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Candidemia due to Non-Albicans Candida Species: Risk Factors, Species Distribution and Antifungal Susceptibility Profile

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Abstract

Background: Recent literature on invasive candidiasis clearly documents a shift towards non albicans *Candida* (NAC) species. A number of risk factors have been identified for candidemia. However the search through available literature has revealed paucity of data regarding differences between the C. albicans and NAC spp. candidemia.

Objective: The aim of this study was to investigate the epidemiology of candidemia and further analyze the risk factors, species distribution and antifungal susceptibility profile of NAC spp.

Results: Candida spp. was fifth among the leading causes of Blood stream infection. Predominance of NAC spp. was noted. *C. tropicalis* followed by C. glabrata were the major Candida isolates. ICU stay was the major risk factor associated with candidemia. Patients with candidemia due to NAC spp. were less likely to have diabetes compared those due to *C. albicans.* ICU stay and fluconazole prophylaxis/treatment were identified as significant risk for candidemia due to NAC spp. Azole resistance was significantly high in NAC spp. Conclusion: The emergence of NAC spp. highlights the importance of species identification along with antifungal susceptibility testing for institution of most appropriate antifungal drug.

Keywords Antifungal susceptibility testing; *Candida albicans*; Candidemia; Fluconazole

Introduction

Last few decades have witnessed a significant rise in the incidence of infections due to mycotic pathogens. Fungal infections have emerged as one of the important cause of morbidity and mortality in immunocompromised and terminally ill immunocompetent individuals [1].

Of various pathogenic fungi, *Candida* spp. is the most pervasive pathogen capable of causing a broad spectrum of clinical manifestations ranging from mucocutaneous overgrowth to disseminated infections [2]. Recent studies have documented the predominance of candidiasis among disseminated mycoses. In United States, *Candida* is fourth among the leading causes of blood stream infections (BSI) [3]. European studies on candidiasis have reported *Candida* as 6th to 10th cause of nosocomial BSI [3]. As only few single centric and no multi-centric studies are available from India, the scenario of candidemia remains largely unclear.

Recent literature on invasive candidiasis clearly documents a shift towards non albicans *Candida* (NAC) species. The emergence of NAC spp. has raised concern because NAC spp. often demonstrates intrinsic or acquired or both resistances to commonly used antifungal drugs [4].

A number of risk factors have been identified for *Candida* BSI. These include malignancy, central venous catheterization, total parenteral nutrition and urinary catheterization [5]. However the search through available literature has revealed paucity of data regarding differences between the *C. albicans* and NAC spp. BSI [6]. Therefore the present study was conducted in a rural tertiary care teaching hospital with an aim to investigate the epidemiology of candidemia and further analyse the risk factors, species distribution and antifungal susceptibility profile of NAC spp. isolated from BSI.

Materials and Methods

Study design

A hospital-based descriptive study was conducted in Department of Microbiology, Rural Medical College and Hospital of Pravara Institute of Medical Sciences (Deemed University), Loni, Maharashtra, India for a period of 9 years (January 2007 to December 2015). *Candida* spp. isolated from blood culture was included in the study. Institutional Ethics Committee approval was obtained for the study protocol. Patient's demographic features, underlying illness and associated risk factors were collected and analysed.

Species identification

Candida isolates were identified up to species level by germ tube test, sugar assimilation test and chromogenic assay on Hichrome Candida agar (Himedia Laboratories Pvt. Ltd. Mumbai, India). Hi Candida identification kit (Himedia Laboratories Pvt. Ltd. Mumbai, India) supplemented the species identification.

Antifungal susceptibility testing

The in vitro antifungal susceptibility testing of *Candida* isolates was performed by broth microdilution (BMD) as described in the Clinical and Laboratory Standards Institute (CLSI) reference method [7].

Candida isolates were tested against antifungal agents like amphotericin B, fluconazole, itraconazole and voriconazole.

Minimum inhibitory concentration (MIC) values were determined as the lowest concentration of drug that caused complete inhibition (amphotericin B) or a significant diminution (≥ 50% inhibition; azoles) of growth relative to that of growth control. Quality control was performed as recommended in CLSI document M27-A3 using *C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019 [7].

Clinical interpretive breakpoints (CBPs) were used evaluate susceptibilities of isolates against azoles. In case of fluconazole isolates showing an MIC of ≤ 8.0μg/mL were considered as sensitive, 16-32 μg/mL as susceptible dose dependent (SDD) and ≥ 64 μg/mL as resistant. For itraconazole, *Candida* isolates with MIC of ≤ 0.125 μg/mL were interpreted as sensitive, 0.25-0.5 μg/mL as SDD and ≥ 1.0 μg/mL as resistant. For voriconazole, Candida isolates with MIC of ≤ 1.0 μg/mL were taken as sensitive, 2.0 μg/mL as SDD and ≥ 4 μg/mL as resistant [8].

Due to lack of CBPs, epidemiological cut- off values (ECVs) were used for interpretation of susceptibility against amphotericin B. *Candida* isolates with MIC of ≤ 1.0 μg/mL were regarded as sensitive and those with MIC of >2.0 μg/mL were considered as resistant.

Statistical Analysis

Descriptive statistics was used to summarize demographic and other clinical features of patients. Qualitative and quantitative data values were expressed as frequency along with percentage. Association between two or more variables was assessed Chi-square test and Fisher's exact test as appropriate. A P<0.05 was considered as significant.

Results

Out of 4216 blood cultures processed in the Department of Microbiology, a total of 1486 (35.2%) were positive. Bacterial pathogens were isolated from 1249 (84.1%) specimens whereas, a total of 237 (15.9%) blood cultures showed growth of Candida spp.

In present study *Candida* spp. was fifth among the leading causes of BSI preceded by *Staphylococcus aureus, E. coli, Klebsiella spp., Pseudomonas spp*. The year wise distribution of *Candida spp.* is shown in Figure 1. Out 237 Candida spp. a total of 39 (16.4%) isolates were identified as *C. albicans* whereas 198 (83.6%) isolates belonged to NAC spp. Hence predominance of NAC spp. was noted in this study. Species wise distribution of *Candida* isolates is shown in Figure 2. *C. tropicalis* followed by *C. glabrata* were major *Candida* isolates. *C. rugosa* was isolated from 6 blood cultures.

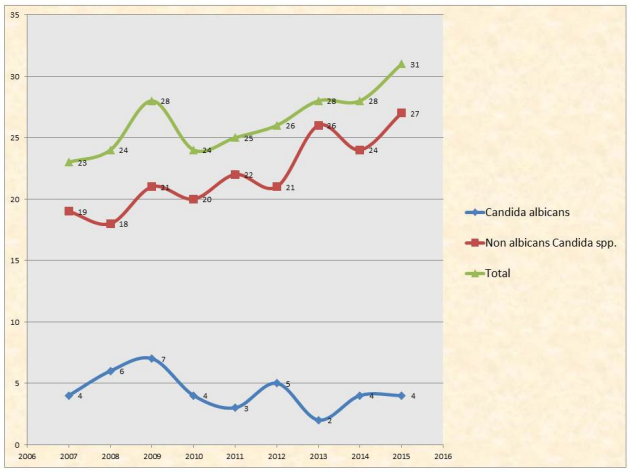

Figure 1: The year wise distribution of Candida spp.

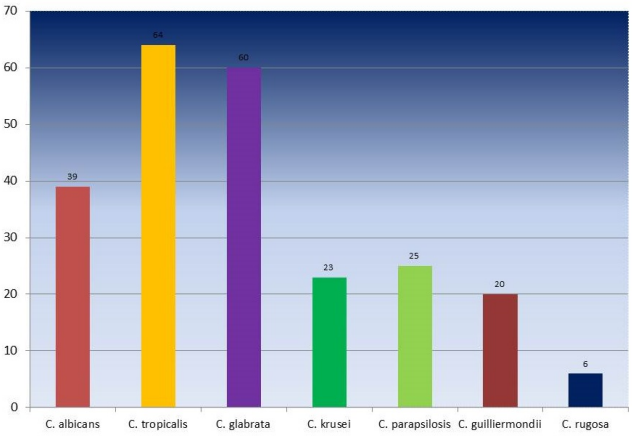

Figure 2: Species wise distribution of Candida isolates.

In the present study, the predominance of male patients was noted. The male to female ratio was 4:1. Majority of *Candida* spp. were isolated from adults patients (75.5%) followed by patients of age group <1 year (13.1%) whereas 11.4% strains were isolated age group 1-15 years. The mean age of patients was 48.2 years (range 7 days-86 years). ICU stay was the major risk factor associated with candidemia. The mean ICU stay of candidemia patients was 8.4 days. Malignancy (19.4%) followed by diabetes (17.2%) were the most common underlying co-morbidities. Other co-morbidities were liver cirrhosis, low birth weight and burns.

Underlying co-morbidities and risk factors associated with candidemia due to *C. albicans* and NAC spp. is shown in Table 1. Patients with candidemia due to NAC spp. were less likely to have diabetes compared to patients with candidemia due to *C. albicans* (Fisher's exact test exact test, P value<0.0001) while other underlying co-morbidities showed no significant difference between candidemia due to *C. albicans* and NAC spp. ICU stay (Fisher's exact test exact test, P value<0.0001) and fluconazole prophylaxis/treatment (Fisher's exact

test r exact test, P value 0.0006) were identified as significant risk for candidemia due to NAC spp.

Characteristics	Total	C. albicans	NAC spp	P value (Fisher's exact test)
Underlying co-morbidity				
Malignancy	46	09 (19.6)	37 (80.4)	0.51
Liver cirrhosis	32	14 (43.7)	18 (56.3)	0.19
Preterm infants with LBW	24	04 (16.7)	20 (83.3)	1
Diabetes	41	36 (87.8)	05 (12.2)	<0.0001*
Burn	18	02 (11.1)	16 (88.9)	0.2
Underlying risk factors				
ICU stay	197	14 (7.1)	183 (92.9)	<0.0001*
Mechanical ventilator support	99	03 (11.5)	23 (88.5)	0.486
Urinary catheterization	147	03 (9.4)	29 (90.6)	0.09
Total parenteral nutrition (TPN)	42	01 (11.1)	08 (88.9)	1
Central-venous catheterization	14	02 (14.3)	12 (85.7)	1
Surgery	82	02 (11.1)	16 (88.9)	0.7
Fluconazole prophylaxis/treatment	94	06 (6.4)	88 (93.6)	0.0006*

Table 1: Comparison of underlying co-morbidities and risk factors associated with candidemia due to *C. albicans* and NAC spp.

Antifungal susceptibility profile of *Candida* spp. is shown in Table 2. As compared to amphotericin B, *Candida* spp. demonstrated high resistance to azole group of antifungal agents. Among azoles, Candida spp., demonstrated good sensitivity against voriconazole (96.2%) followed by itraconazole (88.2%). Fluconazole resistance was seen in a total of 44 (22.2%) of isolates. Azole resistance was significantly higher among NAC spp. (Fischer exact test, P value 0.006) compared to *C. albicans* whereas; there was no significant difference for amphotericin B resistance.

Species	Antifungal agent	MIC (µg/ml)			No. of isolates		
		Range	MIC 50	MIC 90	S (%)	SDD (%)	R (%)
C. albicans **(n=39)**	Fluconazole	0.125-256	0.5	4	32 (82.1)	04 (10.2)	03 (7.7)
	Itraconazole	0.03-16	0.12	0.25	35 (89.7)	03 (7.7)	01 (2.6)
	Voriconazole	0.008-16	0.016	0.032	37 (94.9)	02 (5.1)	-
	Amphotericin B	0.12-8	0.25	0.25	38 (97.4)		01 (2.6)
Non albicans *Candida* **spp. (n=198)**	Fluconazole	0.125-256	8	32	138 (69.7)	16 (8.1)	44 (22.2)
	Itraconazole	0.015-16	0.12	0.25	174 (87.9)		24 (12.1)
	Voriconazole	0.008-16	0.12	0.5	191(96.5)	03 (1.5)	04 (2)
	Amphotericin B	0.12-8	0.25	0.25	197 (99.5)		01(0.5)
Total (n=237)	Fluconazole	0.125-256	4	32	170 (71.7)	20 (8.5)	47 (19.8)
	Itraconazole	0.015-16	0.12	0.25	209 (88.2)	03 (1.3)	25 (10.5)
	Voriconazole	0.008-16	0.032	0.5	228 (96.2)	05 (2.1)	04 (1.7)

	Amphotericin B	0.12-8	0.25	0.25	235 (99.2)		02 (0.8)

Table 2: Antifungal susceptibility profile of Candida spp.

Table 3 shows antifungal susceptibility profile of NAC spp. Fluconazole resistance was significantly high (Fisher's exact test, P value<0.0001) in *C. krusei* compared to other NAC spp. A total of 02 (8.7%) *C. krusei* were found to be SDD to fluconazole. Amphotericin B resistance was noted in a single isolated of *C. glabrata*. A total of 9 (14.1%) *C. tropicalis* isolates showed resistance to fluconazole. All isolates of *C. rugosa* were sensitive to azoles and amphotericin B.

NAC spp.	Antifungal agent	MIC (µg/ml)			No. of isolates		
		Range	MIC 50	MIC 90	S (%)	SDD (%)	R (%)
C. tropicalis **(n=64)**	Fluconazole	0.125-128	4	16	50 (78.1)	05 (7.8)	09 (14.1)
	Itraconazole	0.015-16	0.12	0.25	60 (93.7)		08 (12.5)
	Voriconazole	0.008-16	0.064	0.256	61 (95.3)	01 (1.6)	02 (3.1)
	Amphotericin B	0.12-4	0.25	0.25	64 (100)		-
C. glabrata **(n=60)**	Fluconazole	0.5-256	4	32	42 (70)	09 (15)	09 (15)
	Itraconazole	0.06-16	0.12	0.5	52 (86.7)		08 (13.3)
	Voriconazole	0.008-16	0.25	1	57 (96.1)	02 (1.6)	01 (2.3)
	Amphotericin B	0.12-8	0.25	0.25	59 (98.3)		01 (1.7)
C. krusei **(n=23)**	Fluconazole	Apr-64	64	64	-	02 (8.7)	21 (91.3)
	Itraconazole	0.125-2	0.125	0.25	12 (52.2)		11 (47.8)
	Voriconazole	0.015-5	0.064	0.5	22 (96.3)		01 (2.7)
	Amphotericin B	0.25-2	0.25	0.25	23 (100)		-
C. guilliermondii **(n=20)**	Fluconazole	0.5-8	2	4	19 (95)		01 (5)
	Itraconazole	0.06-2	0.12	0.12	20 (100)		-
	Voriconazole	0.008-0.25	0.25	0.5	20 (100)	-	-
	Amphotericin B	0.25-2	0.25	0.25	20 (100)		-
C. parapsilosis **(n=25)**	Fluconazole	0.125-64	1	8	21 (84)	-	04 (16)
	Itraconazole	0.03-0.5	0.12	0.12	24 (96)		01 (4)
	Voriconazole	0.008-0.125	0.032	0.12	25 (100)	-	0
	Amphotericin B	0.25-4	0.25	0.25	25 (100)	-	0
C. rugosa **(n=06)**	Fluconazole	0.125-256	2	2	6	-	0
	Itraconazole	0.03-16	0.12	0.12	6		0
	Voriconazole	0.008-16	0.032	0.032	6	-	0
	Amphotericin B	0.12-8	0.25	0.25	6	-	0

Table 3: Antifungal susceptibility profile of non albicans *Candida* spp.

Discussion

Many reports in recent years have highlighted increase in the incidence of mycoses in general and candidiasis in particular. Among various clinical types of candidiasis, candidemia is usually associated with high mortality rates. It is also significantly increases health-care costs and duration of hospital stay [9].

Studies available from various parts of the world either claim an increase or a decrease or no change in the incidence of candidemia. Most of these studies are from large health-care setups of developed

countries. The present study reports the scenario of candidemia with special reference to risk factors, species distribution and antifungal susceptibility profile of NAC spp. from a rural tertiary care teaching hospital of Maharashtra, India.

In the current study, *Candida* spp. was the fifth most common pathogen isolated from BSI. Verma, et al. (2003) from north India reported *Candida* spp. to be 8th among all pathogens causing BSI [10]. Although not as prevalent as bacterial BSI, candidemia is often associated with high morbidity and mortality rates in individuals with compromised immune status and terminally ill immunocompetent patient [9]. Additionally it also significantly increases the duration of hospitalization and mechanical ventilation. Only a few Indian studies have reported Candida BSI rates of 6-18% [5]. In the present study the rate of Candida BSI was 15.9%.

In accordance to various studies from different parts of world, the present report also documents the predominance of NAC spp. over *C. albicans.* Several factors are implicated for emergence of NAC spp. These include empirical prophylactic and therapeutic use of azoles, use of chromogenic media and commercially available user-friendly kits for rapid identification of yeasts and yeast like fungi [11].

Available literature on species distribution of *Candida* has pointed out the significant variation with respect to frequency of isolation of NAC spp. from BSI. The highest proportion of *C. parapsilosis* is reported from some hospitals of North America and Europe whereas; the incidence of infection due to *C. glabrata* was reported to high in studies from US and North and Central Europe [12]. The species distribution in Asia varies greatly by the geographic region and type of health-care setup [12].

In the present study, *C. tropicalis* was the predominant Candida spp. isolated from BSI. This finding is in consistent to that of other researchers from India [13,14]. *C. tropicalis* was isolated from 27.1% of cases of candidemia. Epidemiological studies from India have reported this NAC spp. in as many as 67-90% cases of Candida BSI [5]. *C. tropicalis* is often isolated from ICU patients. Prolonged catheterization and broad spectrum antibiotic therapy are risk factors associated with *C. tropicalis* infections [15].

Various studies on candidemia have reported isolation rate of *C. glabrata* from 8 to37% [4]. The rate of isolation of C. glabrata in the present study was 25.3%. Unlike other *Candida* spp., this organism is haploid and lacks the ability of hyphae or pseudohyphae formation [16]. Like *C. albicans*, this NAC spp. is also a commensal of human genitourinary and gastrointestinal tract [17]. Though, C. glabrata is less virulent than *C. albicans* and other commonly isolated NAC spp., it is usually associated with higher mortality rates [16].

C. guilliermondii was previously considered as an animal saprophyte with minimal or no role in human infection [4]. However, in recent years the overall proportion of *C. guilliermondii* infections has increased. The published data on Candida BSI has reported the isolation of this NAC spp. between 0.7 to 5.5% [4]. In the present study, *C. guilliermondii* was isolated from 20 (8.4%) cases of candidemia. *C. guilliermondii* is considered as a rare cause of disseminated candidiasis. As this study was confined to a single health-care setup, our observation underscores the need of multicentric studies to know whether the emergence of this NAC spp. is restricted to our hospital or it also holds true for other health-care setups in India [18].

C. rugosa is an animal pathogen and causes mastitis in cattle [4]. In the present study, *C. rugosa* was isolated from 06 (2.5%) blood cultures. Out of these, 3 were from burn patients. *C. rugosa* is a relatively less common cause of BSIs. Oberoi et al. (2012) from New Delhi, India reported isolation of C. rugosa from 9 cases of BSI [19]. *C. rugosa* has been implicated as a cause of nosocomial BSI in burn and critically ill patients.

Candidiasis is rarely encountered as a primary infection. It is usually seen as a secondary infection in patients with some underlying immunocompromised conditions. A variety of factors are known to predispose disseminated candidiasis. Some of these factors facilitate colonization of tissue whereas, other favours bloodstream invasion. In the present study, ICU stay was the major risk factor associated with candidemia. This observation is in accordance to various investigators [6,14,20]. Almost similar results were reported by the National Epidemiology of Mycoses survey (NEMIS) group [21]. Incidence of candidemia in ICU might be high due to more severely ill and immunocompromised patients being cared for in the unit with most of them being on life support systems.

In the present study, patients with candidemia due to NAC spp. were less likely to have diabetes compared to those due to *C. albicans* while other underlying co-morbidities showed no significant difference Candidemia due to *C. albicans* and NAC spp. similar observation was reported by Wu et al. (2014) [6]. ICU stay and fluconazole prophylaxis/ treatment were identified as major risk for candidemia due to NAC spp. The preponderance of NAC spp. compared with *C. albicans* in ICU patients is reported by various researchers. The issue of role of antifungal prophylaxis/treatment and emergence of NAC spp. was addressed by many studies. Investigators like Verma et al. (2003) have identified a highly significant association between prior fluconazole therapy/prophylaxis and candidemia due to NAC spp [10].

Several classes of antifungal drugs (azoles, echinocandins and polyenes) are available for treatment of candidemia. The choice of antifungal drug depends on various factors the local epidemiology and the patient's co-morbidities. The emergence of NAC spp. has initiated the need of antifungal susceptibility testing of *Candida* isolates. In this study, NAC spp. demonstrated significantly high resistance to azoles compared to *C. albicans.* In contrast to *C. albicans,* antifungal susceptibility varies significantly in NAC spp. Some NAC spp. are inherently or secondarily resistant to antifungal agents [11].

Fluconazole resistance was observed in 19.8% of *Candida* isolates. Resistance to fluconazole is of concern because it is one of the most widely used first line antifungal agents for treatment and prophylaxis of all forms of candidiasis [11].

Fluconazole resistance was high among *C. krusei* (91.3%). Various national and international studies have reported total fluconazole resistant *C. krusei* isolates [18]. In general, *C. krusei* is primarily resistant to fluconazole [4]. However, studies of Bille et al. (1997) and Chakarbarti, et al. (1999) showed that this not always the case [22,23].

In the present study, 8.7% of *C. krusei* isolates SDD to fluconazole. Bille et al. (1997) reported 45% of *C. krusei* as SDD to fluconazole [22]. SDD is a novel interpretive category relates to yeast testing only and is not interchangeable with the intermediate category associated with bacterial and 5-fluorocytosine (5FC) breakpoints [18]. By maintaining blood levels with higher doses of the antifungal, an isolate with SDD endpoint maybe successfully treated with a given azole.

In the present study, fluconazole resistance was noted in 14.1% of *C. tropicalis* isolates. *C. tropicalis* was initially regarded as fluconazole susceptible species; however the scenario has changed over the period

of last few years [24]. The increasing rate of fluconazole resistance in *C. tropicalis* is important because it is one of the most commonly isolated NAC spp. As the reason for rapid emergence of fluconazole resistance in *C. tropicalis* is unclear, the need of further studies is underscored.

In the present study, amphotericin B resistance was noted in only 02 (0.8%) *Candida* isolates, which included a single, isolate each of *C. albicans* and *C. glabrata.* Montagna et al. (2014) reported high amphotericin B resistance in *C. glabrata* isolates compared to other NAC spp [25]. Although *C. albicans* is susceptible to amphotericin B, Montagna et al. (2014) reported the emergence of amphotericin B resistant *C. albicans* strains [25].

To conclude, to best of our knowledge the present is first to report the scenario of *Candida* BSI with emphasis on risk factors, species distribution and antifungal susceptibility profile of NAC spp. from rural part of India. The emergence of NAC spp. highlights the importance of species identification along with antifungal susceptibility testing for institution of most appropriate antifungal drug.

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