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Original Research Article

A MULTI-CENTRIC PROSPECTIVE STUDY ON CANDIDIASIS- THE CLINICO-EPIDEMIOLOGICAL ASPECT AND ANTIFUNGAL SUSCEPTIBILITY PATTERN IN TERTIARY CARE HOSPITALS

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ABSTRACT

Background: The purpose of the study was to determine the prevalence of different Candida species causing infections and their antifungal susceptibility pattern. **Materials and Methods:** Various types of clinical specimen collected from the patients with suspected fungal infection were examined by wet mount preparation and gram staining. Specimens were subsequently cultured on SDCA and incubated at 25ºC and 37ºC aerobically for 4 weeks. Candida isolates thus identified were subcultured on CHROM agar and corn meal agar for speciation. Confirmation of species level identification and antifungal susceptibility pattern were obtained using automated VITEK 2 method. **Result:** 221 culture positive Candida isolates were obtained from 3371 non-repetitive consecutive clinical specimens collected from suspected cases of cutaneous or invasive systemic fungal infections. 16.89%, 12.61%, 12.31%, 9.56%, 7.5% and 2.88% of the tongue scrapings, sputum, nail clippings, urine, esophageal biopsies and blood samples yielded growth of Candida. Candida albicans accounted for 57.92% isolates followed by Candida tropicalis (14.03%), C.auris (5.88%), C.parapsilosis (5.43%) and C.glabrata (5.43%). The study highlighted on different clinico-epidemiological aspects .61.09% of Candidiasis patients were male. Candidiasis was most common among 18-45 years(36.80%). Immunosuppression due to HIV turned out to be the most significant underlying disease. Diabetes mellitus was more common in non-albicans Candidiasis. Candida albicans was completely susceptible in vitro to Voriconazole, Caspofungin and Micafungin. Amphotericine B (24.21%) and Fluconazole (7.81%) were most in-vitro resistant against Candida albicans. Fluconazole, Amphotericine Band Caspofungin were resistant in 36.56%, 29.03% and 20.43% non albicans isolates respectively. Voriconazole (9.68%) and Flucytosine (12.9%) have also reported an increasing trend of resistance against these isolates. **Conclusion:** Echinocandins namely Micafungin was the only drug showing 100% efficacy against Candida isolates. Amphotericine B and fluconazole, flucytosine exhibited increasing resistance against Candida albicans. Caspofungin resistance is alarming as not only a few Flucanozole resistant isolates are showing complete or intermediate resistance to Caspofungin in-vitro but increasing MIC values are observed in few Fluconazole sensitive isolates also. Resistance of non albicans candida against both Azoles and Echinocandin are increasing probably due to an emerging trend of using either of them as first line therapy in invasive infections. Judicious use of these drugs in invasive and nosocomial candidiasis is therefore the need of the hour to prevent rapid emergence of resistance.

INTRODUCTION

Fungal infections are an important cause of mortality and morbidity worldwide, more so in immunocompromised patients. Candidiasis is the most common opportunistic fungal infection reported worldwide being ubiquitous in their presence in the environment. Candida can cause a wide range of diseases from superficial localized cutaneous infections to severe disseminated invasive clinical infections. Candida is considered as part of normal microbial flora of oral cavity, gastro-intestinal and

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genitor-urinary tract in a considerable portion of healthy adult population and it may result in colonization and opportunistic infection in persons with significant predisposing factors and co-morbidities, most significant being immune-compromised individuals. Candida albicans still remains the most common Candida species causing human infections but quite a large proportion of infections are now reportedly to be due to non-albicans species of Candida. There is an emerging trend of in-vitro resistance towards antifungal drugs commonly used among both albicans and non-albicans species of Candida. This changing trend of Candida infections calls for further investigation. Therefore our study was undertaken to determine prevalence of different Candida species causing infections and antifungal susceptibility pattern of those isolates.

MATERIALS AND METHODS

After obtaining approval from Institutional Ethics Committee, the multicentric prospective observational study was conducted at the Department of Microbiology of two tertiary care hospitals in Eastern India for six months from April 2024 to September2024. Consecutive, non-repetitive samples were collected from the patients presenting to us with suspected fungal infection during the study period. Different types of clinical specimens namely sputum, tracheal aspirate, broncho-alveolar lavage, tissue biopsy specimens, nail clippings, cutaneous scrapings, tongue scrapings, blood and body fluids such as ascitic fluid, pleural fluid, and urine were collected from the patients after obtaining informed consent. Detailed history regarding the present illness and co-morbidities was recorded. Data regarding the HIV seropositivity status of the patient was recorded with informed consent maintaining utmost confidentiality.

The specimens were primarily examined by direct examination of wet mount preparation and gram-stained smear. Sputum specimens with Barlett score>1 was accepted for further processing by sub-culture on Sabouraud dextrose chloramphenicol agar (SDCA) media. Presence of Candida isolates as pathogen in urine were confirmed by repeated isolation of the same in urine of patients with a colony count of 105 CFU/ml or higher on at least one occasion with symptomatic UTI. Direct microscopic findings were observed in the wet mount preparations after treating the specimen with 10% KOH and findings in the form of pseudohyphae or budding yeast were recorded. Then the specimens were cultured on SDCA (Sabouraud dextrose chloramphenicol agar) media and incubated at 25ºC and 37ºC aerobically for 4 weeks and observed for the growth on every alternate day during the first week and twice a week for next 3 weeks. Gram-stained smears from the colonies were prepared once growth of pasty and cream coloured colonies observed. Presence of Gram positive single or budding yeast cell with or without pseudohyphae was recorded. Germ tube test at 37ºC was performed to differentiate Candida albicans and Candida dublinensis from other Candida species. Specimen identified as Candida isolates were subsequently subcultured on CHROMagar media and corn meal agar for speciation. Confirmation of species level identification along with antifungal susceptibility pattern was obtained using automated VITEK2 method.

RESULTS

221 culture positive Candida isolates were obtained from a total number of 3371 non-repetitive consecutive clinical specimens collected for fungal culture in our Mycology laboratory. An overall culture positivity rate of 6.56% of Candida infection was observed in this tertiary care hospital inclusive of both cutaneous and invasive systemic fungal infections. Highest percentage (16.89%) of Candida isolates was reported as a causative pathogen from tongue scraping specimen after due consideration of the associated clinical history in each patient. 12.61% of the sputum specimen also yielded growth of Candida species. Cases of onychomycoses caused by Candida species accounted for 12.31% of the nail clipping specimen. Candida isolates were associated with 9.56% & 7.5% of UTI and esophagitis cases respectively. Candidaemia was reported in 2.88% isolates from aerobically incubated blood culture bottle [Table 1].

Candida albicans was the most important species responsible for causing majority of the (57.92%) fungal infections caused by Candida in our study. Candida tropicalis was the most frequently isolated non-albicans species accounting for 14.03% of all Candida infections. Emergence of Candida auris and Candida glabrata as the next most frequent causes of non–albicans Candida infections raises concern because of their well-documented antifungal resistance [Table 2 & 3].

Infections due to Candida was most common among persons aged 18-45 years.14.48% of the isolates were from patients aged below 18 years and non-albicans was responsible for most of the cases in the paediatric age group [Table 4]. Candidiasis was more common (61.09%) in male patients and two-third of the cases in them were caused by C. albicans only whereas non-albicans Candida species were responsible for 51.61% cases in female patients who accounted for 38.91% of total Candida infections [Table 5].

Immunosuppression due to HIV turned out to be the single most significant underlying disease condition favouring fungal infection due to Candida species irrespective of their CD4 T lymphocyte count or whether the patient is on ART therapy or not and the isolates mostly belonged to C.albicans in these patients. Candida albicans was the most frequent isolate in presence of other associated disease conditions known for lowering the immune

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competence such as Tuberculosis, malignancy, auto-immune diseases and chronic kidney disease. However, Diabetes, the second most frequently associated co-morbidity in cases of Candidiasis was more common in patients infected with non-albicans Candida species [Table 6].

Candida albicans isolates have shown highest percentage of in-vitro resistance towards Amphotericine B (24.21%) followed by Fluconazole. 7.81% of Candida albicans isolates were resistant to Fluconazole and 9.34% isolates were susceptible only to higher concentration of the drug. All the C.albicans isolates were completely susceptible in vitro to Voriconazole, Caspofungin and Micafungin [Table 7]. Non albicans isolates of Candida have demonstrated a higher degree of in-vitro resistance in comparison with C.albicans to all the antifungals tested for except Micafungin. All the isolates were completely susceptible towards Micafungin only. Fluconazole was the most resistant (36.56%) antifungal drug against Non albicans Candida isolates closely followed by Amphotericine B and Caspofungin, resistant in vitro against 29.03% and 20.43% of NAC isolates respectively. Voriconazole (9.68%) and Flucytosine (12.9%) have also reported an increasing trend respectively) of resistance against NAC isolates [Table 8].

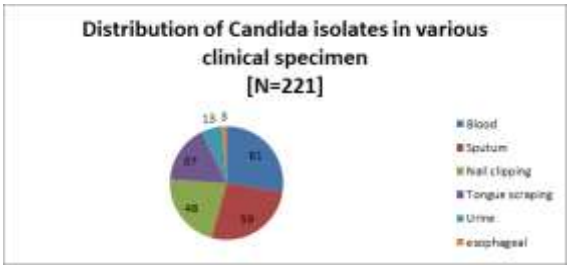

Figure 1: Distribution of candida isolates in various clinical specimen

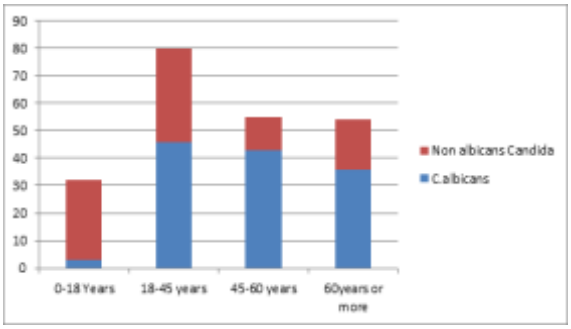

Figure 2: Distribution of candida albicans and non albicans species among culture positive samples in various age groups.

Table 1: Incidence of Candida isolates in various clinical specimen.

Specimen	Total number of specimen collected(N=3371)	Growth obtained (N=221)	Percentage(%) positivity among each type of specimen obtained
Blood	2118	61	2.88
Sputum	468	59	12.61
Nail clipping	390	48	12.31
Tongue scraping	219	37	16.89
Urine	136	13	9.56
Esophageal brushing/biopsy	40	3	7.5

Table 2: Distribution of Candida albicans and non albicans species causing infection in different clinical specimen in tertiary care hospital

Specimen(N=221)	Candida albicans(N=128)	Candida non-albicans(N=93)
Blood	24	37
Sputum	43	16
Nail clipping	19	29
Tongue scraping	37	0
Urine	2	11
Esophageal	3	0

Table 3: Age wise distribution of Candidiasis cases (Candida albicans-CA, Non albicans Candida species-NCA)

Age group	Total (N=221)		%
0-18	32		14.48
	CA	3	
	NCA	29	
18-45	80		36.20
	CA	46	
	NCA	34	
45-60	55		24.89
	CA	43	
	NCA	12	
60-rest	54		24.43
	CA	36	
	NCA	18	

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Table 4: Gender wise distribution of Candidiasis cases

Gender	Total (N=221)		%
Male	135		61.09
	CA	90	
	NCA	45	
Female	86		38.91
	CA	38	
	NCA	48	

Table 5: Co-morbidities associated with cases of Candidiasis

Predisposing Factors	Total (N=221)		%
HIV reactive	52		23.53
	CA	42	
	NCA	10	
Diabetes Mellitus	51		23.07
	CA	19	
	NCA	32	
Malignancy	25		11.31
	CA	18	
	NCA	7	
Tuberculosis	19		8.59
	CA	14	
	NCA	5	
Auto-immune diseases	22		9.95
	CA	18	
	NCA	4	
Chronic renal disease	6		2.71
	CA	3	
	NCA	3	

Table 6: Species wise distribution of Candida isolates causing infection

Micro-organism	N=221	Percentage (%)
Candida albicans	128	57.92
Candida auris	13	5.88
Candida parapsilosis	12	5.43
Candida Ciferri	9	4.07
Candida glabrata	12	5.43
Candida tropicalis	31	14.03
Candida famata	5	2.26
Candida krusei	2	0.90
Candida gulermondii	5	2.26
Candida dublinensis	2	0.90
Candida lipolytica	1	0.45
Candida luzitamiae	1	0.45

Table 7: In-vitro susceptibility pattern of commonly used antifungals against Candida albicans isolates(n=128)

Name of the antibiotic	Sensitive		Intermediate Sensitive		Resistant	
	Number of isolates	Percentage	Number of isolates	Percentage	Number of isolates	Percentage
Fluconazole	106	82.81	12(SDD)	9.34	10	7.81
Voriconazole	128	100	0	0	0	0
Caspofungin	117	90.41	11	8.59	0	0
Micofungin	128	100	0	0	0	0
Amphotericin B	97	75.78	0	0	31	24.21
Flucytocin	125	97.66	0	0	3	2.34

Table 8: In-vitro susceptibility pattern of commonly used antifungals against NAC isolates(n=93)

Name of the antibiotic	Sensitive	Percentage	Resistant	Percentage
Fluconazole	59	63.44	34	36.56
Voriconazole	84	90.32	9	9.68
Caspofungin	74	79.57	19	20.43
Micofungin	93	100	0	0
Amphotericin B	66	70.97	27	29.03
Flucytocin	81	87.1	12	12.9

Table 9: In-vitro resistance pattern of commonly used antifungals against different NAC isolates(n=93)

Micro-organism	Fluconazole (N=34)	Voriconazole (N=9)	Caspofungin (N=19)	Amphotericin B (N=27)	Flucytocin (N=12)
Candida tropicalis(n=31)	6	2	0	4	0
Candida auris(n=13)	9	2	2	7	1

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Candida parapsilosis(n=12)	2	0	0	5	1
Candida glabrata(n=12)	5	2	5	9	4
Candida ciferri(n=9)	9	3	9	0	4
Candida famata(n=5)	1	0	1	0	0
Candida gulermondii(n=5)	0	0	2	0	0
Candida krusei(n=2)	2	0	0	2	2
Candida dublinensis(n=2)	0	0	0	0	0
Candida lipolytica(n=1)	0	0	0	0	0
Candida luzitamiae(n=1)	0	0	0	0	0

Note- All the NAC isolates were in-vitro susceptible against Micafungin, hence the drug was not included in this table.

N – denotes the total number of resistant NAC isolates against the particular drug

n- denotes the total number of isolates of the particular Candida species.

DISCUSSION

The spectrum of the disease caused by Candida varied from localised onychomycoses and oro-pharyngeal candidiasis, urinary tract infection to more severe and invasive systemic ones such as fungal pneumonia and candidemia. Invasive Candidiasis in form of persistent Candidemia was the commonest type of infection being closely followed by fungal pneumonia in our study. Non albicans species were responsible for majority of the cases of candidemia in this study corroborating with other studies reporting a shifting trend acknowledged in most of the continents globaly.[1] Being an important cause of health care associated infection characterised by high morbidity and mortality rate it raises a matter of concern. Non-albicans Candida isolates were more frequently obtained from patients suffering from onychomycoses and urinary tract infection as well corroborating with findings obtained from other studies. Taei et al study suggested an increasing trend of empirical antifungals usage such as azoles, use of indwelling medical devices, malignancies and long term immunosuppressive therapy to be associated with such infections.[2] Candida tropicalis, C.auris, C.glabrata and C.parapsilosis emerged as the most frequently isolated NAC in our study. Recent studies by Ortiz et al,[3] (2022) and Megri et al,[4] (2020) also reported surge in infections by those candida species well known for their resistance towards azoles and echinocandins. NM Reda et al,[5] study done in Egypt in 2023 reported NAC isolates in more than half of the candidemia patients in paediatric age group and C.tropicalis and C.parapsilosis being the most frequent ones. Predominance of NAC isolates was also observed in patients below 18 years in our study though C.albicans was responsible for majority of the cases in all other age groups. Incidences of candidiasis were most frequent among patient aged more than 45 years with a male preponderance correlating with the findings of other studies across the globe including Indian ones.[6-8] An Indian study exclusively carried out in HIV seropositive individuals by Maheswari et al in 2016 detailed that C.albicans continued to be the commonest fungal pathogen in those patients. Findings of our study also corroborated that.[9] NAC isolates prevalent among HIV seropositive cases mostly belonged to C.tropicalis and C.glabrata .Sero-positivity for HIV irrespective of the CD4 count of the cases and Diabetes mellitus were most significant predisposing factors. Immunosuppression either due to malignancy or use of immune-modulators in auto immune diseases was also frequently found to be the underlying cause for candidiasis. Co-morbidities such as active cases of tuberculosis and chronic kidney disease were also associated with fungal disease though less frequently. Candida albicans was the most common isolate in patients with significant co-morbidities except Diabetes mellitus. NCA isolates mostly belonging to C,tropicalis constituted major portion of candidiasis cases in diabetics. C.glabrata, C.krusei and C.auris were also isolated in quite a few cases in diabetics. Chouhan et al study carried out in Bhopal in 2019 indicated a higher carriage rate of NCA species such as C.glabrata & C.tropicalis in oral cavity of diabetics than C.albicans.[10] The factors favouring local or systemic candidiasis in diabetics are attributed to several mechanisms,[11] such as increased adhesion and colonization of pathogen to epithelial surface,[12] increased salivary and blood glucose concentration,[13] increased microvascular degeneration and ineffective microbiocidal activities of PMNs, macrophage and lymphocytes.[11] Increased ability for biofilm production mainly by C.glabrata and also by C.tropicalis and C.albicans are probably responsible for their frequent association with infection in diabetics.[14] In corroboration with other studies carried out in last decade, ours also indicated a changing pattern in the species prevalence of Candida. Though C.albicans continues to be responsible for majority of the cases reported, yet the incidences of NAC namely C.tropicalis, C.auris, C.parapsilosis, C.glabrata and C.ciferri has increased nowadays.[15] A 2016 study from Kolkata reported C.tropicalis, C.haemulonii and C.glabrata as most prevalent ones among NAC isolates. The rising incidence of C.auris and C.parapsilosis as observed by us therefore holds greater significance.[16] Our findings on species distribution of candida isolates were similar to the study on blood stream fungal isolates involving a large no. of countries in Asia-pacific region,[17] (2016) and an Equadorian study,[18] (2020) and an Algerian study(2021) as well.[19]

Candida albicans isolates in this study remarkably showed highest percentage of resistance to

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AmphoterecineB which is not frequently observed worldwide till now.[20] Mutations in the ERG3 gene that encodes a C-5 sterol desaturase, an enzyme involved in ergosterol biosynthesis, thereby lowering the concentration of ergosterol in the fungal membrane is mostly responsible for resistance to Amphotericine B.[21] An increase in catalase activity, with decreased susceptibility to oxidative damage is also thought to render Amphotericine B ineffective.[22] A few azole resistant strains showed cross-resistance to amphotericine B as well indicating the importance of selecting a new class of drug with a different target molecule as the therapeutic choice for drug resistant invasive candidiasis cases.[23] Other than amphotericine B and fluconazole, flucytosine and Caspofungin also exhibited resistance though in less number of cases. Flucytosine monotherapy should therefore be avoided to prevent further development of resistance.[24]

Caspofungin, a rapidly acting Echonocandin with very Low MIC for C.albicans and considered to be fungicidal in vitro is being increasingly prescribed for esophagitis caused by Fluconazole resistant C.albicans.[25-27] Therefore, Caspofungin resistance is alarming as not only a few of the Flucanozole resistant isolates are showing complete or intermediate resistance to Caspofungin in-vitro but increasing MIC values are observed in few Fluconazole sensitive isolates as well.

Resistance of NAC against both Azoles and Echinocandin are increasing probably due to an increasing trend of using either of them as first line therapy in cases of invasive infections. C.krusei is intrisincally resistant to Fluconazole.[28] C.glabrata isolates in our study showed higher proportion of resistance towards Fluconazole, Amphotericine B and Caspofungin though they remain highly susceptible against Voriconazole or Micafungin supporting a worldwide trend of increasing resistance of C.glabrata towards all first line antifungals. C.auris isolates were mostly resistant towards Fluconazole and one of the isolate was pan-resistant being in-vitro susceptible to Micafungin only.[29,30] Candida tropicalis, the commonest NAC species isolated was in-vitro susceptible to most of the antifungals. The alarming finding though was significant proportion of C.tropicalis isolates being resistant to both amphotericine B and Fluconazole. The Candida parapsilosis isolates in our study showed a higher proportion of in-vitro resistance towards Amphotericine B.[31]

Echinocandins namely Micafungin was the only drug to show 100% efficacy in this study against all Candida isolates. These drugs have now been used extensively as first line therapy in invasive and nosocomial candidiasis to reduce mortality. Judicious use of these drugs is therefore the need of the hour to prevent rapid emergence of resistance.

Limitation of the study: Vulvo-vaginal candidiasis cases could not be included in this study. Molecular study specially to determine the surge in amphotericine B resistance in the albicans group could not be carried out.

CONCLUSION

Antifungal stewardship needs to be extensively planned and implemented specially taking account of the need for prophylactic and empirical therapy for the immunocompromised patients to reduce unnecessary use of antifungals as well as to reduce the cost of health care and prevent emergence of further drug resistance. Evaluation of different commercially available fungal marker detection tests in this regard can also be sought for.

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