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COMPARISON OF INCIDENCE, RISK FACTORS, OUTCOME AND ANTIFUNGAL SUSCEPTIBILITY BETWEEN *CANDIDA ALBICANS* AND NON-*ALBICANS CANDIDA* SPECIES IN PATIENTS OF CANDIDEMIA IN INTENSIVE CARE SETTING

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ABSTRACT: Candidemia is associated with a high mortality. The most common cause of candidemia is *Candida albicans*, though infections by non-*albicans Candida* are being increasingly reported. The present study was conducted to determine the incidence of candidemia, the risk factors and antifungal susceptibility in intensive care unit (ICU). This study was conducted from January 2012 to June 2013 and prospectively included patients admitted in ICU for >48 hours. The blood culture isolates were identified as per standard mycological procedures and DNA (26S rDNA) sequencing. Antifungal susceptibility test was carried out by broth micro-dilution method in accordance with CLSI standards. A total of 48 isolates were identified in 1890 ICU admissions. Majority of the isolates were identified as non-*albicans Candida i.e.* 38 out of 48 isolates which is 79.2% while only 10 isolates were that of *Candida albicans i.e.* 20.8%. Among the non albicans species, *Candida tropicalis* (42.1%) was the predominant one followed by *Candida rugosa* (26.3%), *Candida parapsilosis* (15.8%) while *Candida pelliculosa*, *Candida glabrata*, *Candida lusitaniae* and *Kodamea ohmeri* were identified from one case each *i.e.* 2.6% and two were *Candida auris* (5.3%). The association of central venous catheter with non-*albicans Candida* species was found to be statistically significant (P = 0.01). There was significant resistance among *Candida auris* and *Candida rugosa* isolates to commonly used antifungals hence it is important to diagnose the infection during its early course for a good outcome.

INTRODUCTION: Candidemia usually occurs in immuno-compromised and/or hospitalised patients. The most common cause of candidemia is *Candida albicans*, though infections by non-*albicans Candida* such as *C. glabrata, C. krusei, C. parapsilosis* and *C. tropicalis* are also on the rise [1].

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Candida species are the fourth most common cause of blood stream infections after coagulase-negative Staphylococci, *Staphylococcus aureus* and *Entero cocci* in intensive care units (ICU) in the United States as per the National Nosocomial Infection Surveillance program.

Candidemia is not only associated with high mortality rates (30 - 40%) but also increases the duration of hospital stay thereby cost of the medical care [2]. During the past decade, the incidence of candidemia has increased substantially which is likely due to an increased prevalence of susceptible hosts, prolonged hospitalisation as in ICU,

immunosuppressive therapies and transplantation procedures [3]. Major risk factors for candidemia include intravascular catheters, parenteral hyperalimentation and broad-spectrum antibiotics use [1]. India has a high prevalence of candidemia due to a number of contributory factors like favourable climatic conditions, a large population of immuno-compromised patients including diabetics, people with HIV/AIDS, steroids and antibiotics misuse [4].

Candida albicans remains the most common species implicated in candidemia and is usually susceptible to fluconazole. Other species are less susceptible to azoles and therefore rather costly alternatives like echinocandins have to be used for non-*albicans Candida* species. Thus, differentiation between the *albicans* and non-*albicans Candida* is important to plan the treatment [1]. A substantial delay in therapy may almost double the risk of death [5].

A marked increase in the incidence of non-*albicans Candida* species is being reported from many countries nowadays probably due to use of triazoles as prophylactic therapy. Although it led to a decrease in use of parenteral antifungals as well as reduction in incidence of both superficial and invasive candidiasis but it led to an emergence of non-*albicans Candida* strains like *Candida krusei* which is intrinsically resistant to some triazoles and *Candida glabrata* which responds only to their higher doses [6].

Certain new species have been identified as emerging causes of candidemia in hospitalised patients like *Candida auris* and *Candida rugosa* which are usually found to be resistant to fluconazole. These species are also important because they are often misidentified and confirmation is possible only by DNA sequencing. Vitek 2 system cannot differentiate between *Candida auris* and identifies it as *Candida haemulonii* [7]. In view of these facts it becomes important to identify the species involved in candidemia in time to initiate the treatment at the earliest. The present study was conducted to determine the incidence of candidemia, risk factors associated with different *Candida* species and determine the antifungal susceptibility of the isolates from these cases.

MATERIAL AND METHODS: This study was conducted in the Department of Microbiology in collaboration with the Departments of Anaesthesia and Intensive Care and the Department of Paediatrics, Government Medical College Hospital, Chandigarh. Study was conducted for a period of eighteen months from January 2012 to June 2013 on all consecutive cases. Patients admitted in intensive care unit for >48 hours were included.

Clinical Information: The data collected included demographic details, risk factors like broad spectrum antibiotic use, use of invasive mechanical ventilation, central venous line, urinary catheterisation, prosthetic devices, previous gastrointestinal surgery, dialysis, diabetic status, organ transplantation, ICU days and other site candidiasis. In case of neonates, history of preterm birth and low birth weight were also recorded.

Microbiological Examination: Blood was collected for culturing after taking all the aseptic precautions and inoculated into biphasic blood culture bottles containing brain heart infusion (BHI) broth and BHI Agar slant. Subcultures were done on Sabouraud dextrose agar (SDA) tube slants with chloramphenicol and gentamicin after 24 hrs, 48 hrs and a week. Once the growth was seen, isolates were identified as per standard mycological procedures.

Germ tube test was done for presumptive identification into *albicans* and non-*albicans Candida* species, culture on CHROMAgar, sporulation on corn meal agar, sugar fermentation and assimilation tests were put up. The isolates were also sent to PGIMER, Chandigarh where 26S rDNA sequencing was done, results of which were considered as final. Antifungal susceptibility testing was carried out for all isolates by broth micro-dilution method in accordance with CLSI M27-A3 standards [8].

Statistical Analysis: Analyses were conducted using SPSS for Windows (version 17.0; SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as the mean ± SD and categorical variables as percentage. The continuous variables were compared by independent t test and categorical variables were compared by chi square test and fisher exact test between the two groups.

All statistical tests were performed at a significance level of α = .05 (two-sided) and the difference was considered significant if the p value was <0.05.

OBSERVATIONS AND RESULTS: During the study period a total of 720 patients were admitted in adult ICU, 540 were admitted in PICU and 630 neonates were admitted in NICU for more than 48 hours. An overall incidence of candidemia was found to be 2.5%. The incidence in adult ICU was found to be 5.8% or 58 cases per 1000 admissions while for PICU and NICU, it was 3.7 cases per 1000 admissions and 6.3 cases per 1000 admissions, respectively. For the results, the data was pooled from both the ICUs. The mean age of the patients was found to be 43.35 ± 23.57 years, 52.1% were males and 47.9% were females.

Majority of the isolates were identified as non-*albicans Candida i.e.* 38 out of 48 isolates which is 79.2% while only 10 isolates were that of *Candida albicans i.e.* 20.8%. *Candida tropicalis* (42.1%) was the predominant species while *Candida rugosa* constituted 26.3% of the isolates. Other species like *Candida pelliculosa, Candida glabrata, Candida lusitaniae* and *Kodamea ohmeri* were identified from one case each with a percentage of 2.6% each among the non-*albicans Candida.* Another species *Candida parapsilosis* constituted 15.8% while two *i.e.* 5.3% of the isolates were *Candida auris.*

Among isolates of *Candida albicans*, 90% were isolated from male patients and 10% from females while from a total of 38 strains of non-*albicans Candida*, 42.1% were isolated from males while 57.9% from females. The difference in gender distribution between these two groups was statistically significant (p = 0.01). Few species were found in females only like *Candida parapsilosis, Kodamea ohmeri* and *Candida lusitaniae* while certain species like *Candida pelliculosa* and *Candida glabrata* were isolated from male patients only **Table 1**.

In order to see the seasonal effect on occurrence of candidemia cases we calculated the number of cases per month in four seasons. The frequency was 3.75 in rainy, 4 in autumn, 1.8 in summer and 2 in winter.

TABLE 1: GENDER DISTRIBUTION OF CANDIDA SPECIES

Species	Males	Females	p value 0.01
***Candida albicans* (10)**	**9**	**1**	
Non albicans candida(38)	16	22	
Candida tropicalis	8	8	
Candida rugosa	5	5	
Candida parapsilosis	0	6	
Candida auris	1	1	
Candida pelliculosa	1	0	
Candida glabrata	1	0	
Candida lusitaniae	0	1	
Kodamea ohmeri	0	1	

Risk factors like invasive mechanical ventilation (IMV), broad-spectrum antibiotic use (BSA), uretheral catheter (UC) were present in all the patients in both *albicans* and non-*albicans* group while central venous catheter was present in 66.7% (32 out of 48) of cases but a higher percentage (78.9%) was seen in non-*albicans Candida* group than in *albicans* group. The association of CVC with non-*albicans Candida* species was found to be statistically significant (p = 0.01). It was present in all the patients of candidemia due to *C. parapsilosis* (100%; 6/6), *C. lusitaniae* (100%; 1/1) and in 75% and 70% of those due to *C. tropicalis* and *C. rugosa*, respectively **Table 2**.

TABLE 2: PREVALENCE OF RISK FACTORS IN CANDIDEMIA PATIENTS

Risk factors	Overall Percentage (numbers) (n = 48)	*Candida albicans* percentage (numbers) (n = 10)	Non-*albicans Candida* percentage (numbers) (n = 38)	p value
Invasive mechanical ventilation	100 (48)	100 (10)	100 (38)	1.00
Broad spectrum antibiotics use	100 (48)	100 (10)	100 (38)	1.00
Urinary indwelling catheter	100 (48)	100 (10)	100 (38)	1.00
Central venous catheter	66.7 (32)	20 (2)	78.9 (30)	0.001

Previous Gastrointestinal surgery	29.2 (14)	20 (2)	31.6 (12)	0.70
Other surgery	16.7 (8)	20 (2)	15.8 (6)	0.66
Diabetes mellitus	14.6 (7)	30 (3)	10.5 (4)	0.14
Steroid use	18.8 (9)	20 (2)	13.4 (7)	1.00
Trans-parenteral nutrition	33.3 (16)	20 (2)	36.8 (14)	0.46
Other site candidiasis	47.9 (23)	40 (4)	50 (19)	0.71
Haemodialysis	6.3 (3)	0	7.9 (3)	1.00
Previous antifungal use	2.1 (1)	0	2.6 (1)	1.00
Concomitant bacterial infection	68.8 (33)	60 (6)	71.1(27)	0.70
Duration in ICU[#] till development of candidemia* (mean ± SD in days)		10.5 ± 6.1	18.03 ± 13.94	0.06

Intensive care unit, * Development of candidemia corresponds to culture positivity

Other risk factors like previous gastrointestinal surgeries, other surgeries, diabetes mellitus, steroid use, total parenteral nutrition (TPN), other site candidiasis, haemodialysis, previous antifungal use and concomitant bacterial infection were present in both groups in various proportions but there was no significant difference statistically. The duration of stay in ICU was studied and analyzed to see the impact of longer duration of stay as a risk factor for Candidemia with *Candida albicans* and non-*albicans Candida* species.

The patients who developed candidemia with non-*albicans Candida* stayed for longer with mean duration of 31.39 ± 21.56 days as compared to candidemia with *Candida albicans* who stayed for 21.60 ± 12.18 days in the ICU. The mean duration of stay till development of candidemia was found to be 10.5 ± 6.1 days for *Candida albicans* and 18.03 ± 13.94 days for non-*albicans Candida* candidemia and the difference was statistically not significant (p = 0.06). Among the cases of *Candida albicans*, 70% patients died while in non-*albicans Candida* group, 41.4% patients expired. These differences in results were statistically non-significant (p = 0.30).

All the isolates were susceptible to amphotericin B, voriconazole, posaconazole, anidulafungin and micafungin. All the *C. albicans* isolates were susceptible to all the antifungal agents. Both the *Candida auris* isolates were resistant to fluconazole. As shown in the **Table 3**, the resistance to itraconazole was maximum followed by caspofungin and fluconazole. The percentage of resistance to itraconazole among the isolates was maximum i.e. 16.67% among all the antifungal agents (8 out of 48 isolates) while caspofungin resistance was also observed to be 6.25% *i.e.* 3 out of a total of 48 isolates. The species *Candida tropicalis* (4), *Candida rugosa* (1), *Candida auris* (2) and *Candida pelliculosa* (1) were resistant to itraconazole. Caspofungin resistance was seen in 2 isolates of *Candida rugosa* and one isolate of *Candida auris.*

TABLE 3: PERCENTAGE OF RESISTANCE TO VARIOUS ANTIFUNGAL DRUGS

Antifungal agent	Resistant isolates (%), n = 48	Species (numbers)
Fluconazole	4.16%	*Candida auris* (2)
Itraconazole	16.67%	*Candida auris* (2), *Candida rugosa* (1), *Candida tropicalis* (4), *Candida pelliculosa* (1)
Voriconazole	0	-
Posaconazole	0	-
Anidulafungin	0	-
Caspofungin	6.25%	*Candida auris* (1), *Candida rugosa* (2)
Micafungin	0	-
Amphotericin B	0	-

DISCUSSION: Incidence of candidemia has been found to be lower in our institute than that reported in other studies. A similar study conducted by Sahni *et al.*, from Maulana Azad Medical College, New Delhi found the incidence rate of candidemia in to be 6.9% in the hospital settings [7]. In a 5 year study from All India Institute of Medical Sciences (AIIMS), New Delhi, Xess *et al*., found the prevalence of candidemia to be 6% [9]. Thus, compared to the Indian scenario our institution has

a lower incidence which might be due to better infection control measures like surveillance, training of staff, patient segregation, implementation of hand hygiene practices, catheter care which are being followed.

A study conducted in a Greek ICU reported an incidence of 3.8% in ICU [10]. In the present study the incidence in adult ICU was found to be 5.8% or 58 cases per 1000 admissions. This rate is lower than that reported by Bassetti *et al., i.e.* 173 episodes per 1000 admissions [11]. This may be due to lesser exposure of the patients to the ICU environment in our country as compared to the developed parts of the world. Incidence of candidemia varies among the studies depending on the patient selection and hospital settings. Some other studies from Northern hemisphere have also quoted a lower incidence, which can be explained by better implementation of the infection control measures and training of staff and medical personnel [12].

We observed a higher frequency of cases in rainy and autumn season the cause of which is not clear but may be attributed to higher moisture content in the air resulting in conductive environment for infections which become invasive in a suitable host. We observed an increased incidence of non-*albicans Candida* (79.2%) while *Candida albicans* constituted 20.8% of the isolates. In the previous studies, *C. albicans* was the predominant species causing blood stream infections. In a retrospective study conducted in Canada, it was observed that the *C. albicans* species constituted the majority of the isolates during the period from 1992 to 1996 [13].

Recently a change in this pattern has been observed and many studies have documented a rise in non-*albicans Candida* species. In a study conducted to evaluate the epidemiological trends in nosocomial candidemia in Italy. (from 1999 to 2003) it was observed that the percentage of *C. albicans* dropped from 60% to 24% with a median percentage reduction of 13% during the study period while the percentage of non-*albicans Candida* species increased from 21% to 67% during the latter half of the study period [14]. Similar distribution pattern has been observed in our study in which non-*albicans Candida* have been found to be more prevalent.

In a study conducted by Pratikaki *et al.*, it was observed that 66.7% of the cases of candidemia were due to non-*albicans Candida* species alone. Our findings too are in agreement with their results [10]. In our study, majority among non-*albicans Candida* was observed for *Candida tropicalis* for which the percentage was 42.1%. In the Indian scenario, *C. tropicalis* has emerged as the most common cause of nosocomial candidemia in the past few decades and it has been implicated in 67-90% of the cases of candidemia in various epidemiological studies. The increased use of fluconazole has been observed to be the major cause of predominance of non-*albicans Candida*, mainly for *C. tropicalis*. It was also found to be the most common cause of candidemia in 2 studies from South India by Shivaprakasha *et al*., and Adhikary *et al.*, which observed (35.6% and 39.7%, respectively) [15]. Xess *et al*., from AIIMS, New Delhi also found *C. tropicalis* to be the most common species of *Candida* in blood isolates during the five year study from Northern India [9].

An Indian study conducted in 2010 analysed 825 cases of suspected neonatal septicaemia and observed the emergence of non-*albicans Candida*, *C. tropicalis* being most common as a cause of septicaemia [16]. The present study also demonstrated *C. tropicalis* as the most prevalent *Candida* species although different results have been quoted from other parts of the world [11]. This may be due to difference in geographical prevalence of this species.

Candida rugosa is also an emerging fungus which was first identified as a cause of catheter related fungemia in US in1985 [18]. Recently, *C. rugosa* has been cited as an emerging species causing candidemia. A study by Dube *et al.*, reported 15 cases of candidemia due to *C. rugosa* in burn patients in a US hospital [19]. Our study has revealed a high incidence of this *Candida rugosa* species *i.e.* 26.3% which may be due to better laboratory capabilities to identify this species. Two of the ten isolates were found to be resistant to caspofungin but not to azoles which is in contrast to the previous studies which reported the species to be less susceptible to azoles. Another newer finding in this study is the revelation of *C. auris* as a rare causal agent of candidemia which has been reported in a study of Delhi conducted by

Chaudhary *et al.,* which reported a case series of 12 candidemia episodes from two hospitals from 2009 to 2011 [20]. All the isolates were reported to be resistant to fluconazole and the mortality rate was high (33%). C*andida auris* was first identified in a Japanese patient from external ear in 2009 by sequencing of nuclear rRNA [21]. Fifteen isolates of this species were reported from otitis media patients in South Korea in the same year but fungemia was rare in this series [22]. Isolates from our study were resistant to azoles and one of these was resistant to caspofungin also.

We also found a single case of fungemia due to *Kodamaea ohmeri* species. The first case of fungemia due to this species was reported in 1998 [23]. It was initially thought to be an environmental isolate and is phenotypically similar to *Candida tropicalis.* Majority of the cases have been reported from immuno-compromised patients, a case series published by Capoor et al from Delhi also reported a case of Kodamaea ohmeri fungemia in a patient with haematological malignancy [24]. The largest case series of 30 cases of fungemia due to this species was recently published from India [25]. It has been shown to be usually susceptible to antifungals. In our study also, the isolate was susceptible to azoles but had a higher MIC value (4.0 µg/ml) for fluconazole. One of the isolates in the present study was identified as *Candida lusitaniae* and it was susceptible to the antifungals. It is thought to be less susceptible to polyenes due to defect in ergosterol biosynthesis.

In the present study we have found that *C. glabrata* constituted a very low proportion of the isolates (2.6%, n = 1) and none of the isolates was *C. krusei* while most of the studies have reported a high incidence of the candidemia due to these species [26]. The lower incidence observed in our study may be due to infrequent use of prophylactic fluconazole therapy which is a much more common practice in the other parts of the world. Moreover *C. glabrata* has been found to be associated with older age group and in this study, lesser number of the patients were in this age group.

Various studies have been conducted to evaluate the risk factors which may predispose to candidemia are associated with it. A study conducted by Yapar *et al.,* in 2011 found that the presence of urethral catheter, previous use of antibiotics, red blood cell transfusions and total parenteral nutrition are independently associated with candidemia [27]. The study also reported an increased risk of *C. albicans* candidemia with neutropenia and surgical procedures. In a prospective study conducted in Athens, the use of glucocorticoids, central venous catheters and candiduria were found to be independently associated with candidemia due to non-*albicans Candida* species [10]. We have evaluated essentially the same risk factors in the present study except neutropenia because none of the patients included in the study had neutropenia prior to or after developing candidemia. When we compared risk factors in *albicans* and non-*albicans* group, we found association of female gender and central venous catheter with non-*albicans Candida* to be statistically significant.

Indwelling vascular catheters have been implicated as an important risk factor in candidemia patients worldwide. The *Candida* species strongly adhere to materials used in intravascular devices and provide a potential nidus of infection. In the present study central venous catheter was present in 66.7% of candidemia patients. Our results are in agreement with the study conducted by Giri *et al.,* which found central venous catheter as a risk factor in 56.4% of candidemia patients [28]. In another study conducted by Chow *et al*, central venous catheter was found to be associated with 90% of candidemia patients [1]. Central venous catheter was present in 80% of non *albicans Candida* candidemia cases of which all cases of candidemia due to *Candida parapsilosis* were associated with the presence of a central line. This is in agreement with many studies which have found the association of central venous catheters with candidemia due to non *albicans Candida* [1].

In the present study *C. albicans* was associated with male gender while non-*albicans Candida* was associated with female gender. In *albicans* group 90% were male while in non-*albicans* group 57.9% were female. This difference in gender was found to be statistically significant (p = 0.01). This is in agreement with report of Holley *et al.*,[29] In contrast, Davis *et al.,* reported association of male gender with non-*albicans Candida* while Chow *et al.,* reported no gender preponderance [1, 30].

The association of female gender with non-*albicans Candida* observed in our study may be due to increased colonisation of the female genital tract with the non-*albicans Candida* species and given the conditions of ICU, these may invade the blood stream during the hospitalisation. In the present study, fluconazole resistance was less frequent compared to other studies probably because isolation of *C. glabrata* and *C. krusei* were less in this study which are known to be intrinsically resistant to fluconazole.

Thus, as found in this study, the zero resistance of *C. albicans*, *C. tropicalis* and *C. parapsilosis* which are the commonest blood stream infection causing agents to azoles reinforces the belief that the antifungal susceptibility testing may not be done for every isolate routinely, rather it may be restricted to only those patients who do not respond to antifungal therapy or acquire breakthrough candidemia while still on fluconazole prophylaxis. This also highlights the need for more detailed studies for understanding of resistance mechanisms with a large number of isolates.

The limitations of the study have been primarily the lack of controls to strengthen the results of association of the various risk factors with candidemia. Moreover the study was conducted in a single institution which may not reflect the actual epidemiology of candidemia in this region of the country. The colonisation with *Candida* species was not evaluated because surveillance cultures were not taken. The HIV status was not known in many patients and there were no cases of organ transplantation and malignancies so their association with candidemia and the distribution of the *Candida* species could not be evaluated.

No long-term follow up of patients was done after the diagnosis of candidemia so conclusions about mortality rates for different species could not be reached by this study. In addition, the culture based methodology used in the study though widely used but requires skill and time unlike the newer non-culture based T2 biosystems which are rapid and easy to perform. This system can detect the presence of five important species of *Candida.* The overall sensitivity and specificity has been reported to be 91.1% and 99.4% respectively in a clinical trial [31, 32].

CONCLUSION: This study demonstrates significant association of female gender and central venous catheter as risk factors with the non-*albicans Candida* in comparison to *Candida albicans*. We also demonstrated significant drug resistance among certain new species like *Candida auris* and *Candida rugosa* to commonly used antifungals which would mean increased morbidity and health care cost. So it becomes important to diagnose these infections in time by increasing lab capacity in terms of newer diagnostic techniques. This study has revealed that these newer emerging species are still susceptible to Amphotericin B which may be reliably used to treat candidemia due to these species where susceptibility testing is awaited or not available.

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CONFLICT OF INTEREST: Nil.

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