows for rapid, accurate identification at the species level.

Antifungal Susceptibility Testing

Antifungal susceptibility testing was performed using the VITEK-2 Compact system (bioMérieux, France) designed for yeast-like cells. The isolates were subjected to antifungal susceptibility testing according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. The antifungal agents tested included Fluconazole, Amphotericin B, Caspofungin, Voriconazole, and Micafungin. Zone of inhibition diameters and Minimum Inhibitory Concentrations (MIC) were determined after 48 hours of incubation at 35°C. Based on CLSI M44-A and CLSI M27-A3 guidelines, the isolates were classified into resistant, intermediate, and sensitive categories.

Quality Control

To ensure the accuracy of the identification and susceptibility testing, known reference strains of Candida albicans ATCC 90028 and Candida glabrata ATCC 2001 were used as controls throughout the process.

Results

Samples collected from December 2022 to March 2024 were included, with a gender distribution of 29.9% male and 71.1% female. Table 1 provides an overview of the distribution of various Candida species isolated from patients across five distinct age groups: 0-8 years, 9-16 years, 17-32 years, 33-64 years, and 65+ years. The species included are Candida albicans, Candida tropicalis, Candida kefyr, Candida glabrata, and a general category for other Candida species (Candida spp.). Candida albicans is the most frequently identified species, with a total of 854 cases, predominantly found in the 65+ age group (338 cases) and the 33-64 age

group (291 cases). Other species, such as Candida tropicalis (36 cases), Candida kefyr (11 cases), and Candida glabrata (8 cases), are less common but are also seen across the age groups. The total number of cases is distributed relatively evenly among the younger age groups, with 20 cases each in the 0-8 years and 9-16 years groups, while older age groups (17-32 years, 33-64 years, and 65+ years) show a significant rise in cases, particularly in the 65+ group (525 total cases).

Table 1: Age-wise Distribution of Candida Species in Different Age Groups

Age (years)	**0-8 y**	**9-16 y**	**17-32 y**	**33-64 y**	**65+ y**	**Total of each species**
Candida albicans	13	15	197	291	338	854
Candida tropicalis	1	0	7	11	17	36
Candida kefyr	0	0	1	8	2	11
Candida glabrata	0	0	0	2	6	8
Candida spp.	6	5	98	171	162	442
Total in each age group	20	20	303	483	525	

The majority of isolates are sensitive to most antifungals, with Fluconazole showing the highest sensitivity (834 sensitive cases). Amphotericin, Caspofungin, Flucytosine, Micafungin, and Voriconazole also exhibit high sensitivity rates, though varying levels of resistance and intermediate sensitivity are noted, especially with Amphotericin (243 intermediate sensitive cases). Resistance is generally low across all antifungals (Table 2).

Table 2: Antifungal Susceptibility Pattern of *Candida albicans* (n=854) Against Various Antifungal Agents

Antifungal	**Candida albicans (n=854)**			
	Sensitive	Resistance	Intermediate Resistance	Intermediate Sensitive
Amphotericin	580	18	10	243
Caspofungin	638	15	2	196
Fluconazole	834	12	1	4
Flucytosine	645	6	11	189
Micafungin	638	28	1	184
Voriconazole	648	14	3	186

Candida tropicalis isolates are mostly sensitive to all tested antifungal agents, with Amphotericin and Voriconazole showing the highest sensitivity (35 sensitive cases each). Resistance is minimal, with slight resistance observed for Caspofungin, Flucytosine, and Micafungin (2 resistant cases each). Intermediate sensitivity is noted only for Caspofungin, Flucytosine, and Micafungin, where 3 isolates fall into this category (Table 3) .

Table 3: Antifungal Susceptibility Pattern of *Candida tropicalis* (n=36) Against Various Antifungal Agents

Antifungal	**Candida tropicalis (n=36)**			
	Sensitive	Resistance	Intermediate Resistance	Intermediate Sensitive
Amphotericin	35	1	Nill	Nill
Caspofungin	31	2	Nill	3
Fluconazole	32	1	Nill	Nill
Flucytosine	31	2	Nill	3
Micafungin	31	2	Nill	3
Voriconazole	35	Nill	Nill	1

Candida kefyr isolates demonstrate complete sensitivity to Amphotericin, Flucytosine, and

Voriconazole (11 sensitive cases each), with no resistance or intermediate responses observed for these drugs. There is no susceptibility data for Caspofungin, Fluconazole, or Micafungin, as these antifungals show no recorded results in any sensitivity categories (Table 4).

Table 4: Antifungal Susceptibility Pattern of *Candida kefyr* (n=11) Against Various Antifungal Agents

Antifungal	Candida kefyr (n=11)			
	Sensitive	Resistance	Intermediate Resistance	Intermediate Sensitive
Amphotericin	11	Nill	Nill	Nill
Caspofungin	Nill	Nill	Nill	Nill
Fluconazole	Nill	Nill	Nill	Nill
Flucytosine	11	Nill	Nill	Nill
Micafungin	Nill	Nill	Nill	Nill
Voriconazole	11	Nill	Nill	Nill

Candida glabrata demonstrates complete sensitivity to Flucytosine, Micafungin, and Voriconazole (8 sensitive cases each). For Amphotericin, 6 isolates are sensitive, while 2 show resistance. With Caspofungin, 5 isolates are sensitive, 1 shows intermediate resistance, and 2 are intermediate sensitive. There is no susceptibility data for Fluconazole, as none of the isolates exhibited sensitivity or resistance (Table 5).

Table 5: Antifungal Susceptibility Pattern of *Candida glabrata* (n=8) Against Various Antifungal Agents

Antifungal	Candida glabrata (n=8)			
	Sensitive	Resistance	Intermediate Resistance	Intermediate Sensitive
Amphotericin	6	2	Nill	Nill
Caspofungin	5	Nill	1	2
Fluconazole	Nill	Nill	Nill	Nill
Flucytosine	8	Nill	Nill	Nill
Micafungin	8	Nill	Nill	Nill
Voriconazole	8	Nill	Nill	Nill

Candida spp. exhibits the highest sensitivity to Voriconazole (276 sensitive isolates) and Fluconazole (273 sensitive isolates). Resistance is most prominent against Fluconazole (122 resistant isolates) and Micafungin (103 resistant isolates). Amphotericin and Caspofungin have intermediate sensitivity in a significant portion of isolates, with 123 and 134 intermediate sensitive cases, respectively. The data also highlight considerable intermediate resistance across the antifungal agents, especially for Flucytosine with 41 intermediate resistant cases.

Table 6: Antifungal Susceptibility Pattern of *Candida spp* (n=442) Against Various Antifungal Agents

Antifungal	Candida spp (n=442)			
	Sensitive	Resistance	Intermediate Resistance	Intermediate Sensitive
Amphotericin	213	88	18	123
Caspofungin	203	88	17	134
Fluconazole	273	122	Nill	47

Flucytosine	227	32	41	142
Micafungin	194	103	11	134
Voriconazole	276	45	10	111

The figure 1 shows the percentage of Candida species sensitive to Voriconazole. Candida kefyr and Candida glabrata exhibit full sensitivity (100%), while Candida tropicalis also shows high sensitivity (97.2%). Candida albicans has a slightly lower sensitivity rate of 75.8%, indicating it is the least sensitive species to Voriconazole among the listed ones. The figure 2 represents the sensitivity of various Candida species to Amphotericin. Candida kefyr and Candida tropicalis show the highest sensitivity, with Candida kefyr being fully sensitive (100%) and Candida tropicalis at 97.2%. Candida glabrata has a moderate sensitivity of 75%, while Candida albicans shows a lower sensitivity at 67.9%. Candida spp. exhibits the lowest sensitivity to Amphotericin at 48.1%, indicating significant resistance in this group.

Figure 1: Sensitivity of Various Candida Species to Voriconazole

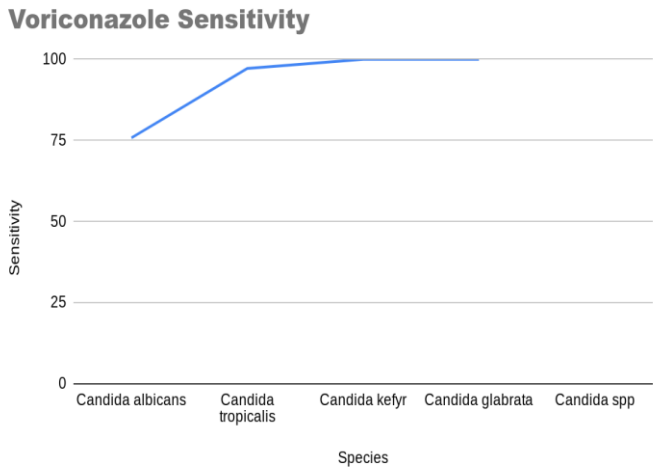
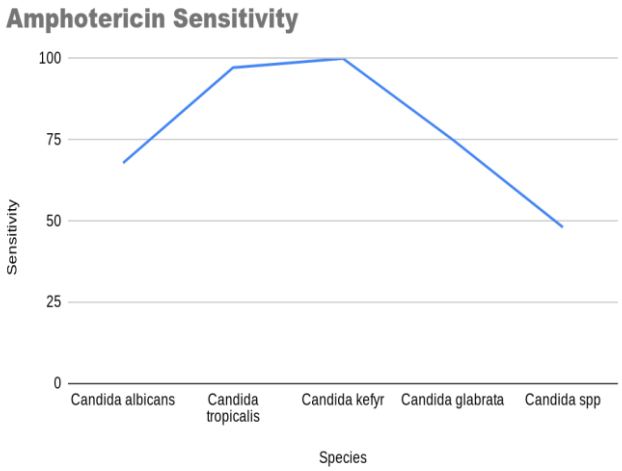


Figure 2: Sensitivity of Various Candida Species to Amphotericin



Discussion

In the past, compared to other bacterial and viral pathogens, fungal infections were thought to be a relatively uncommon source of clinically significant disease (14) but in recent years there has been an alarming rise in the frequency of patients with Candida infections due to major advances in healthcare and increasing load of critically ill patients (15). The predominance of *Candida albicans* in older age groups, particularly the 65+ group, aligns with previous studies demonstrating that aging populations and those with comorbidities are more susceptible to *Candida* infections due to weakened immune responses . The distribution of *C. albicans* across all age groups also underscores its role as the most common pathogenic species in urinary tract infections (UTIs), a finding consistent with other literature on candiduria prevalence (16) . This has posed significant diagnostic and therapeutic challenges in healthcare as antifungal options are limited due to undesirable side effects and rapid development of resistance. The injudicious use of antifungal drugs and evolving sensitivity patterns of both Candida and NACs has made it imperative to correctly identify the prevalent causative species in our society. Early diagnosis intervention and appropriate antifungal are warranted for proper patient management as well as to prevent the emergence of drug resistance (17).

Candidal patients in our study ranged from a few months to 65+ years of age. The study population was divided into age groups comprising pediatric, adult, middle aged and elderly populations out of which patients aged 65 and above showed the highest number of candida isolates (525). This has been similarly reported in several studies globally

(18-19) and locally (20) and is widely attributed to immunocompromised states and frequent hospital admissions in the elderly. Concurrent with local as well as international studies, (19-20) a higher incidence of candiduria was seen in women (65.75%) as compared to men (34.24%) with a ratio of (2:1) as the female lower urinary tract anatomy and its proximity to the genitals facilitates colonization by the organism, in addition female reproductive hormones have receptors for candida due to which these organisms colonize and infect female genitalia (mainly vagina) (21).

Candida albicans was the most frequently prevalent species (854, 63%), followed by a broad category of C. spp (442, 32.7%), C. tropicalis (36, 2.6%), C. kefyr (11, 0.8%) and C. glabrata (8, 0.6%). A similar study by U. Tasneem et al (19) had results that were concurrent with ours, as C. albicans was the predominant species (47, 60.42%) and C. tropicalis was the principal NACs (10, 12.8%) An interesting discrepancy to note is that however in our neighboring country India (22-23).

C. tropicalis is the chief causative organism implicated in UTIs It is believed that Candida albicans is innately susceptible to almost all the antifungal drug classes, so resistance to antifungal drugs must be acquired (24). Our study showed that Candida albicans is most sensitive to flucytosine (98.59%) followed by fluconazole (98.3%), voriconazole (97.4%), caspofungin (97.35%), amphoterecin B (96.6%) and micafungin (95.3%) (24). The high sensitivity of *Candida albicans* to Fluconazole (97.6%) contrasts with increasing resistance rates seen in global reports, where azole resistance is becoming a more significant clinical challenge . However, your study's findings on moderate resistance to Amphotericin, especially intermediate sensitivity in 243 cases, indicate the evolving complexities of treating candiduria with polyene drugs, particularly in older or immunocompromised patients (25) . Although *Candida glabrata* exhibited 100% sensitivity to Flucytosine and Voriconazole, its resistance to Amphotericin in 2 cases (25%) is concerning. This resistance pattern is in line with known challenges in treating *C. glabrata* infections, as this species is often associated with higher resistance to first-line antifungal therapies (26). The high resistance of *Candida spp.* to Fluconazole (27.6%) is noteworthy and mirrors findings in recent research that suggest non-*albicans Candida* species, particularly in nosocomial infections, are increasingly resistant to azoles. This could indicate a need to re-evaluate treatment guidelines and surveillance for emerging resistance patterns in clinical isolates (27). Data showing full sensitivity of *Candida kefyr* and *Candida glabrata* to Voriconazole highlights this drug's efficacy in treating resistant strains, suggesting its potential as a key therapeutic option in severe or refractory candiduria cases . However, the lower sensitivity of *C. albicans* (75.8%) to Voriconazole may reflect a growing trend of resistance among common species, necessitating careful antifungal stewardship (28).

Conclusion

This study highlights the variability in antifungal susceptibility among different *Candida* species isolated from urine samples. While *Candida albicans* remains the most prevalent species, resistance to certain antifungals like Amphotericin is notable, particularly in older age groups. Less common species such as *Candida tropicalis* and *Candida kefyr* exhibit high sensitivity across most antifungals, indicating effective treatment options. However, *Candida spp.* demonstrates considerable resistance, underscoring the need for regular susceptibility testing. These findings emphasize the importance of personalized antifungal therapy based on species-specific resistance patterns.

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