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Choice of initial antifungal therapy in critically Ill patients

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***Abstract*---**Background: In the recent years, there has been a significant rise in the invasive candida infections. Epidemiological studies have demonstrated a shift in the trend of Candida species being isolated and their susceptibility patterns. The present study was carried out to evaluate the single institution experience of the burden of invasive candidemia. Methods: This prospective study was carried out among 48 candida isolates from blood and urine samples among patients hospitalized in intensive care unit (ICU) for a period of two years. Gram staining, culture and anti-fungal susceptibility testing were carried out on all the samples. Results: Highest occurrence of candidemia was in the age group of 41-60 years with a 50% male predominance. The case fatality rate among the study participants was 54%. Type 2 diabetes mellitus was a significant risk factor, with 45.8% of the candidemia patients being diabetic and 72.7% of the diabetics who developed candidemia expired (p value 0.035). In this study, 23% were Candida albicans and 77% non albicans species. Candida tropicalis (n=24) was the most frequently isolated organism. Out of the patients who expired, 27% of the isolates were albicans species and 73% of the isolates were non albicans species (p value 0.177). ICU stay (p value 0.036) and Mechanical ventilation (p value 0.016) were other significant risk factors for mortality. Conclusion:

Candida tropicalis was the most commonly isolated organism in blood and urine. Fluconazole, the most widely used empirical agent, showed to have the highest levels of resistance in this study.

***Keywords*---**Candida, Candidemia, Diabetes Mellitus, Intensive care, Antifungal agents.

Introduction

Opportunistic infections have been established as a major cause for mortality among hospitalized and immunocompromised patients. Among these, fungal infections with *Candida* species accounts for over 90% of all the opportunistic blood stream infections.[1] With increasing burden of chronic hospitalization and requirement for aggressive care in the intensive units (ICU), the risk of these infections have been alarmingly on the rise.[2,3,4,5]Various studies have documented the incidence of candidemia infections among ICU patients to range from 0.24 to 34.3 patients/1000 ICU admissions. Furthermore, the mortality rates associated with these infections range from 30%-81%.[2,3,4,5]

The clinical management of candidemia has been equally challenging due to the rampant rise in antifungal resistance. Recent reports from the Centre for Disease Control and Prevention (CDC), has not only documented the rise in antifungal resistant *Candida* infections among 34,000 cases, but also recorded the emergence of multidrug resistance in *Candida auris*infection.[6,7,8]

Although there are some Indian studies on the burden of Candidemia among hospitalized patients, the available literature on antifungal susceptibility patterns in India is scarce. This scenario puts into perspective the questionable use of empirical and targeted antifungal therapy for candidemia. [9,10,11]The increasing pattern of antifungal resistance warrants many clinical studies to evaluate the clinical profile of these species, their associated risk factors and anti-fungal susceptibility patterns.[12,13] It is hypothesized that a clinical evaluation in this regard can help clinicians to make informed choice of antifungal therapy and thereby combat the morbidity and mortality associated with this disease. The present study was carried out to characterize candidemia with relation to species distribution, determine underlying risk factors, predict antifungal susceptibility patterns and evaluate hospitalization outcomes.

Methodology

Study setting and participants

This study was carried out as a prospective study among all the patients admitted to the intensive care unit of our tertiary teaching institution for a period of two years between November 2016 and October 2018. A total of 48 isolates were studied. All patients above 18 years with isolates of Candida species in blood culture were included.

Ethical approval and informed consent
Approval was obtained from the Institutional Ethics Committee prior to the commencement of the study.

Data collection

A structured proforma was used to document the clinical history and risk factors including underlying disorders such as Malignancy, Cardiac disease, GI disease, Neurological diseases, Autoimmune, Pulmonary, Polytrauma, Renal disease, T2DM, PTB were recorded. ICU stay, Mechanical Ventilator, bladder catheterization, HD line, Sepsis and use of Broad-spectrum antibiotics. Blood samples were collected in BactAlert culture bottles under strict aseptic procedures and incubated at 370C for 10 days. When BactAlert indicates a positive, bottles are unloaded, preliminary Gram stain and subcultures are made on 5% sheep blood agar. These are then further identified into species level by carbohydrate assimilation tests using VITEK 2 compact system (bioMerieux). Anti-fungal susceptibility against fluconazole, voriconazole, itraconazole, ketoconazole and amphotericin B in VITEK 2 compact system was done. Culture positive patients were identified from laboratory culture records.

Data analysis
Data was entered and analysed using SPSS software ver.17. The prevalence of candidemia, its risk factors and associated hospital outcomes were expressed as percentages. Chi square test was used to evaluate the statistical significance between risk factors and candidemia. A p value <0.05 was considered statistically significant.

Results

In this study, majority of the participants belonged to the age group of 41-60 years (24%) and were males (58.3%). (Table 1) Urosepsis and Respiratory sepsis were the most common clinical diagnosis (25% each) followed by sepsis with multi organ dysfunction syndrome (MODS) (14.6%). The other minor causes of Candidemia among the study participants included soft tissue infections (8.3%), acute cerebrovascular accidents (CVA) (6.3%), carcinoma (4.2%), chronic kidney disease(4.2%), and pyogenic meningitis (4.2%). (Table 2)

C tropicalis was the most commonly isolated species (50%) followed by C albicans (23%) and C haemulonii (15%). (figure 1) The drug sensitivity pattern was individually analyzed for various drugs across the species isolated. It was observed that Amphotericin was found to be highly sensitive in infections with C albicans, C famata and C parapsilosis (100% each) while Fluconazole was highly sensitive in infections with C famata (100%) and C tropicalis (83.3%). Itraconazole was found to be highly sensitive for most of the species (100%) except C haemulonii which showed 57.1% sensitivity. Ketoconazole and Voriconazole showed similar sensitivity patterns. (Table 3)

Majority of the study participants with candida infections expired (54.2%) while 39.6% recovered. With regards to the individual infections, all (100%) of the

infections with C parapsilosis recovered completely while all (100%) of the infections with C famata, 63.6% of infections with C albicans expired. (Table 4)

Tables and figures

Table-1: Background characteristics of the study participants

S. No	Particulars	Frequency (n=48)	Percentage (%)
1	Age (in years)		
	20 – 40	9	18.8
	41 - 60	24	50.0
	61 - 80	13	27.1
	> 80	2	4.2
2	Gender		
	Male	28	58.3
	Female	20	41.7

Table-2: Clinical diagnosis among the study participants:

S. No	Diagnosis	Frequency (n=48)	Percentage (%)
1	Acute Cerebrovascular accidents (CVA)	3	6.3
2	Carcinoma	2	4.2
3	Chronic Kidney Disease (CKD)	2	4.2
4	Diffuse axonal injury / Road traffic accidents (RTA)	2	4.2
5	Post renal transplant	1	2.1
6	Pyogenic meningitis	2	4.2
7	Respiratory sepsis	12	25.0
8	Sepsis with multi organ dysfunction syndrome (MODS)	7	14.6
9	Soft tissue infections	4	8.3
10	Urosepsis	12	25.0
11	Vasculitis	1	2.1

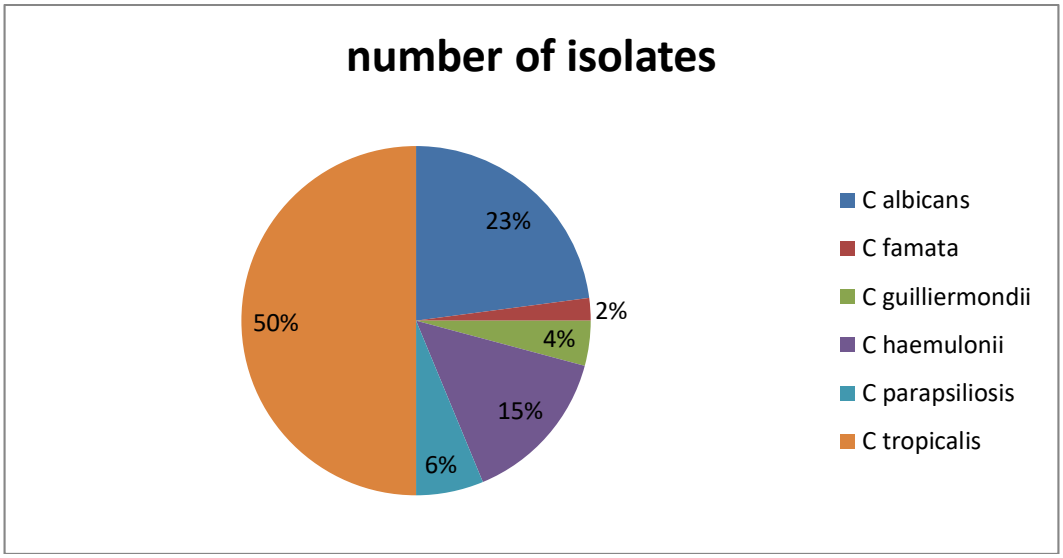

Figure-1: Candida species isolated:

Table- 3: Drug sensitivity pattern

Drug	Sensitivity pattern	Specimen						P value
		C albicans	C famata	C Guilliermondii	C haemulonii	C parapsilosis	C tropicalis	
Amphotericin	Sensitive	100	100	50	14.3	100	95.8	0.001*
	Resistant	0	0	50	57.1	0	14.2	
	Intermediate	0	0	0	28.6	0	0	
Fluoconozole	Sensitive	81.8	100	50	0	66.7	83.3	0.018*
	Resistant	18.2	0	50	71.4	33.3	12.5	
	Intermediate	0	0	0	28.6	0	4.2	
Itraconazole	Sensitive	100	100	100	57.1	100	87.5	0.139
	Resistant	0	0	0	42.9	0	12.5	
	Intermediate	0	0	0	0	0	0	
Ketoconazole	Sensitive	90.9	100	50	42.9	100	83.3	0.268
	Resistant	9.1	0	50	42.9	0	16.7	
	Intermediate	0	0	0	14.3	0	0	
Voriconazole	Sensitive	90.9	100	100	71.4	100	95.8	0.207
	Resistant	9.1	0	0	0	0	4.2	
	Intermediate	0	0	0	28.6	0	0	

*statistically significant

Table-4: Clinical outcomes of patients based on the Candida species isolated from blood culture

S. No	Species	Outcomen (%)		
		Recovered	Discharged against medical advice	Expired
1	C albicans	4 (36.4)	0(0)	7(63.6)
2	C famata	0(0)	0(0)	1(100)
3	C guilliermondii	0(0)	1(50)	1(50)
4	Chaemulonii	3(42.9)	0(0)	4(57.1)
5	Cparapsilosis	3(100)	0(0)	0(0)
6	C tropicalis	9(37.5)	2(8.3)	13(54.2)
7	Total	19(39.6)	3(6.3)	26(54.2)

Table-5: Comparison of antifungal resistance pattern with published literature:

ANTIFUNGAL RESISTANCE PATTERNS

CANDIDEMIA	**Candida albicans**			**Candida tropicalis**			**Candida parapsilosis**			**Candida haemulonii**			**Candida guilliermondi**		
	AMPHOTERICIN	FLUCONAZOLE	VORICONAZOLE	AMPHOTERICIN	FLUCONAZOLE	VORICONAZOLE	AMPHOTERICIN	FLUCONAZOLE	VORICONAZOLE	AMPHOTERICIN	FLUCONAZOLE	VORICONAZOLE	AMPHOTERICIN	FLUCONAZOLE	VORICONAZOLE
Basseti et al	0.00%	2%	2%	0.00%	3%	2%	0.00%	2%	0.00%	NA	NA	NA	NA	NA	NA
Rodriguez et al	1.10%	0.60%	NA	2.90%	2.90%	NA	2.60%	2.60%	NA	NA	NA	NA	0.00%	0.00%	NA
Jaswinder et al	0.00%	0.00%	0.00%	0.00%	9.50%	3.85%	0.00%	33.90%	8.40%	72.40%	100%	36.20%	0.00%	25.00%	0.00%
PRESENT STUDY	0.00%	18.20%	9.10%	4.20%	12.50%	4.20%	0.00%	33.30%	0.00%	57.10%	71.40%	0.00%	50%	50%	0.00%

- NA- NOT AVAILABLE IN THE STUDY

Discussion

Candidemia is a serious and life threatening infection in hospital settings, especially among patients admitted in intensive care units. The present study was carried out among 48 isolates of candida infections among patients admitted to the tertiary care hospital with various septic foci, predominantly urosepsis and respiratory sepsis.Colombo et al [14] showed that the majority of patients had underlying disorders like malignancy (41.1%), diabetes (11.2%), surgical intervention (45.1%), immuno compromised states like HIV (0.9%) and organ transplantation (1.4%). Karabinis et al [15] identified positive peripheral cultures for Candida species (p value 0.02), central catheterization (p value 0.03), and neutropenia (p value 0.05) as significant risk factors.

C tropicalis was the most commonly isolated species (50%). Pfaller et al [16] showed a decrease in C.albicans and an increasing trend in C.tropicalis and C.parapsilosis. C.albicans and C.glabrata were most frequently

identified in Denmark and the United States, where as in South America there were lower rates of these species [15].

It was observed that Amphotericin and Fluconazole showed statistically significant sensitivity outcomes with most of the major candida species including C albicans, C famata and C tropicalis. The antifungal resistance pattern for various species documented in literature is elaborated in the table 5. Overall, it may be interpreted that Amphotercin and Fluconazole have improved sensitivity patterns and therefore could be used effectively in the management of Candidemia. The other drugs including Ketoconazole, Itraconazole and Voriconazole, all though demonstrating high sensitivity and low resistance to various species, did not document statistically significant association, in the present study. This may be attributed to the lower sample size.

Recent studies have demonstrated growing resistance to antifungals, especially the azole group of drugs, predominantly comprising of fluconazole, ketoconazole, etc. Apart from various co-moribidites in the host, several molecular mechanisms have been implicated in the antifungal resistance. These include over-expression of membrane transporters due to various mutations thereby triggering macrophage mediated phagocytosis in most of the fungal species, especially C albicans. In addition, some of the recent studies have demonstrated genomic variations including loss of heterozygosity and aneuploidy in the trigger of antifungal resistance with Azole group of drugs. Among the various other mechanisms involved in the resistance to other non azole drugs, biofilm formation, overexpression of ergosterol pathway genes and acquired resistance due to prolonged exposure to antifungals could also be attributed. [14]

The present study demonstrated increased mortality (54.2%) among the candidemia patients. Most of the species except C parapsilosis are associated with increased mortality in the present study. It has been documented that use of appropriate evidence based mechanisms to combat antifungal resistance can ensure low rates of antifungal resistance, thereby improving therapeutic outcomes and reduced mortality. These mechanisms include use of antifungals that are not substrates of efflux pumps, like Amphotercin. Recent studies have also explored the potential role of development of inhibitors of efflux pumps that inhibit azole tolerance by binding to immunophilins. By this mechanism, it has been proposed that these drugs aid in synergestic action of azole group of drugs thereby combating resistance.[17]

Conclusion

Candida infections account for an increasing number of nosocomial blood stream infections. Several risk factors including underlying co-morbid conditions, hemodialysis, prolonged ICU stay, Mechanical ventilation and usage of Broad-spectrum antibiotics are attributed to candida infections. In the present study, sepsis was the most common risk factor and C tropicalis was the most commonly isolated organism in blood and urine. Anti-fungal susceptibility patterns indicated increasing resistance to azole group of drugs. Aggressive treatment of candida infections can indeed lower the overall mortality rates.

Declaration
Conflict of interest- *nil*
Funding **–** *nil*
Ethical approval **–** *obtained*

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