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Research Article

EPIDEMOLOGICAL PROFILE, RISK FACTORS AND PREDICTORS OF MORTALITY OF CANDIDEMIA PATIENTS IN TERTIARY CARE HOSPITAL OF NORTH INDIA

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A B S T R A C T

Background &objective: Candidemia is a life threatening infection causing high mortality in admitted patients.
Methods: This study was done in the department of Microbiology, DMCH for a period of one year (jan-dec2016) in patients >18yrs admitted in the hospital. Blood culture was taken from the patients clinically suspected with sepsis. Demographic details, risk factors, APACHE II and Candida score were recorded in a predesigned proforma. Patients with blood culture positive for growth of yeast were included. Identification and antifungal susceptibility was done in VITEK 2 System.
Results &Interpretation: A total of 92 patients who had candidemia were studied and the positivity percentage of candidemia was 0.5%. Prevalence was found to be 1.6/1000 admitted patients in the hospital. Among all the isolates obtained, "non-albicans candida" (66.3%) were predominant than *Candida albicans* (33.7%). *Candida tropicalis* was (47.8%) predominant among NAC. The antifungal susceptibility profile reveals that the NAC to be more sensitive to antifungals. Maximum sensitivity was observed for echinocandins and amphotericin-b followed by azoles. Patients discharged 38% in satisfactory condition and 62% died.
Conclusion: Candidemia was prevalent in the patients with sepsis. The scoring system i.e APACHE II score and Candida score are good physiological score for predicting the mortality of the patient. The susceptibility pattern shows much higher sensitivity to echinocandins.

INTRODUCTION

Candidemia remains a life threatening complication in hospitalized patients with prognosis comparable to septic shock. Candidemia represents 5-10% of all nosocomial infections. *Candida* species are ranked fifth among hospital-acquired pathogens and fourth among BSI pathogens, according to the data provided by the Center for Diseases Control and Prevention (CDC) and the National Healthcare Safety Network. [1]It manifests late in the course of disease, so early presumptive or empirical antifungal treatment has been shown to improve prognosis.

Candidiasis covers a wide range of diseases from more superficial and milder clinical manifestations such as oesophageal or oropharyngeal candidiasis to serious infections including Blood Stream Infections (BSI) and disseminated candidiasis. Invasive Candidiasis (IC) encompasses severe diseases such as candidemia, endocarditis, central nervous system infections, endophthalmitis, and osteomyelitis.

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[2]Blood stream infections by *Candida* spp. are increasingly common and often are associated with high mortality rates. Recently, an important increment in the frequency of non-albicans species of *Candida* such as *C.glabrata, C.krusei, C.tropicalis* and *C.parapsilosis* as cause of candidemia is seen. [3]

Risk factors for IC are immunosuppressive diseases, neutropenia, age, and a deteriorating clinical condition due to underlying diseases, catheter use, total parenteral nutrition, surgical interventions, improper use of antimicrobial drugs and long hospital or ICU stay due to invasive interventions ,indwelling intravascular catheters, hyper alimentation fluids, indwelling urinary catheters, parenteral glucocorticoids, respirators, abdominal and thoracic surgery, cytotoxic chemotherapy, and immunosuppressive agents for organ transplantation. Patients with severe burns, HIV-infected patients with low CD4+ T cell counts and patients with diabetes are susceptible to mucocutaneous infection, which may eventually develop into the disseminated form when other predisposing factors are encountered [4].

As the early signs and symptoms, suggestive of invasive fungal infections are easily missed due to the associated co-

morbid conditions, so it is important to rapidly identify the causative organism. Many regions in the world are witnessing a surge in "non-albicans candida"spp., which have diverse virulence and susceptibility profiles. *Candida albicans* are found to be more resistant than "non-albicans candida". This study was done, to know the disease burden, speciation of the *Candida* causing disease, antifungal sensitivity and correlating it with risk factors and outcome in patients with candidemia.

MATERIAL AND METHODS

This prospective study was approved by institutional ethic committee and was carried out in the Department of Microbiology, Dayanand Medical College and Hospital (1500 bedded tertiary care hospital) for a period of one year (Jan-Dec 2016). All the patients of > 18 years with candidemia were included. All the data enlisted in the pre designed Proforma (Name, Age, Sex, CR number, clinical diagnosis, date of admission, risk factors etc.) was collected. Physiological score like APACHE II (acute physiology and chronic health evaluation II) score uses a point score based upon initial values of 12 routine physiologic measurements - history of severe organ failure or immunocompromised state, acute Renal Failure, temperature, mean arterial pressure, pH, heart rate / pulse, respiratory rate, sodium, potassium, creatinine, hematocrit, white blood cell count, PaO_2 (if FiO_2< 0.5), GCS, Age and previous health status to provide a general measure of severity of disease was calculated. An increasing score (range 0 to 70) was closely correlated with the subsequent risk of hospital death. [4] Candida score - it's a bedside scoring system for giving early antifungal treatment in non-neutropenic critically ill patients. The "Candida score" was calculated using Leon Score (Sepsis-2, Previous surgery-1, TPN-1, Malignancy -1) at the onset of sepsis or shock. [5]

Blood samples for culture received in the Microbiology laboratory were included and processed as per standard protocol. The inoculated blood culture bottles were loaded in the Bactec or Bac-T/Alert microbial detection system and incubated for a maximum period of 7 days or till the bottle was indicated positive by the system. Smears were prepared from positive flagged bottles and subculture was done on blood agar. Blood culture positive for growth of yeast were included. Isolates were identified using VITEK 2 SYSTEM and antifungal susceptibility was done using Clinical and Laboratory Standards Institute (CLSI) broth microdilution.[6]The drugs tested were fluconazole, voriconazole, amphotericin-b, caspofungin, micafungin .

Outcome of the patients was studied in terms of discharge/death within 30 days of admission of the patient. Statistical data analysis was done using chi square and p values.

RESULTS

A total of 17504 blood samples for blood culture were received in the laboratory, out of which 92 patients were found to be positive for candidemia and thus the observed positivity percentage was 0.5%. Prevalence was found to be 1.6/1000 admitted patients in the hospital and in the ICU'S (4.58/1000 admitted patients). In the sex wise distribution, male patients (65%) were found to be predominant .The mean age of the patients with candidemia was observed to be 51.79 years. Maximum number 25% of patients belonged to elderly age group i.e. 61-70 years followed by patients in the age group of 18-30 and 51-60 years (17.4%) each .Majority of the patients (74%) were from various ICU"s and remaining (26%) from various wards. Among all the risk factors studied intravenous catheterisation and urinary catheterisation were found to be present in 96.7%patients followed by sepsis in 91.3% patients. (Figure 1)

APACHE II SCORE-The mean score was 23.17. Majority of patients 23.9% had score in range of 15-19 and 16.3% fell in range of 20-24.(Table 1) Candida score was >=2 in 43.5% of patients and >=3 in 37% of patients.(Table 2)Among the various yeast isolates *Candida tropicalis* was found to be most common (47.8%) followed by *Candida albicans(33.7%)*. Overall "non-albicans candida" (66.3%) was found to be more common than *Candida albicans*(33.7%). *(*Figure 2)

Antifungal susceptibility profile showed maximum sensitivity to echinocandins and amphotericin-B followed by azoles. (Table3).MIC breakpoints using VITEK-2 system were obtained for all the isolates (Table 4). Non-albicans candida showed higher sensitivity to antifungals than *Candida albicans* but difference was not statistically significant. (Table 5). High mortality was seen in patients with non-albicans candida than *Candida albicans* and 62% patients of candidemia died and 38%were discharged in satisfactory condition. Multivariate analysis using logistic regression predictive model summarizing various factors for 30-day mortality in adult candidemia in admitted patients was studied .The most significant independent predictors of 30-day crude mortality include age, sepsis, intubation, APACHE II score at admission, Candida score, antifungals administrated .(Table 6).

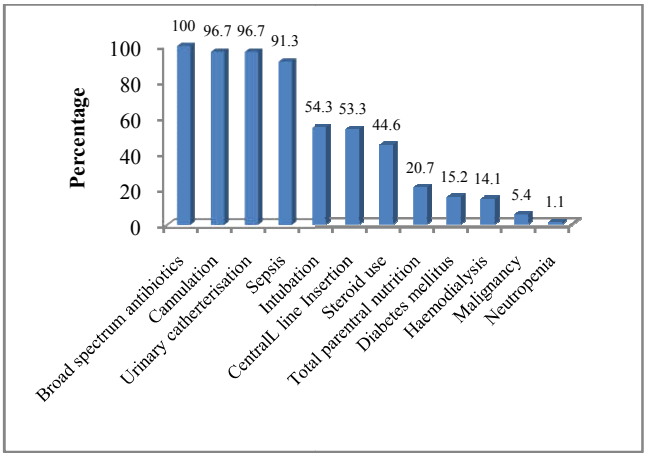

Figure 1 Distribution of risk factors in patients with candidemia. (n=92)

Table 1 Distribution of APACHE II SCORE in patients with candidemia (n=92)

Apache II Score	Number of Patients	Percentage
0-4.0	0	0.0
5-9.0	5	5.4
10-14.0	11	12.0
15-19.0	22	23.9
20-24.0	15	16.3
25-29.0	14	15.2
30-34.0	14	15.2
>34	11	12.0

Table 2 Distribution of CANDIDA SCORE in patients with candidemia (n=92)

Calculated Candida Score	Number of Patients	Percentage
0 score	3	3.3
1 score	5	5.4
2 score	40	43.5
3 score	36	39.1
4 score	7	7.6
5 score	1	1.1

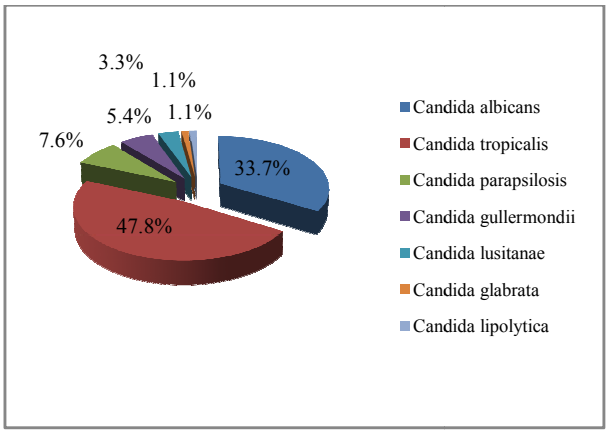

Figure 2 Distribution of various *Candida species* isolated (n=92)

Table 3 Antifungal suspectibility profile of various *Candida species* isolated (n=92)

	Fluconazole	Voriconazole	Caspofungin	Amphotericin-b	Micafungin
Candida albicans(n=31)	83.9%	83.9%	96.8%	83.9%	96.8%
Candida tropicalis(n=44)	93.2%	95.5%	90.9%	93.2%	97.7%
Candida parapsilosis(n=7)	71.4%	71.4%	100.0%	100.0%	100.0%
Candida guilliermondii(n=5)	60.0%	80.0%	80.0%	100.0%	100.0%
Candida lusitaniae(n=3)	100.0%	100.0%	100.0%	100.0%	100.0%
Candida glabrata(n=1)	0.0%	0.0%	0.0%	0.0%	0.0%
Candida lipolytica(n=1)	100.0%	100.0%	100.0%	0.0%	100.0%
Total	85.9%	88.0%	92.4%	89.1%	96.7%
chi-square value	12.737	12.858	27.619	28.109	48.003
p-value	0.047	0.045	0.006	0.005	0.000

Table 5 Comparison of various antifungals sensitivity in *Candida albicans* and non-albican Candida.(n=92)

	Fluconazole	Voriconazole	Caspofungin	Amphotericin-b	Micafungin
Candida albicans (n=31)	(26/31) 83.9%	(26/31) 83.9%	(30/31) 96.8%	(26/31) 83.9%	(30/31) 96.8%
"Non-albicans candida" (n=61)	(53/61) 86.8%	(55/61) 90.1%	(55/61) 90.1%	(56/61) 91.8%	(59/61) 96.7%
chi-square value	0.154	0.773	2.13	1.868	2.984
p-value	0.695	0.379	0.345	0.393	0.225

Table 6 Logistic regression predictive model summarizing various factors for 30-day mortality in adult candidemia in admitted patients.

	OR	p-value	95% C.I. for EXP(B)	
			Lower	Upper
Age	1.061	0.005	1.018	1.107
Sepsis	1.891	0.706	0.069	52.063
Intubation	2.531	0.154	0.706	9.067
Calculated Candida Score	2.966	0.050	0.982	8.955
APACHEII Score	1.162	0.001	1.061	1.273
Antifungals[a]	0.171	0.013	0.043	0.686

OR odds ratio, CI confidence intervals, APACHE II Acute Physiology and Chronic Health Evaluation II

[a]-Therapy instituted after definitive microbiological diagnosis of candidemia

DISCUSSION

Candida bloodstream infection (Candidemia) is a life threatening infection in intensive care unit (ICU) patients. While *Candida* is the fourth most common pathogen isolated in blood cultures in the USA, in Europe, it ranks amongst the

Table 4 Distribution of antifungals and its MIC breakpoints with *Candida species* isolated.

	ANTIFUNGALS	RESISTANT	MIC BREAKPOINTS										
			0.06	0.12	0.25	0.5	1	2	4	8	16	32	≥64
	FLUCONAZOLE (≥64)	(≥8)					40	1	0	0		1	2
	VORICONAZOLE(≥64)	(≥1)		41	1		0		2	0			
Candida tropicalis(n=44)	CASPOFUNGIN	(≥1)			40	1	1		2				
	AMPHOTERICIN-B	(≥4)			19	21	1	1	1	0	1		
	MICAFUNGIN	(≥1)	42	0		1	0	0	1				
	FLUCONAZOLE	(≥64)					26	0	0	0		3	2
	VORICONAZOLE	(≥1)		26	0		0		3	2			
Candida albicans(n=31)	CASPOFUNGIN	(≥1)			29	2	0		0				
	AMPHOTERICIN-B	(≥4)			7	9	10	2	1	2	0		
	MICAFUNGIN	(≥1)	28	2		1	0	0	0				
	FLUCONAZOLE	(≥8)					5	0	0	1		0	1
	VORICONAZOLE	(≥1)		5	0		1		1	0			
Candida parapsilosis(n=7)	CASPOFUNGIN	(≥8)			2	3	2		0				
	AMPHOTERICIN-B	(≥4)			1	4	2	0	0	0	0		
	MICAFUNGIN	(≥8)	2	1		2	1	1	0				
	FLUCONAZOLE	(≥64)					0	2	1	0		0	2
	VORICONAZOLE	(≥1)		4	0		0		1	0			
Candida guilliermondii(n=5)	CASPOFUNGIN	(≥8)			2	0	2		1				
	AMPHOTERICIN-B	(≥4)			2	3	0	0	0	0	0		
	MICAFUNGIN	(≥8)	2	0		1	0	2	0				
	FLUCONAZOLE	(≥64)					3	0	0	0		0	0
	VORICONAZOLE	(≥1)		3	0		0		0	0			
Candida lusitaniae(n=3)	CASPOFUNGIN	(≥0.5)			3	0	0		0				
	AMPHOTERICIN-B	(≥4)			0	3	0	0	0	0	0		
	MICAFUNGIN	(≥0.25)	0	3		0	0	0	0				
	FLUCONAZOLE	(≥64)					0	0	0	0		0	1
	VORICONAZOLE	(≥1)		0	0		0		1	0			
Candida glabrata(n=1)	CASPOFUNGIN	(≥0.5)			0	0	0		1				
	AMPHOTERICIN-B	(≥4)			0	0	0	0	0	1	0		
	MICAFUNGIN	(≥0.25)	0	0		0	0	0	1				
	FLUCONAZOLE	(≥64)					1	0	0	0		0	0
	VORICONAZOLE	(≥1)		1	0		0		0	0			
Candida lipolytica(n=1)	CASPOFUNGIN	(≥0.5)			1	0	0		0				
	AMPHOTERICIN-B	(≥4)			0	0	0	0	0	0	1		
	MICAFUNGIN	(≥0.25)	1	0		0	0	0	0				

The positivity percentage of candidemia was found to be 0.5% in our study . Prevalence was found to be 1.6/1000 admitted patients in the hospital and in ICU'S (4.58/1000 admitted patients). In a recent survey of intensive care units (ICUs) worldwide, the prevalence of candidemia was found to be 6.9 per 1000 patients. (11)

In our study majority of the patients (74%) were from various ICU"s and remaining (26%)from various wards .In comparison a study by Chander J *et al* observed that 88.9% patients with candidemia were admitted to the ICU, while only 11.1% occurred in patients in other hospital wards.(12)

In our study, candidemia was found to be predominant in male patients (65.2%) than in female patients (34.8%).The male to female ratio is 1.87:1. The mean age of the patients with candidemia was observed to be 51.79 years. Maximum number (25%) of patients belonged to elderly age group i.e 61-70 years. In a study done by Chakrabarti A*et al* adult candidemia patients were considerably younger (mean 49.7 years) than in other countries which is comparable to our study.[13]

Among all the risk factors studied, intravenous catheterisation was found to be present in 96.7% of patients with candidemia which is distinct to a study by Tak V *et al* (20.4%). The central venous catheterisation is a high risk for acquiring candidemia due to direct access into the blood stream was observed in 53.3% patients whereas different studies in literature showed 75.8% and 74.0 % of patients having CVC as risk factor.[13,14] Urinary catheterisation as risk factor (75.9%)[13] was observed in a study conducted at 27 ICU'S of India which was in contrast to present observation of 96.7%.Sepsis was observed in 91.3% of our patients which is by far ,much higher than the other studies conducted by Eggimann P *et al* and Guery BP *et al* who observed sepsis in the range of 8% - 30% and 23% - 38%, respectively.[15,16] Intubation, was seen in 54.3% of our patients which is in concordance with the observation done by Chakrabarti A *et al*(52.9 %)[13]. Among the other significant risk factors, Total parenteral nutrition was found to be given in 20.7% of our patients, and it is complementary to the observation by Tak V *et al*% [14]where 23.6% of patients on TPN developed candidemia, but was at variance to the observation by a different study in which it was on lower side (13.4 %).[13]

The calculated APACHE II SCORE was seen to be maximum in the range of 15-19 in 23.9%of the patients. The mean APACHE II score was calculated to be 23.17, whereas a study by Pappas *et al* and Marin K *et al* observed mean APACHE II score to be 18.6 [17]and 27.5 [18] respectively. Another physiological score studied was the Candida score and maximum number of patients (43.5%) had Candida score of 2 followed by 37% patients with score of 3 in our study which is in contrast to observation by Leroy *et al*. where 67% of the patients had a score of >3[19].

Among all the species of *Candida, Candida albicans* earlier was the predominant cause of invasive fungal infections but recently "non-albicans candida*" (NAC)* has been on the rising trend in causing candidemia. In our study the observation was NAC (66.3%) was found to be more common than *Candida albicans*(33.7%). Among NAC, *Candida tropicalis* was found to be most common 47.8% and *Candida parapsilosis* was 7.6% ,which is almost comparable to the observation by different authors reporting *Candida tropicalis* (38.7%)[14](41.6 %)[13](40.8%), [12] *Candida parapsilosis* (10.9%)[13] and (20.3%)[14] respectively. *Candida albicans* was isolated in 33.7% patientsin our study, whereas it was reported less frequently (13.7%)[14]and (20.9%)[13]in different studies.

The antifungal susceptibility profile of various *Candida* species in our study reveals that the NAC are more sensitive to antifungals than *Candida albicans*. Isolates of *Candida albicans* had overall good susceptibility to all antifungals ranged between 84-97% .Overall NAC had better sensitivity to azoles (88.5%) as compared to *C. albicans* (83.9%) in our study .This is different to observation by Kothari *et al*., 2008[20] undertaken in New Delhi where sensitivity to fluconazole was 64%, and voriconazole was 44%. Another study by Kumar *et al*., 2005 done at Chennai showed sensitivity to fluconazole as 82.8%.[21]which is comparable to our observation. Echinocandins like caspofungin showed better sensitivity in *C. albicans* with 96.8% versus 90.1% in NAC in our study. Micafungin had similar susceptibility (96.8%) in both *C. albicans* and NAC. Amphotericin-B had lower sensitivity in *C .albicans* (83.9%) as compared to NAC (91.8%).Among NAC 100% susceptibility to azoles, echinocandins was observed for *Candida lipolytica* and *Candida lusitaniae*. The one isolate of *Candida glabrata* obtained was found to be pan-resistant.

MIC breakpoints were studied using VITEK-2 system in our study and were interpreted using CLSI guidelines for yeast panel and results were that maximum isolates of different *Candida spp*. had minimum MIC for Echinocandins (<0.06-micafungin and 0.25-caspofungin) and for fluconazole most common MIC observed was 1.

Outcome was studied in terms of discharge or death within 30-days of admission. 62% of patients who were studied had a fatal outcome while 38% were discharged under satisfactory condition. The primary cause of death was not due to candidemia, although candidemia added to the risk of fatal outcome. . In a study conducted by TakV *et al*the observation was that, 68 out of the 157 patients (43.31%) had a fatal outcome. [14]

A logistic regression predictive model summarizing various factors for 30-day mortality in adult candidemia in admitted patients was studied and the most significant independent predictors of 30-day crude mortality include age, sepsis, intubation, APACHE II score at admission, Candida score, antifungals administrated .This was comparable to the observation made by Chakrabarti A.*et al* where the most significant independent predictors of 30-day crude mortality were admission to public sector hospital, APACHE II score at admission, underlying renal failure, central venous catheterization and steroid therapy. [13]

CONCLUSION

In our study, candidemia was prevalent in the patients with sepsis. The scoring system i.e APACHE II score and Candida score are good physiological score for predicting the mortality of the patient. The susceptibility pattern shows much higher sensitivity to echinocandins and resistance to azoles vary with the species isolated. So, ideally empirical treatment should be focused on the use of echinocandins and further change of antifungals can be made according to the species isolated and its susceptibility profile. There is very high mortality in these patients,even when the candidemia was the secondary diagnosis.

Conflict of interest-None
Acknowledgement-None

Highlights

- Among 92 patients with candidemia, maximum number was from ICU'S (73.9%) and mean age of the patients was 51.79±17.45 years.
- Intravenous catheterisation, urinary catheterisation and sepsis were found to be major risk factors. The mean APACHE II score was 23.17. Maximum number of patients (43.5%) had Candida score of 2.
- *Candida tropicalis* was most common among all the *Candida* species isolated 47.8%.
- Isolates of *Candida albicans* had overall good susceptibility to all antifungals ranging from 84-97%.

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