ORIGINAL ARTICLE

Isolation Rate and Antifungal Susceptibility Patterns of Bloodstream Candida Species in a North Indian Hospital Setting between 2017-2021

Veenu Gupta, Rama Gupta, Manisha Aggarwal, Jyoti Chaudhary, Menal Gupta

Abstract

Background: Candidemia is an increasingly important healthcare-associated fungal infection that is associated with high morbidity and mortality. The epidemiology of candidemia varies according to geographical region, period and the population involved. An increased incidence of non-albicans candidemia has been reported in recent studies. **Aim:** To study the prevalence of *Candida* species and their susceptibility profile over a period of five years (2017– 2021). **Materials and Methods:** This retrospective study was performed in the microbiology laboratory. Specimens were collected and culture was performed using the BacTAlert3D / BacTec culture system. All the isolates were identified and their antifungal susceptibility testing was performed. **Results:** Year-wise positivity rates of candidemia were 0.85%, 0.68%, 0.73%, 0.82% and 0.71%. Majority of the isolates were from the age group 51-60 years with male predominance. *Candida tropicalis* was the most common species followed by *C.albicans* & *C. parapsilosis*. Candida isolates showed good susceptibility to Amphotericin B & Echinocandins whereas increased resistance to azoles (20-30%) was observed in *C. tropicalis* & *C. parapsilosis*. **Conclusion:** The emergence of a few Candida species, which were not previously isolated is alarming. NAC being more resistant / intrinsically resistant to fluconazole strengthens the need for antifungal susceptibility testing on a priority basis.

Key Words

Candidemia, *Candida albicans*, Non albicans candida, Antifungal susceptibility

Introduction

In recent years, the incidence and prevalence of invasive candidiasis have been on the rise worldwide.[1,2] It has emerged as an important public health problem and is associated with a high mortality rate. The most common presentation of invasive candidiasis is candidemia which has been frequently reported from various intensive care units (ICUs), and is mostly associated with immune suppression, prolonged broad-spectrum antibiotic usage, intravenous devices and parenteral nutrition. It prolongs the hospital stay and increases the financial burden of healthcare.[2,3] Though, *Candida albicans* (*C. albicans*) remains the most commonly isolated Candida species in patients with candidemia in a large number of studies, there is an obvious steady shift towards non-albicans Candida (NAC) species which collectively account for the remaining 60-70% cases of candidemia.[1,2,4-7] This distribution varies according to the geographical region, study period, age & underlying clinical condition of the patient, type of survey, and the population involved.[2,8] Many Asian countries have reported *Candida tropicalis* as the predominant non-albicans Candida species whereas Europe & the USA havereported a high prevalence of *Candidaglabrata*. Nevertheless, *Candidaparapsilosis*

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is the leading NAC species reported from Spain and Brazil.[5,9] Various studies across India, have reported an increased incidence of NAC species with *C. tropicalis* as a major contributing species.[1,10] However, Gupta*et al* reported *C. glabrata* as the most common NAC species from a neonatal intensive care unit.[11]

Antifungal resistance amongst the Candia species is an evolving issue worldwideand concomitant resistance to more than one antifungal drug classes further complicates the problem of selecting the empiric antifungal treatment.[1,3,4]

Primary Objective: To study the distribution & susceptibility profile of Candida species over a period of five years.**Secondary Objective:** To analyze the year-wise trends of Candida species and susceptibility profile.

Materials and Methods: This retrospective, observational study was performed in the Microbiology laboratory of a tertiary care hospital in Punjab, North India, for a period of 5 years (Jan 2017 –Dec 2021after IEC clearance vide IEC No.:2023/825.

Inclusion Criteria: Blood samples from indoor patients suspected with blood stream infections. **Exclusion Criteria:** All the duplicate isolates from the same patients and OPD patients.

Specimen collection and Identification of Candida isolates Specimens were collected taking standard aseptic precautions. Blood culture was carried out by BacTAlert3D /BacTec automated blood culture system. Once a blood culture bottle flagged positive, a Gramsstain was done from the broth in the bottle to look for yeast cells. Then, subculturewas done on blood agar plates and sabouraud Dextrose Agar (SDA) agar for isolation and incubated at 37°C for 24 hrs. Suspected colonies of yeasts were identified on the VITEK 2 Compact system (BioMérieux) using YST-ID cards.

Antifungal susceptibility Testing

In vitro, antifungal susceptibility testing of Candida isolates to polyenes (amphotericin B), azoles (fluconazole and Voriconazole) and echinocandins (caspofungin and micafungin)was performed on VITEK 2 Compact system using YST-YS07 cards. The results of antifungal susceptibility are evaluated in accordance with the European Committee on Antimicrobial Susceptibility Testing(EUCAST)/Clinical Laboratory Standards Institute (CLSI) guidelines by the VITEK 2 system depending upon the availability of break points.[12]

Statistical Analysis

Five- year epidemiological trends of candida isolates in terms of demographics, species distribution and antifungal susceptibility are evaluated. Statistical analysis is performed by using a chi-square test or Fisher's exact test as appropriate and probability levels <0.05 by the two-tailed test is considered statistically significant.

Results

A total of 108057 blood samples were received in the Microbiology laboratory during the study period, for culture. Of these 815 candida isolates (0.75%) were obtained. The comparative year-wise positivity of candidemia from 2017 to 2021 was found to be 0.85% (199/23333), 0.68% (169/24927), 0.73% (184/25135), 0.82% (131/16071), and 0.71% (132/18591) respectively. Male patients 63.5% (517/815) predominates over the female patients and the age group of 40-60 years was primarily affected. A gradual increase in the number of male patients with candidemia was observed over a period of 5 years from 62.1% to 75.8%. However, there is no remarkable difference seen in the age distribution of these patients over the years, except in the year 2021. In the year 2021, the predominant age group affected was 61-70 years (Figure 1, 2)

During the study period, 12 different *Candida spp*. were isolated with a predominance of non albicans *Candida species* (79.6%, 649/815). *C. tropicalis* was the most frequently isolated species 421 (51.7%), followed by *C.albicans* (n=166, 20.4%), C.*parapsilosis* (n=130, 15.9%), *C.gulliermondii* (n=30, 3.7%). The remaining isolates were *C.lusitaniae* (n = 12, 1.7%), *C.ciferrii* (n = 18, 2.2%), *Candidakrusei* (n = 9, 1.1%) etc. (Table 1).

The year wise distribution of Candida species has been described in Table 1. The percentage of candidemia cases due to non albicans Candida species remained stable from 2017-2020 (approximately 78%). However, a steep rise of non albicans Candida was observed during the year 2021 (86.4%) (Figure 3). The major contributors toward the increase in the incidence of NAC species were *C.guilliermondii* (from 3.5% to 8.3%) and *C. ciferrii* (from 0.5% to 9.1%).

Trends of the antifungal susceptibility of these isolates over the years has been shown in Table 2. A statistically significant decrease in the susceptibility of fluconazole was observed over the years ($p<0.05$), however, the change in susceptibility profile of other antifungal agents was not found to be significant.

The susceptibility profile of predominant isolates obtained during the study period has been evaluated in Table 3. It has been observed that there was a significant ($p<0.05$) increase in sensitivity (to 100%) of *C. albicans* towards all the antifungals tested except Voriconazole. Further, a significant ($p<0.05$) variation in the sensitivity of *C. tropicalis* towards echinocandins was observed over the years. The caspofungin and micafungin resistance varied from 0.9%-10% & 2.7%-15%

Fig 1: Year wise trends of sex distribution in patients with candidemia.

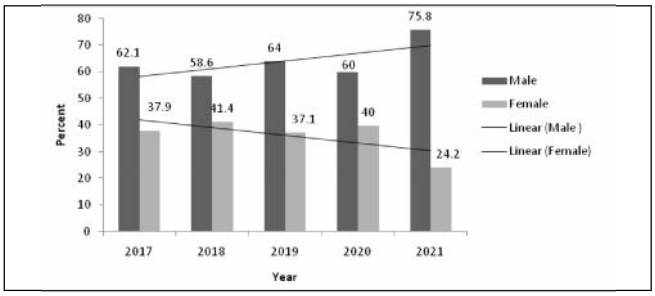


Fig 2: Year wise trends of age distribution in patients with candidemia.

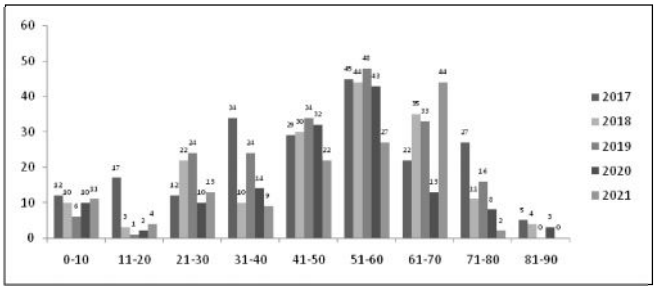


Table 1: Year wise distribution of Candida isolates (2017-2021) in patients with Candidemia

	2017		2018		2019		2020		2021		Total	
	(n=199)	%	(n=169)	%	(n=184)	%	(n=131)	%	(n=132)	%	(N=815)	%
Candida albicans	**44**	**22.1**	**36.0**	**21.3**	**39**	**21.2**	**29.0**	**22.1**	**18.0**	**13.6**	**166**	**20.37**
Non albicans candida	**155**	**77.9**	**133**	**78.7**	**145**	**78.8**	**102**	**77.9**	**114**	**86.4**	**649**	**79.63**
Candida tropicalis	105	52.8	93	55.0	87	47.3	60	45.8	76	57.6	421	51.66
Candida parapsilosis	28	14.1	25	14.8	39	21.2	25	19.1	13	9.8	130	15.95
Candida gulliermondii	7	3.5	4	2.4	7	3.8	1	0.8	11	8.3	30	3.68
Candida lusitaniae	4	2.0	2	1.2	4	2.2	1	0.8	1	0.8	12	1.47
Candida ciferrii	1	0.5	2	1.2	2	1.1	1	0.8	12	9.1	18	2.21
Candida Utilis	4	2.0	1	0.6	-	-	-	-	-	-	5	0.61
Candida famata	2	1.0	-	-	1	0.5	6	4.6	-	-	9	1.10
Candida glabrata	2	1.0	1	0.6	2	1.1	1	0.8	-	-	6	0.74
Candida kefyr	1	0.5		0.0	2	1.1	2	1.5	1	0.8	6	0.74
Candida krusei	1	0.5	4	2.4	1	0.5	3	2.3	-	-	9	1.10
Candida dubiliensis	-		1	0.6	-		2	1.5	-	-	3	0.37

respectively, over the years. However fluconazole and voriconazole resistance has a wide-range from 7.7%-28.9% & 6.5% - 18.4% respectively, during the study period and these variations were found to be statistically significant. Significantly reduced sensitivities to fluconazole & voriconazole were observed in the case of *C. parapsilosis*, whereas susceptibility to Amphotericin B and caspofungin has increased over the five years. (Table 3)

Discussion

Candidemia is an emerging infection worldwide, due to various factors *viz* increase in a number of patients on immunosuppressant, the growing elderly population, rise in the survival of patients with previously considered lethal diseases, increase in invasive & more extensive surgical procedures, increased antibiotic usage and the number of patients with diabetes mellitus.[3,13]

The various studies, across India have shown a varied rate of Candida isolation from suspected septicemia cases. It ranged from 1.74% to 32.5%.[3,4,5] However, the present study showed a comparative low incidence of candidemia ranging from 0.68% to 0.85% during the

study period. The similar incidence (0.21-0.58%) has also been reported in few studies from various other countries. However the incidence varied with geographical region, among different populations, local epidemiology, age group, study period, type of hospital and other risk factors.[1,14] In the present study, peak age group was 41-60 years during 2017-2020 except in the year 2021 where predominantly patienys belong to 61-70 years. This shift in age during 2021 may be correlated with the COVID-19 period as advanced age is one of the risk factors for hospitalization and the use of immunosuppressive in these patients further explains the increase in the frequency of Candidemia.[15] In our study incidence of candidemia varied from 3.7% (year 2019) to 14.3% (2017) in the age group 0-20 years. These findings are in corroboration with a previous study which reported a cumulative incidence of 12.8% in 0-15 years of age group.[17] Contrary to our findings, another study carried out only on ICU patients have reported an incidence of 63.5% in pediatric population. [16]

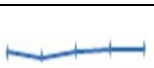
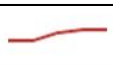
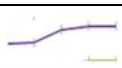
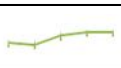
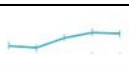
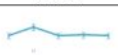
As per study, a total of 15 different Candida species are responsible for most of the human diseases and invasive candidiasis.[3,17] However, in the present study, from the patients suspected of Candidemia 12 distinct species has been isolated with the predominance of *C.tropicalis*, *C.albicans*, *C. parapsilosis*, *C. gulliermondii*, and *C. ciferrii*, in that sequence. Few other studies have also reported *C. tropicalis* being the most common species isolated, followed by *C. glabrata* and *C. albicans*.[10] Nevertheless, others have reported *C. parapsilosis* as the leading species among the NAC and it has emerged as an important nosocomial pathogen.[1] The distribution of Candida *spp*. has shifted from *C. albicans* to non-candida albicans (NAC) species over the years due to multiple factors like shift in demographics of the patients, increase in patients with cardiovascular disease & also due to improvements in the diagnostic modalities.[1,7] Our study has also demonstrated that the majority of Candida isolates belonged to NAC species during all the years of the study period. Although a steep shift (increase) was observed in the isolation of NAC species, during the year 2021 from approximately 78% (2017-2020) to 86.4%. The major contributors toward the increase in incidence of NAC species were *C.guilliermondii* and *C.ciferrii*, probably due to decreased susceptibility of C.*gulliermondii* to azoles/echinocandins[18] and *C.ciferrii* being resistance to fluconazole.[19]

In the current study, the antifungal susceptibility profile of Candida species revealed that there were statistically insignificant variations in the susceptibility over the years (2017-2021) except amphotericin B and fluconazole. Although, the variation in susceptibility towards amphotericin B was found to be significant, but susceptibility remained substantially high ranging from 90.5-97.8%, which was much higher than reported by Bhattacharjee (69.4%).[10] Fluconazole exhibited a significantly decreased (from 87% in 2019 to 69.7% in

Table 2: Year Wise Trends of Antifungal Susceptibility of Candida Isolates (n=815)

Year	No of isolates	Amphotericin-B	Caspofungin	Micafungin	Fluconazole	Voriconazole
2017	199	189 (95%)	178 (89.4%)	178 (89.4%)	159 (79.9%)	172 (86.4%)
2018	169	153 (90.5%)	153 (90.5%)	152 (89.9%)	142 (84.0%)	147 (87%)
2019	184	180 (97.8%)	170 (92.4%)	165 (89.7%)	160 (87%)	165 (89.7%)
2020	131	127 (96.9%)	117 (89.3%)	115 (87.8%)	109 (83.2%)	119 (90.8%)
2021	132	125 (94.7%)	118 (89.4%)	116 (87.9%)	92 (69.7%)	109 (82.6%)
p value		0.048	0.70	0.90	0.007	0.517

Table 3: Antifungal Susceptibilities of Predominant Candida Isolates, Over the Years

Year	Amphotericin B	Caspofungin	Micafungin	Fluconazole	Voriconazole
	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)
***Candida albicans* (n=166)**					
2017 (n=44)	42(95.4)	35(83.3)	36(83.7)	37(88.1)	37(88.1)
2018(n=36)	31(86.1)	33(91.6)	32(91.4)	30(83.3)	28(77.8)
2019 (n=39)	38(97.4)	38(97.4)	39(100)	37(94.9)	31(79.5)
2020 (n=29)	29 (100)	29 (100)	29 (100)	29 (100)	26 (88.9)
2021 (n=18)	18 (100)	18 (100)	18 (100)	18 (100)	15(83.3)
p value	0.054	0.03	0.009	0.06	0.12
Trend line					
***Candida tropicalis* (n=417)**					
2017 (105)	102(97.1)	99(94.2)	99(94.3)	84 (79.8)	87(82.9)
2018 (93)	91(100)	88 (97.8)	88(94.6)	86 (92.3)	87(93.5)
2019 (87)	84(96.5)	72 (90.7)	72(87.2)	70 (83.90	75(90.8)
2020 (60)	57 (95)	51 (90)	51(85)	52 (86.7)	56(93.3)
2021 (76)	75 (98.7)	75 (99.1)	74(97.3)	54 (71.1)	62(81.6)
p value	0.285	0.047	0.018	0.004	0.034
Trend Line					
***Candida parapsilosis* (n=130)**					
2017 (28)	25(88.2)	26(92.8)	23(85.1)	24(85.7)	26(92.8)
2018 (25)	22(88)	24(96)	23(95.8)	22(88)	21(84)
2019 (39)	39(100)	39(100)	39(100)	37(94.9)	38 (97.4)
2020 (25)	25(100)	25(100)	25(100)	19(76)	23 (92)
2021 (13)	13(100)	13(100)	12(92.3)	07(53.4)	10 (76.9)
p value	0.056	0.283	0.023	0.008	0.15
Trend Line					

2021) susceptibility towards candida isolates. This can be attributed to the fact that, in our hospital fluconazole is the most commonly used antifungal drugempirically, as these drugs are easy to administer with fewer side effects. Similar observation has also been reported by various studies from India with a high incidence of fluconazole resistance among all isolates of Candida species (31-64%).[2,20] Fluconazole resistance in Candida species is of concern because it is very often used as a therapeutic alternatives to amphotericin B. Further we noticed a decreasing trend in susceptibility of fluconazole to *C. parapsilosis* and *C. tropicalis* from a peak of 94.9% and 92.3% to 53.4% and 71.1%, respectively. On the other hand *C. albicans* showed an increase in susceptibility from minimum 83.3% in the year 2018 to 100% in 2021. Ahmet *et al* have also reported reduced susceptibility to fluconazole in most of the non-candidaalbicans species (NAC) as compared to *C.albicans*.[2]

Echinocandins are used as an alternative for the candida species resistant to azoles. However in recent years emergence of echinocandins resistance has been reported against Candida isolates. Sustained exposure of Candida isolates to these drugs may have contributed to decreased efficacy of echinocandins.[21]

In our hospital susceptibility of echinocandins varied from 85.2 to 91.4% over the five years of surveillance. In case of *C. albicans* a cross resistance has been observedbetween caspofungin and micafungin, as the trends in susceptibility of both the drugs are comparable over the years in the present study. The cross resistance amongst echinocandins has been reported and linked to FKS1 gene mutations.[22] Additionally during the year 2020-21, no *C. albicans* isolate was found to be resistant to echinocandins, in our study. Fuller *et al* have also reported 99.9% susceptibility of echinocandins to *C albicans*.[4] On the basis of available literature, it has been assessed that *C. tropicalis* is relatively less resistant

to echinocandins.[21] However in the present study variable resistance tocaspofungin and micafungin i.e.0.9%-10% & 2.7% -15% respectively, has been observed.

According to CLSI guidelines, MIC breakpoints in the case of *C. parapsilosis* and *C gullermondii*, for echinocandins are much higher than other common Candida species (S,I,R: <2 µg/ml, 4 µg/ml, >8 µg/ml vs < 0.25 µg/ml, 0.5 µg/ml, >1 µg/ml) Consequently repeated exposure to echinocandins may lead to the development of resistance.[17] On the other hand, in our study susceptibility of *C. parapsilosis*, to echinocandins has increased over the five years. This can be attributed to stringent antibiotic audits as per antibiotic policy of the hospital, during the recent years.

In conclusion, NAC species continuously replace *C. albicans* in causing blood stream infections (BSIs). The emergence of drug-resistance in Candida species has a significant clinical impact on the prognosis of the patients with candidemia specifically in elderly and immunocompromised patients. Therefore, continuous surveillance to strengthen the antibiotic stewardship policy is the key to minimizing the acquired antifungal resistance.

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