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Candiduria in a Tertiary Care Hospital

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Abstract--- The presence of Candida species in urine (candiduria) is a common clinical finding, which may frequently represent colonization or contamination of specimens, however, they may be etiological agents in urinary tract infections (UTIs) or be indicators of underlying pathology in the genitourinary system or disseminated candidaemia. C. albicans is the most frequently isolated species of the genus, however, an increase in the occurrence of non-albicans Candida species (NACS) has been reported, which may be attributable to frequent exposure to fluconazole.

As urinary tract infections (UTIs) considered as one of the most important systemic infections. I, however candiduria has been considered as more problematic infection for patients, laboratory workers and physicians.

Due to increasing numbers of several predisposing factors, such as antibacterial agents, urinary tract instrumentation, diabetes mellitus, invasive therapies, and prolonged hospital stay, candiduria develops among the hospitalized patients, especially hospitalized in intensive care units (ICUs) and neonatal intensive care units (NICUs). According to the epidemiological studies, *Candida albicans* is the most common isolated species from candiduric patients. However, during the recent years, due to increasing resistance to antifungal drugs, non-*albicans Candida* species including, *C. glabrata, C. krusei, C. parapsilosis* and *C. tropicalis* have been also implicated. We found that the mean prevalence of candiduria among Iranian patients was lower (16.5%) than worldwide ratio and also males were more frequently affected than females (M:F, 1.2:1). Similar to other countries

Backgound : Urinary tract infection (UTI) is one of the most commonly diagnosed infections in both hospital and community settings. The *Candida* species in the urinary tract system (Candiduria) is seen 10–15% worldwide. Hence *Candida* species identification with antifungal susceptibility plays a important role in labourites. As , *C. albicans* was most common infectious agent followed by non-*albicans Candida* species including, *C. glabrata, C. tropicalis* and *C. krusei*. the non-*albicans Candida* species, such as *Candida krusei,* are intrinsically resistant or less susceptible to several classes of antifungals, whereas others, including *Candida glabrata,* have develop acquired resistance to antifungal agents.

Materials And Methods: A total of 7141 urine sample analyzed in our tertiary care hospital for candiduria. 216 [3%] candida isolates were processed, isolated and identified as various species of *Candida* on the basis of their morphological and biochemical reactions. Anti-fungal Susceptibility tests were performed according to standard protocols.

I. INTRODUCTION

The term candiduria refers to the presence of yeast in urine and *Candida albicans* is the most common agent.The genus *Candida* includes several species implicated in human pathology. *Candida albicans* is by far the most common species causing infections in humans. However, the emergence of non-*albicans Candida* (NAC) species as significant pathogens have been well recognized during the past decade. Various studies have showed the increased incidence of NAC species among hospitalized and immune-suppressed patients. Although this increased reporting may be caused by increased laboratory recognition, the change in host susceptibility due to the growing number of immune compromised individuals in the population as a result of the HIV pandemic and the use of long-term immuno-suppressive therapy in cancer and organ transplant patients has favored the emergence of these opportunistic pathogens[1,7].

Candida species are one of the major causes of nosocomial infection worldwide ranking 7th most common[2, 3]. They are the fourth most common blood pathogen in the United States and also common urinary tract pathogen. About 165 species of *Candida* have been identified, of which 20 are human pathogens. *Candida albicans* is the most commonly isolated species. Most of the *Candida* infections of non-*albicans* species are caused by *C. glabrata, C. parapsilosis and C. tropicalis* [4,5].

Candida albicans and non-*albicans Candida* species are closely related but differ from each other with respect to epidemiology, virulence characteristics and antifungal susceptibility. All species of *Candida* have been shown to cause a similar spectrum of disease ranging from mucosal disease like oral thrush to invasive disease, however difference in disease severity and susceptibility to different antifungal agents have been reported[5]. Despite the availability of an expanded antifungal armamentarium the mortality associated with invasive *Candida* infection remains high ranging 19% to 49%[6].

The incidence and associated mortality due to Candidiasis can be influenced by several factors including characteristics of the population at risk, standard of healthcare facilities available, distribution of *Candida* species and prevalence of resistance[7]. There is a change in

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epidemiological trend in some countries. The inappropriate use of antifungal drugs and the availability of over-the-counter drugs in countries worldwide has predisposed to the development of resistance to antifungal drugs. In addition to the acquired resistance, antifungal resistance may be innate as typified by some non-albican species such as *C. krusie.* Epidemiological information available for one center may not be applicable for another region.

Evidence suggests that some species of *Candida* have a great propensity to cause systemic, nosocomial and superficial infections; therefore, *Candida* species identification is important for successful management[8].

There is an increase in isolation of non-*albicans Candida* species. In addition to variation in geographical distribution of these species there is also a gradual shift in the antifungal susceptibility profile. Therefore, there is the need to monitor laboratory data for possible emergence of resistance and to select the most appropriate Antifungal agents[9].

Difference in the expression of putative virulence factors and in antifungal susceptibility has raised the need for species level identification.

Candidiasis which account for 66.80% of fungal mortality rate of 25% is caused by opportunistic yeast belonging to genus *Candida*. *Candida* is usually a commensal of digestive tract, genitourinary tract, skin mainly originates endogenously and turn pathogenic because of alteration of host immunity. Among *Candida*, *Candida albicans* is by far most common species isolated, but now India showing predominance of non *albicans Candida* , among which *Candida tropicalis* is on peak and it is commonest cause of invasive *Candidasis* in neutropenic patients[7,9].

Candida is small (4-6 µm) oval, thin-walled yeast like fungi that reproduces by budding process. The main components of cell wall are phosphorylated mannans, glucans and smaller amount of chitin. Polypeptide and proteins are intimately bound with cell polysaccharides, and the fine structure of the various wall phospho-glycopeptide oligomers and polymers account for differences among *Candida* species in antigenic structures, gross hydrophobic properties and specific adhesions to host cells and other surfaces[5,10-13]. Yeast cells and germ tubes are similar in their cell wall composition, although the relative amount of β glucans, chitin and mannan may vary[14].

The state of the host is of primary importance in determining *Candida* pathogenicity. However, there are factors associated with the organism, which contributes to its ability to cause disease and explain the differences among species in their pathogenicity. The most relevant virulence factors of *Candida* species are[15-19]

- Toxins
- Complement receptors
- Adhesion
- Phenotypic switching
- Enzyme production

II. MATERIALS AND METHODS

The study was conducted in the Microbiology department of Rajarajeswari Medical College & Hospital over a period of two year from January 2016 to December 2020. A total of 7141 urine sample received in our laboratory, 216 [3%] *candida* was isolated. The study was reviewed and approved by the Institutional Ethical Committee RRMCH.

Urine samples, wet film was prepared and observed for budding yeast cells and pseudo hyphae. The colonies on blood Agar were sub cultured on to two SDA plates, incubated one at room temperature and the other at 37^0C to get a pure growth. The isolated colonies were stained by Gram's stain and then the confirmed yeast colonies were selected for further processing like germ tube test, corn meal agar, Hichrome candida differential agar, sugar assimilation, fermentation test and Antifungal Susceptibility testing by Disk Diffusion method.

III. RESULTS

The present study was carried over 7141 clinical urine samples which yielded 216 *Candida*. The age of the patients ranged from new born to 80 years. Males were predominant in our study when compared to females.

TABLE ;1 ANTIFUNGAL SUSCEPTIBILITY PATTERN

SL.NO	ANTIFUNGAL AGENT	SYMBOL	DISC SIZE	*C. albicans* ATCC90028	*C. parapsilosis* ATCC22019	*C. krusei* ATCC6258	*C. tropicalis* ATCC750
1	Amphotericin - B	A P	100Units	10-17	11-20	9-14	8-12
2	Clotrimazole	CC	10 mcg	18-32	16-30	14-24	10-20
3	Flucanazole	FLC	10 mcg	27-38	22-33	-	16-25
4	Ketoconazole	KT	10 mcg	20-32	14-29	10-14	17-28
5	Voriconazole	VO	1 mcg	31-42	28-37	15-25	-
6	Nystatin	NYS	100 UNITS	19-27	16-25	15-20	16-21

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Fig.1- Gramstain of Candida

Fig. 2 – Candida on SDA

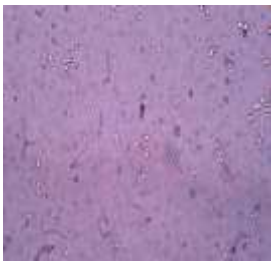

Fig. 3 - Germ Tube (*Candida albicans*)

Fig. 4 Chlamydospore of *Candida albicans*

FIG 5: Candida on HiCrome agar

FIG 6:Anti-fungal susceptibility test

TABLE – 2: AGE WISE DISTRIBUTION OF *CANDIDA* ISOLATES

AGE (in Years)	FEMALE	MALE	TOTAL (PATIENTS)
0-15	8	5	13
16-25	22	16	38
26-50	23	17	40
51-60	29	20	49
>61	36	40	76
TOTAL	**118**	**98**	**216**

Majority of the patients where Candida *was* isolated were from the age group of more than 60 years 35% (76), followed by the age group of 51-60 years 22.6% (49) . The least *Candida* species isolated was in the age group of 0-15 years 10.5% (13) cases. Out of total 216 samples received 54.6% (118) were from females and 45.4% (98) were from male's patients. The incidence was higher in females.

TABLE;3 DISTRIBUTION OF SAMPLES IN DIFFERENT CLINICAL DEPARTMENTS.

DEPARTMENT	NO. OF SAMPLES (%)
UROLOGY	47 (21.7)
MEDICINE	46(21.2)
ICU	43(19.9)
OBG	33(15.2)
SURGERY	29(13.4)
PAEDIATRICS	8(3.7)
OTHERS	10(4.6)
TOTAL	**216(100.0)**

Table – 4: Antifungal susceptibility pattern of *Candida* species

Species(n)	CC .n(%)	Flu.n(%)	Ke.n(%)	VO .n(%)	Am-B n(%)	Nys.n(%)
C. albicans(76)	59(77.6)	50(66.1)	61(80.6)	72(95.2)	76(100.0)	76(100.0)
C. tropicalis(58)	47(86.1)	41(72.2)	51(88.9)	58(100.0)	58(100.0)	58(100.0)
C. parapsilosis(27)	17(64.3)	11(42.9)	9(35.7)	27(100.0)	27(100..0)	27(100.0)
C. glabrata(21)	13(60.0)	0(0)	15(70.0)	19(90.0)	21(100.0)	21(100.0)
C. krusei(12)	12(100.0)	0(0)	8(66.7)	12(100.0)	12(100.0)	12(100.0)
C. famata(8)	4(50.0)	4(50.0)	8(100.)	8(100.0)	8(100.0)	8(100.0)
C. lusitaniae(6)	3(33.3)	0(0)	6(100.0)	6(100.0)	6(100.0)	6(100.0)
C.guliermondii(5)	2(33.3)	2(33.3)	4(66.7)	5(100.0)	5(100.0)	5(100.0)
C.lipolytica(2)	2(100.0)	2(100.0)	2(100.0)	2(100.0)	2(100.0)	2(100.0)
C. kefyr(1)	1(100.0)	0(0)	1(100.0)	1(100.0)	1(100.0)	1(100.0)
Total (216)	**160(74)**	**110(50.9)**	**165(76.3)**	**210(97.2)**	**216(100.0)**	**216(100.0)**

CC = Clotrimazole; Am-B = Amphotericin B VO = Voriconozole
Ke = Ketoconazole; Nys=Nystatin Flu = Fluconazole
R = Resistant; S = Susceptibility

IV. DISCUSSION

Candida infections are one of the commonest nosocomial infections. *Candida* albicans has been the most frequently isolated species from clinical specimens, but now non albicans species of *Candida appear* to be increasing which

have high azole resistance and are refractory to treatment. This highlights the importance of identifying Candida species within clinical urine samples in order to provide the physician information concerning the proper treatment to their patients. This study has been done to correlate the clinical picture like age, sex, clinical departments in relation to *candida* species isolated along with their anti-fungal susceptibility.

- Antifungal susceptibility pattern of *Candida* species by disk diffusion method showed overall 26% (56/216) resistance to Clotrimazole, 49% (106 /216) to Fluconazole, 23.7% (51/216) to Ketaconazole and only 2.8% (6/216) resistance to Voriconazole.
- We noticed 100% resistance to Fluconazole by *C. glabrata, C. krusei*, *C. lusitaniae* and C. *kefyr* (Intrinsic resistance). 32.4% resitance in *C. albicans*, 13.9% in *C. tropicalis*, 57.1% in *C. parapsilosis*.
- 22.4% of *C. albicans*, 13.9% *C. tropicalis*, 35.7% *C. parapsilosis*, 40% C. *glabrata* showed resistance to Clotrimazole.
- In case of Ketaconazole, 19.4% of *C. albicans*, 11.1% (4/36) *C. tropicalis*, 64.3% *C. parapsilosis*, 30% C. *glabrata* were resistant.
- Voriconazole showed 95.2% sensitive to all *Candida* spp except 4.8% resistance in *C. albicans* and 10% to *C. glabrata*.
- All 216 isolates showed 100% sensitive to Amphotericin B and Nystatin.

There is a steady rise in isolation of *Candida* non-*albicans* species over the last few decades. These non albican yeasts are relatively nonpathogenic but ultimately gets selected and start appearing more frequently because of wide spread abuse of the antifungal drugs.

Their culture is valuable for identifying the species of *Candida* and to monitor the changing trends in the microbiology of Candidiasis which is essential for complete and prolonged treatment of patients.

In the present study, among the non-*albicans* species, *Candida tropicalis* (26.8%), *Candida parapsilosis* (12.5%) and *Candida glabrata* (9.7%) constituted major isolates.

V. SUMMARY

In the present study total clinical urine Samples of 7141, 216 with suspected *Candida* infection were collected and processed in the Department of Microbiology, RRMCH, Bangalore, during the period January 2016 to December 2020.

- A total of 216 isolates from patients with significant patient history was studied, of which, 35% were from patients above 61 years, followed by 22.6% among 51-60 years, and only 10.5% among less than 15 years.
- Females (54.6%) were more affected than males (45.4%).
- *Candida* albicans constituted for 35.1% and other *Candida* species constituted 64.9% of total isolates obtained.
- The most common underlying clinical condition noticed was diabetes mellitus 34.2%, followed by COPD 14.3% and pregnancy 10.7%.
- Most common risk factors were prolonged antibiotics (25%), followed by indwelling catheters (24.3%) and steroid therapy (12.1%).
- Antifungal susceptibility tests show 100% resistance to fluconazole by *C. glabrata, C. krusei*, *C. lusitaniae* and C. *kefyr* (Intrinsic resistance).
- 100% resistance to Fluconazole by *C. glabrata, C. krusei*, *C. lusitaniae* and C. *kefyr* (Intrinsic resistance). 32.4% resitance in *C. albicans*, 13.9% in *C. tropicalis*, 57.1% in *C. parapsilosis*.
- 22.4% of *C. albicans*, 13.9% *C. tropicalis*, 35.7% *C. parapsilosis*, 40% C. *glabrata* showed resistance to Clotrimazole.
- 19.4% of *C. albicans*, 11.1% (4/36) *C. tropicalis*, 64.3% *C. parapsilosis*, 30% C. *glabrata* were resistant to Ketaconazole, .
- 95.2% sensitive to all *Candida* spp except 4.8% resistance in *C. albicans* and 10% to *C. glabrata to* Voriconazole.
- 100% sensitive to amphotericin B and nystatin by all *Candida* species.
- Hence *Candida* infections require culture and identification and its correlation with clinical manifestations, development of antifungal resistance among different species emphasizes the need for the routine susceptibility testing for *Candida*.

VI. CONCLUSION

Throughout the world, the dominance of C. *albicans* has been challenged by the increased prevalence of serious infections caused by Candida non–*albicans* spp. Several studies have identified multiple risk factors for candidiasis. Major risk factors include use of central venous catheters, receipt of multiple antibiotics, extensive surgery and burns, renal failure and hemodialysis, mechanical ventilation and prior fungal colonization.[20]

In the present study, there is a clear shift in the number of cases from that of *Candida* albicans 35.1% to those of *Candida* non- *albicans* 64.9%.

The key to successful management lies in early recognizing high risk cases by diagnosing species with the aid of Hi-Chrome agar which takes only 24 to 48 hrs for speciation, as it serves as a comfortable alternative to conventional

methods.

Among antifungal drugs in our study, Voriconazole is a better alternative to the other azoles for the treatment. Amphotericin-B can be used as a reserved drug for non-responding *Candida* infections.

Preventive measures against hospital infections are crucial in acquiring in the best policy. A high standard of hand hygiene and hygienic techniques while inserting and maintaining intravenous catheters becomes very essential. Education should be provided about CAUTI, other complications of catheterization and alternatives to indwelling catheter use.

Pharmacological interventional strategies should be emphasized including prudent use of antibiotics.

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