Section: Microbiology

Original Research Article

EMERGING TRENDS IN URINARY CANDIDIASIS: SPECIES SPECTRUM AND AZOLE RESISTANCE IN A CROSS-SECTIONAL STUDY AT TERTIARY CARE HOSPITAL, TAMILNADU

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Received *: 05/02/2026*
Received in revised form *: 19/03/2026*
Accepted *: 04/04/2026*

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DOI: 10.70034/ijmedph.2026.2.79

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2026; 16 (2); 467-472

ABSTRACT

Background: Candidiasis is the most common cause of fungal infections, leading to a range of muco-cutaneous infections to life threatening invasive diseases. Opportunistic infections by Candida sp are becoming quite common in hospitals today with antifungal resistance. Candida species account for almost 10-15% nosocomial UTIs. Candida albicans has been the commonest species causing infection for many years but indiscriminate use of azole group of drugs has led to increase in Non Albicans Candida infection and resistance to antifungal drugs in Candida species. **Aim:** To determine the isolation pattern, species distribution and antifungal susceptibility pattern of Candida species in urine samples particularly, their azole resistance pattern in the department of Microbiology, Chengalpattu Medical College and Hospital.

Materials and Methods: From August 2022 – July 2023, from a total of 644 urine samples,71 Candida species were isolated, speciated by various phenotypic methods and antifungal susceptibility testing done under standard mycological procedures.

Results: In this study, predominanace of Non Albicans Candida species is evident, with C.tropicalis (34%) as the predominant species followed by C.albicans (23%) .Fluconazole resistant found to be 37% in this study which is higher due to prevalance of Non Albicans Candida species.

Conclusion: This study highlights the predominance of Non-albicans Candida (NAC) species, being an important cause of urinary tract infections. Non - albicans Candida (NAC) species are more resistant to antifungal drugs than Candida albicans owing to higher prevalance of azole resistance. Therefore, the species identification of Candida isolates along with their antifungal susceptibility pattern can help the clinician in better treatment of patients with candiduria. Due to appropriate management with antifungal agents, there will be significant decrease in the length of stay of hospitalized patients, who may be already immunocompromised, thereby reducing the chance of acquiring nosocomial infections and healthcare costs.

Keywords: Susceptibility, candidiasis, antifungal resistance, immunocompromised.

INTRODUCTION

Urinary tract infections (UTIs) are the most frequently encountered infections in both outpatient and inpatient settings. Most fungal UTIs are attributed to Candida species, and these infections typically occur as complicated, healthcare-associated conditions. Candida spp. becoming quite common in hospitals today with antifungal resistance, an increasing problem in many wards.[1] With

interventions and management of diseases becoming more invasive and complicated, patients immunity can be affected due to various reasons, which may lead to hospital acquired infections.[2] In Hospital acquired infections Candidiasis is the one of the leading causes of infection with mortality rate reported between 15-35%.[3]

Candida species normally inhabit the human body as commensals, particularly on mucosal surfaces and the external genital region. Colonization is more frequently observed around the urethral meatus in healthy, premenopausal women. The commensal microorganisms become pathogenic once when the pathogenic mechanisms of host are weakened and these organisms have the ability to cause a variety of superficial and systemic infections4,5. Several factors predispose individuals to candiduria, including extremes of age, female gender, immunosuppressive therapy, presence of intravenous or indwelling urinary catheters, urinary flow obstruction, radiation exposure, and genitourinary tuberculosis. Virulent factors attributed to the shift of commensal to pathogen includes, adherence to host tissues and medical devices, biofilm production, and the release of extracellular hydrolytic enzymes.

Notably a gradual shift toward non-albicans Candida has been reported, largely driven by factors such as profound immunosuppression, extensive use of broad-spectrum antibiotics, and increased empirical antifungal therapy. Non-albicans Candida species often present with clinical features similar to those of C. albicans, making them difficult to distinguish based solely on symptoms. Moreover, many of these species exhibit intrinsic or acquired resistance to commonly used antifungal agents.

Early and effective antifungal intervention is essential for the optimal clinical outcome. For the treatment of invasive Candida infections, only a limited number of antifungal classes of drugs are available which include polyenes (amphotericin B),the azoles (voriconazole , fluconazole itranazole) and the echinocandins (caspofunfin, micafungin).These drugs exhibit a broad spectrum activity against the Candida species. Due to the good tolerability and bioavailability of the azoles, they have been widely used in practice.

As the azole antifungals have been increasingly used in the treatment of systemic Candida infections, there is an emerging resistance of azoles especially in patients with severe immunodeficiency. Antifungal therapy, when it fails to respond may be due to two types of resistance -mycological resistance or clinical resistance. Both the types of resistance to azole drugs are seen in Candida species. The key to predict the response in a clinical setting is to constantly monitor the resistance trends based on the mechanism of resistance. Antifungal drug administration with invitro activity, if it fails to eradicate a fungal infection, then it is termed as clinical resistance. Mycological resistance is defined as the ability of the fungus to grow in the presence of antifungal drugs that would otherwise kill them or limit their growth invitro.

In Candida species, the major mechanisms of azole resistance are the development of bypass pathways, ERG 11 gene alterations encoding the target enzyme and the gene upregulation encoding efflux pumps. The chief enzyme involved in the ergosterol biosynthesis is α-sterol demethylase, which is encoded by the ERG11 gene. This inhibits the fungal growth by altering the structure and function of the cell membrane.

These azoles do not interfere with the cell wall of host cells as the major target components of cell wall-chitin, glucan and mannan are absent in the human body because of the differences in structures of ergosterol and cholesterol.

Candida strains which are drug resistant pose a global threat and have serious clinical impacts worldwide. A better understanding and knowledge about the alarming rise of the intrinsic resistance of Candida species is essential to increase the efficacy of the treatment and to prevent such clinical outcomes. This study extensively elucidates the significance of resistance mechanisms of azole resistant

Aim & objectives

Aim

To investigate the prevalence and clinical implications of azole-resistant Candida species in urine samples isolated from patients admitted in a tertiary care hospital, Chengalpattu Medical College and Hospital, Chengalpattu and to explore potential strategies for managing and mitigating antifungal resistance.

Objectives

- To isolate the Candida species from the urinary samples received in a tertiary care hospital
- To identify the antifungal susceptibility pattern of the isolated candida species.
- To identify the azole resistance in candida species.
- To propose and evaluate strategies for managing and controlling azole-resistant Candida infections.

MATERIALS AND METHODS

Urine samples from patients admitted in various wards and intensive care units were collected and inoculated by calibrated loop (0.01 ml) onto Blood agar and Mac Conkey agar medium, incubated at 370 C and read at 24 hours and 48 hours interval. Dry creamy white opaque colonies on blood agar and tiny dry lactose fermenting pink colonies on Mac Conkey agar medium that resemble Candida were confirmed by gram stain.[8,9] Candida isolates were then subcultured on Sabouraoud's Dextrose Agar and CHROM agar candida medium and Corn meal agar with Tween 80 for speciation.

Antifungal drug susceptibility testing

Mueller-Hintonagar (HiMedia M1084) was to be made in accordance with the manufacturer's

specifications using commercially available MHA base. For one litre of Mueller-Hinton agar, 100µL of the methylene blue dye (0.5µg/mL) and 20g of glucose (2%) (HiMedia RM016) were added. After autoclaving, let it cool in a water bath set between 45 and 50°C. On a level, horizontal surface, the medium was poured into glass or plastic petri dishes until it was about 4 mm thick. After letting the medium set, the plates were kept at refrigerator temperature (2–8 °C).

Procedure

Mueller-Hinton agar plus 2% dextrose and 0.5 µg of methylene blue dye/ml were the agar mediums utilized. Five separate colonies, each about 1 mm in size, were selected from a 24-hour-old culture cultivated on SDA to create the inoculum. Five milliliters of sterile 0.85% saline were used to suspend the colonies. To modify the turbidity, this suspension was vortexed for 15 seconds. A stock inoculum suspension was used to create the test inoculum, which was then adjusted to meet the turbidity of a 0.5 McFarland standard, or 1x106 - 5x106 CFU/ml. Lawn culture was made from adjusted inoculums within 15minutes. Discs containing Fluconazole (25mcg), Itraconazole (10mcg), Voriconazole (1mcg), Amphotericin B(20mcg) & caspofungin (5mcg) were placed for antifungal susceptiblity testing as per CLSI guidelines M44.After placing each disc evenly about 24mm apart, the plates were inverted and incubated at 350C. The plates were examined after 20-24hrs for zone of inhibition. If insufficient growth is there, read again after 48hrs of incubation. Clear, uniformly circular zones of inhibition will be produced. Measure the zone diameter at the point at which there is a prominent reduction in growth.

Antifungal discs

Commercially available [Hi-media] discs of amphotericin B,fluconazole, itraconazole and voriconazole were used. Antifungal disks were placed in the centre of control as well as the test strains with the help of forceps. The plates were incubated at 35oC for 48 hours and measurements of zone of inhabitation were taken. After the measurement of zone of inhibition the result of antifungal susceptibility testing were interpreted accordingly.

Figure 1: Colonies in SDA slant

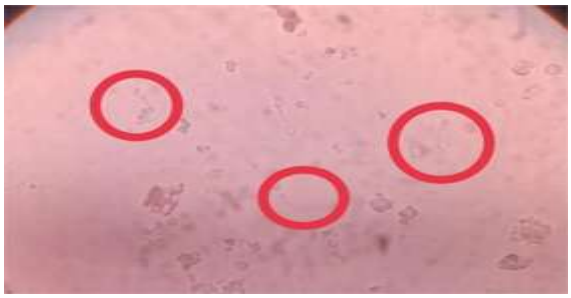

Figure 2: GTT positive

Table 1: Interpretation of CHRO Magar Candida medium growth color

Species	Colony colour
C.albicans	Light green
C.dubliensis	Dark green
C.glabrata	Cream to Pink or purple ,glorry
C.tropicalis	Blue to metallic blue
C.krusei	Pink to purple,fuzzy
C.kefr	white
C.parapsilosis	Cream /off white

Table 2: Cornmeal tween-80 agar (Dalmau plate technique) test Interpretation

S.NO	CANDIDA SPECIES	CHARACTERISTIC FEATURE
1.	C. albicans	Elongated pseudohyphae with grape-like clusters of blastoconidia at the septa. Chlamydospores are present at the end of the hyphae or their short, lateral branches
2.	C. tropicalis	Abundant branched pseudhyphae composed of elongated cells. Blastoconidiaare seen singly or in small groups along mycelia and show characteristic "**pine forest arrangement**".
3.	C. parapsilosis	Pseudohyphae are long, thinand branched. Single or small clusters blastospores see along the pseudomycelia.Large, mycelia elements, called giant cells is the characteristic feature.
4.	C. guilliermondii	Abundant or sparse, very fineand short pseudohyphae. Smallblastoconidia seen in smallchains or in clusters. Absence of terminal chylamydospores
5.	C. kefyr	Abundant production ofpseudohyphae. Cells areelongated and fall apart and lieparallel, like **"logs in a stream"**.
6.	C. dubliniensis	Abundant chlamydosporesoften in clusters or contiguous pairs on the true hyphae. Presence of solitary or cluster of blastoconidia is an important characteristic feature
7.	C. glabrata	Absence of hyphae orpseudohyphae is the characteristic feature

8.	C. krusei	Elongate cells forming a branched mycelium easily disintegrated. "Crossed sticks" of septa seen
9.	C. lusitaniae	Avoid yeast cells arranged inpairs and chains. Abundant branched pseudohyphae may be seen. Pseudohyphae are curved.

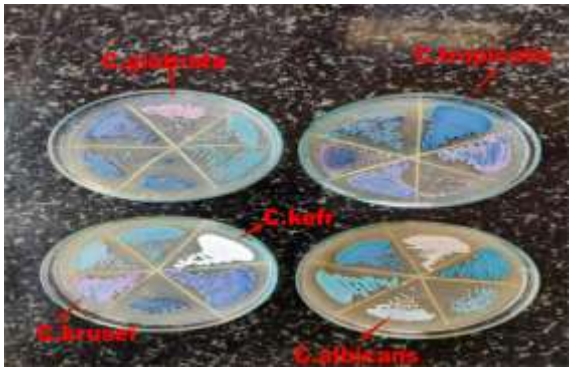

Figure 3: Candida CHROM agar images

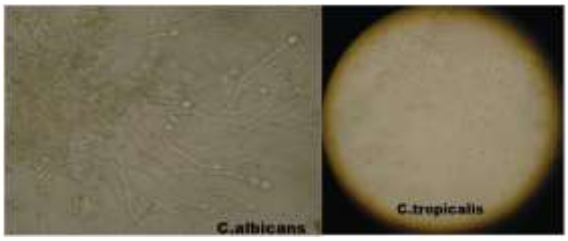

Figure 4: CMA with Tween 80 - Chlamydospores of Candida species

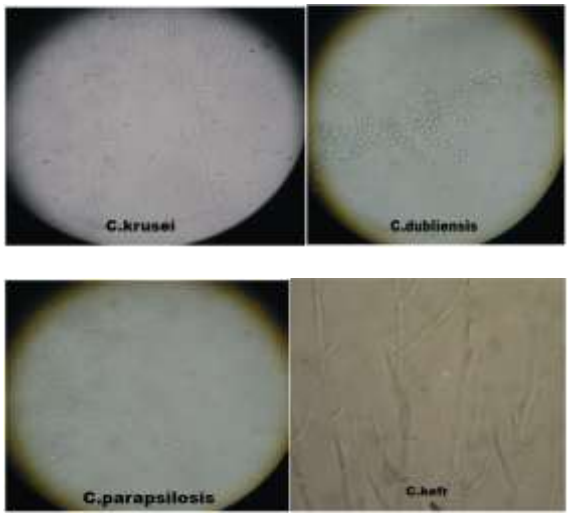

Table 3: Interpretation of carbohydrate fermentation tests

S.No	Species	Glu	Lac	Suc	Mal	Gal	Tre
1	C.albicans	AG	-	A	AG	AG	AG
2	C.tropicalis	AG	-	AG	AG	AG	AG
3	C.glabrata	AG	-	-	-	-	AG
4	C.krusei	AG	-	-	-	-	-
5	C.kefr	AG	AG	AG	-	AG	-
6	C.parapsilosis	AG	-	-	-	-	-
7	C.guillermondii	AG	-	AG	-	AG	AG
8	C.dubliensis	AG	-	-	AG	AG	AG

Note: Glu = Glucose, Lac = Lactose, Suc = Sucrose, Mal =Maltose, Gal = Galactose, Tre = Trehalose, A = Acid Production, G = Gas Production

Table 4: Intrepretation of Zone Size as PER CLSI

Antifungal agents	Zone diameter in mm		
	Sensitive	SDD	Resistant
Fluconazole (10 µg)	≥ 19	15-18	≤ 18
Itraconazole(10 µg)	≥ 17	14-16	≤ 13
Voriconazole (1 µg)	≥ 17	14-16	≤ 13
Amphotericin B(20 µg)	≥ 15	13-14	≤ 12

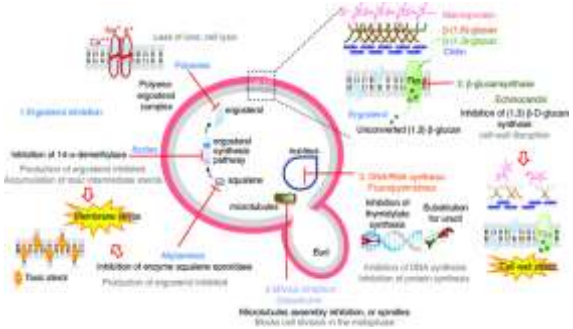

Figure 5: MECHANISM OF AZOLE RESISTANCE

RESULTS AND DISCUSSION

In this study, a total of 644 urine samples were screened for the presence of Candida species. Out of which 71 candida isolates were identified on the basis of microscopic stained smear examination from the colony grown in culture media. Following which candida isolates were speciated based on various phenotypic methods and antifungal susceptibility pattern was studied.

Males (54%) in the age group >50 year were predominantly affected. Isolated species were more susceptible to Voriconazole (98%), Amphotericin B (80%) and itraconazole (87.3%) and least susceptible

to fluconazole (63%). Data were entered in excel spreadsheet and variables were coded accordingly. Statistical analysis were performed in SPSS version 20 trial software.

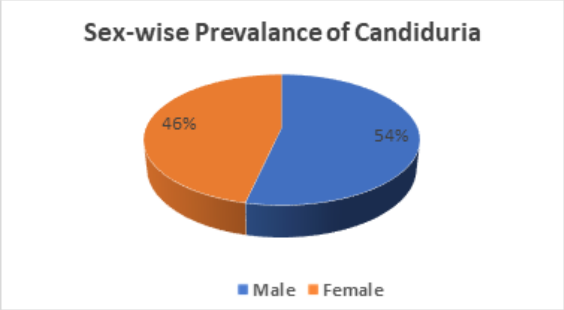

Figure 6: Sex wise distribution of total cases observed in the study (n= 71)

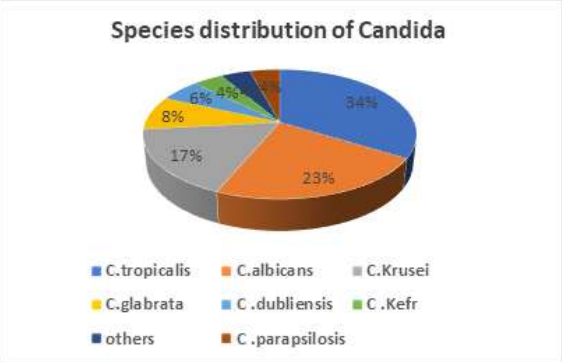

Figure 7: Species wise distribution of Candida isolates(n=71)

Table 5: Antifungal susceptibility pattern for Candida species

Speciation	Tota. No	Fluconazole		Itraconazole		Voriconazole		Amphotericin B	
		S	R	S	R	S	R	S	R
C.tropicalis	24	17(71%)	7 (29%)	19(79%)	5 (21%)	19(79%)	5 (21%)	19 (79%)	5 (21%)
C.albicans	16	15(94%)	1 (6%)	15(94%)	1 (6%)	16(100%)	0	15 (94%)	1 (6%)
C.Krusei	12	0	12(100%)	10(83%)	2 (17%)	11(92%)	1 (8%)	9 (75%)	3 (25%)
C.glabrata	6	3(50%)	3 (50%)	5 (83%)	1 (17%)	6 (100%)	0	4 (67%)	2 (33%)
C .dubliensis	4	3(75%)	1 (25%)	2 (50%)	2 (50%)	3 (75%)	1 (25%)	3 (75%)	1 (25%)
C .Kefr	3	2(67%)	1 (33%)	3 (100%)	0	3 (100%)	0	2 (67%)	1 (33%)
C .parapsilosis	3	2(67%)	1 (33%)	3 (100%)	0	2 (67%)	1 (33%)	3 (100%)	0
others	3	2(67%)	1 (33%)	3 (100%)	0	3 (100%)	0	2 (67%)	1(33%)

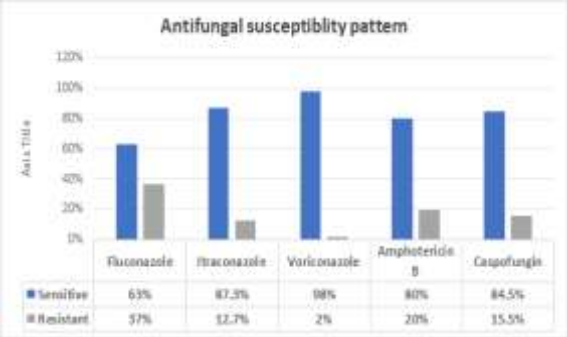

Figure 8: Overall Antifungal susceptiblity pattern for Candida species (N= 71)

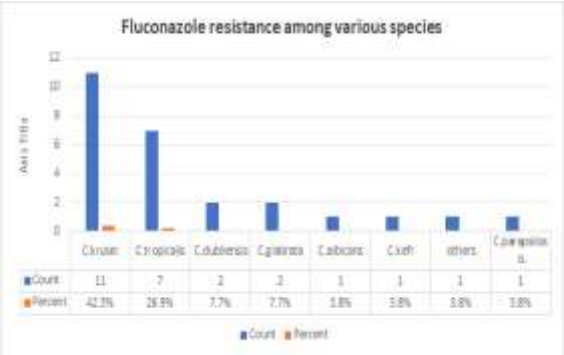

Figure 9: Fluconazole resistance among various species

The majority of cases occurred in patients older than 60 years. Foley catheterization was the leading predisposing factor for candiduria (90%), followed by diabetes mellitus (75%), intravenous catheter use (65%), frequent antibiotic exposure (55%), and recent surgical interventions (34%). Among the isolates, Candida tropicalis was the predominant species

Prolonged antibiotic therapy was identified as the most frequently associated risk factor in this study, accounting for 26% of cases, followed by diabetes (21%). Chakrabarthi A and Shivaprakash MR observed a higher rate of Candida infections in patients who received antibiotics for more than seven days or were treated with 3 or more antibiotics. The use of broad-spectrum antibiotics may suppress the normal microbial flora, thereby allowing fungal overgrowth; additionally, any compromise in mucosal immunity further increases susceptibility to Candida infections. Hyperglycaemia in diabetes can undermine the immune response, making these individuals more susceptible to fungal infections.

Pandey et al. found that the predominant species in candiduria among diabetic patients was C. tropicalis (34%), followed by C. albicans (30%), C. parapsilosis (16%), C. glabrata (14%), and C. krusei (6%), indicating a notable emergence of NAC species in urine samples. In our study similar findings were observed. Consistently, Falhati M et al. isolated C. glabrata (50%), C. albicans (31.6%), C. krusei (10.5%), C. tropicalis (5.3%), and C. kefyr (2.6%) from urine samples of 305 diabetic outpatients. Both studies highlighted the increasing prevalence of non-albicans Candida species which is very similar to our present study.

CONCLUSION

Our study confirms the predominance of NAC compared to C. albicans and ensures the inappropriate empirical usage of antifungal agents especially in fungal infections. Accurate identification of Candida spp. is mandatory in critical infections, along with antifungal susceptibility testing using disc diffusion method allowing more appropriate use of antifungal agents and better clinical outcomes.

Reports regarding resistance to antifungal agents are relatively uncommon (when compared to antibacterial agents); however, they have become significantly more prevalent with the introduction of new classes of antifungal agents, particularly the azoles (notably fluconazole), which have been extensively utilized against Candida infections.

Consequently, the emergence of resistance to the currently employed azole antifungal agents has become an escalating concern. This issue is especially pertinent for patients requiring long-term treatment and those undergoing antifungal prophylaxis, underscoring the necessity of antifungal stewardship. Indiscriminate and widespread use of fluconazole for the prophylaxis and treatment of candidiasis has led to a reduction of infections due to Candida albicans but that has led to the emergence of Candida infections caused by fluconazole resistant NAC.

In these patients, resistance may be either stable or transient, depending on the azole treatment administered. Over the last decade, acquired echinocandin resistance has surfaced, particularly in C. glabrata. Furthermore, there is an increasing recognition of the evolving epidemiology of fungal infections, with a trend towards species that are intrinsically resistant to the most frequently used antifungal agents (specifically, fluconazole).

Conflict of Interest: Nil

Sponsorship: Nil

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