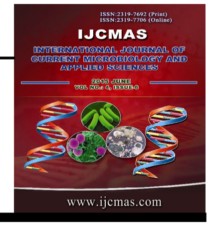

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Original Research Article

Prevalence of Candidemia in ICU in a Tertiary Care Hospital in North India

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A B S T R A C T

The incidence of candidemia, despite under-reporting, is rising worldwide, species distribution in recent years shifting from *Candida albicans* towards non-albicans species, with increasing resistance to antifungal drugs, especially the azoles. Aim of this study was to determine the current prevalence of candidemia among patients admitted to ICU and antifungal resistance profile to help the clinicians to develop an empirical antifungal therapy in this region. A prospective observational study was conducted on a total of 75 patients admitted to the ICU of tertiary care institute over 12-month period and screened for the presence of candidemia by performing blood cultures. The prevalence of candidemia among ICU patients with features of SIRS was 16% (n=12) in our study. *Candida albicans* with six isolates was the commonest species (50%) isolated from candidemic patients (n=12), followed by *C. glabrata* with three isolates (25%) and *C. krusei* with two (16.6%). The least common species in our study was *C. tropicalis* (8.3%) with only one isolate. Results of this study make it clear that routine screening of *Candida* isolates to the species level followed by confirmation of resistant strains by antifungal susceptibility testing is essential, and could assist clinicians in developing important prophylactic and treatment guidelines for improved management.

Keywords

Antifungal drug resistance, Candidemia, *Candida albicans*, non-albicans *Candida*

Introduction

Candida spp. are the most common cause of opportunistic fungal infections worldwide.[1] Candida are generally a part of normal microbial flora of skin and mucous membrane in immunocompetent individuals but may cause severe systemic infections in critically ill patients with underlying disease such as diabetes mellitus, prolonged duration of stay in ICU, or other factors which may suppress the immunity.[2] They causes a wide variety of infections, ranging from mild mucocutaneous to severe invasive infections that can involve virtually any organ.[3] Approximately 200 *Candida spp.* are known till date, of which about 10 % are recognized to cause infections in human, most commonly by *Candida albicans* .[4]

The term Candidemia describes the presence of *Candida spp* in blood stream. It is a life-threatening fungal infection associated with a mortality rate of 38%. It also prolongs hospital stays by as much as 30 days and increases the cost of medical care.[5] *Candida spp.* is one of the most common causes of bloodstream infection among the patients admitted in the intensive care unit (ICU).[6,7] Although *Candida albicans* remains the most prevalent species, there has been a clear shift towards non-albicans species namely *Candida tropicalis, Candida parapsilosis, Candida kruzei* particularly found in the neutropenic patient and *Candida glabrata* found especially in patients with solid tumor.[7-9]

Several retrospective studies have demonstrated that a number of predisposing factors are responsible for spread of *Candida* infections in the ICU.[10-12] The commonly associated factors are total parenteral nutrition (TPN), use of multiple broad spectrum antibiotics, major surgeries, central venous catheter insertion, urinary catheter, mechanical ventilation, persistent neutropenia, renal failure, glucocorticosteroid treatment, burns, and hemodialysis.[13] Preexposure to antifungals particularly azoles, mostly in the form of prophylaxis, and to a lesser extent with echinocandins, have been associated with the occurrence of breakthrough infections with resistant Candida species. Although *C. glabrata* and *C. krusei* have been the predominant isolates in these settings, other resistant non-albicans Candida species are being increasingly observed.[14,15]

The increasing incidence of candidemia due to non-albicans species in different regions of country and emergence of antifungal resistance due to irrational use of drugs necessitates the formulation of empirical therapy for treatment of patients suffering from candidemia and antifungal prophylaxis for patients at risk of developing the infection.[16,17] There are very few studies from India, especially in Himalayan region of Northern India, on the pattern of fungal infections in Intensive Care Unit patients. The knowledge of current prevalent strain and their drug resistance profile are key determinants in the selection of appropriate antifungal prophylaxis and empirical therapy. Therefore, the study was conducted to determine the current prevalence of candidemia among patients admitted to ICU and antifungal resistance profile of the isolates to help the clinicians to develop an empirical antifungal therapy in this region of country.

Subjects and methods

The study was a prospective, observational and non-interventional study carried out in a Tertiary care Institute, over a period 12-month from January 2013 to December 2013. Seventy five clinically suspected cases of systemic inflammatory response syndrome (SIRS) patients, with more than 48 hours duration of stay in ICU were included in the study. A written informed consent was obtained from the patient and/or from blood relatives. Patient's clinical and epidemiological information was recorded on pre-defined questionnaire. Prior to the conduction of study ethical clearance was obtained from the Institute.

Single blood specimen of 8-10 ml were collected aseptically from each patient and inoculated in proprietary fungal blood culture bottle and incubated in an automated blood culture detection system (BACTEC 9050). Bottles were incubated for up to 14 days before being reported negative. Broth from positive bottles was smeared and Gram-stained, and sub-cultured on Sabouraud's Dextrose Agar (SDA) medium and incubated aerobically at 37°C for 24-48 hours. *Candida* isolates, characterized by smooth, creamy and pasty appearance of colonies on SDA, were subjected to speciation by Germ tube test, Sugar fermentation test, Sugar assimilation test, morphological characters on Corn meal agar with 1% Tween 80 (CMA) and colour production on CHROM agar media. An episode of candidemia was identified when the Candida was isolated from the blood culture of the patient.

The recovered *Candida* isolates were then subjected to antifungal susceptibility testing by broth microdilution method using sterile, disposable, multiwell microdilution plates (96 U shaped well) as per standard CLSI guidelines (M27-A3).[18] Antifungal susceptibility testing was done for Voriconazole, Fluconazole, Ketoconazole and Amphotericin B. The concentration gradient used for voriconazole was 0.125 to 64 mg/litre, whereas for fluconazole, ketoconazole and amphotericin B was 0.0313 to 16 mg/litre. The broth medium used for the test was RPMI 1640. The endpoints were read visually by naked eyes. The turbidity was graded from 0 to 4 with 0 indicating optically clear and 4 indicating no reduction in turbidity compared to the turbidity of the drug-free control well. For amphotericin B, the endpoint was the lowest concentration that inhibits visual growth or an endpoint score of 0. The endpoint for the azoles was the concentration where there was a decrease in turbidity of approximately 50% or an endpoint score of 2. The control strains used were *C albicans* ATCC- 5314 and *C krusei* ATCC- 6258.

Data was analyzed for statistical significance between various sub-groups within the study population by using IBM SPSS statistics version 21. Mean, median and standard deviation were calculated as per standard definition. P value <0.05 was taken as level of significance.

Results and Discussion

A total of 75 patients, suspected of sepsis, admitted in the ICU were included during the study period. Twelve out of 75 patients were positive for candidemia with prevalence rate of 16 %. Out of 75 patients, culture was positive in 28 (37.3%) patients which were confirmed as cases of sepsis. Among these 28 isolates, 16 (57.1%) were aerobic bacterial pathogens and 12 (42.9%) were organisms belonging to *Candida* species.

Table 1 demonstrates that majority of patients in the study group comprised of males (n=57, 76%). The male to female ratio was 3.2:1. Out of 57 male patients, 7 (12.3%) had candidemia, whereas 5 (27.7%) out of 18 female patients had candidemia. Culture positivity among males and females was insignificant in the study (p=0.145). Out of 75 patients the maximum number of patients were in the age group of 60-69 years (n=17, 22.6%) followed by patients (n=14, 18.6%) in 40-49 years age group.

Table 2 shows the distribution of *Candida* species among culture positive patients. *C. albicans* was found to be the commonest species isolated (n=6, 50%). Among non albicans, *C. glabrata* predominated being (n=3, 25%) following which, *C. krusei* (n=2, 16.6%) and *C. tropicalis* (n=1, 8.3%) were recovered.

Table 3 shows out of 6 *Candida albicans* isolates, there was 33.3% resistance to fluconazole and ketoconazole and 16.7% resistance to voriconazole. Whereas among non albicans, none of the isolates of *Candida glabrata* was resistant to amphotericin B (0%) and 33.33% were resistant to voriconazole whereas 2 isolates (66.6%) were resistant to fluconazole and ketoconazole. *C. tropicalis* was sensitive to all the drugs. *C. krusei* due to their intrinsically resistant properties, sensitivity to fluconazole was not reported. None of the isolates of *C. krusei* were resistant to amphotericin B (100%) and 50% were resistant to ketoconazole and voriconazole. Thus, no resistance to amphotericin B was observed in our isolates whereas 25% resistance to voriconazole, 41.7% to ketoconazole and 50% resistance to fluconazole was observed.

As shown by table 4, 33.33% of *Candida albicans* were resistant to fluconazole and ketoconazole whereas only 66.66% non albicans *Candida* were resistant to fluconazole and 50 % to Ketoconazole respectively. There was 16.7% and 33.3% resistance to voriconazole among *albicans* and non albicans *Candida* respectively. But there was no difference in sensitivity to amphotericin B as all the isolates were sensitive to it.

All the 12 patients with candidemia were treated with antifungals and out of 12, 9 patients died with mortality being 75%, although direct correlation of candidemia as the cause of death in any of the patients could not be ascertained due to multiple underlying pathologies.

Candidemia in critically ill patients is usually a severe and life-threatening condition and is difficult to diagnose leading to delayed treatment, prolonged hospitalization, increased health care costs, and more importantly, increased morbidity and mortality.[19] *Candida* has emerged as an important cause of nosocomial blood stream infection. But, the actual prevalence of candidemia in India is lacking due to unavailability of sufficient data from various parts of the country. However, a study from Lucknow reported an incidence rate of 1.61 per 1000 hospital admissions for candidemia.[20] A New Delhi based study gave a prevalence rate of 18% while a study in South India reported an incidence rate of 5.7% for candidemia.[21, 22] A study by Sahni *et al.* from Maulana Azad Medical College, New Delhi, found an incidence rate of 6.9% for *Candida* species in BSI.[23] Our study reported a prevalance rate of 16% for candidemia in ICU. These studies suggest wide variations in the prevalence of candidaemia in different geographical location of India.

In the present study the age of recruited patients ranged from 20 to 88 years. The largest percentage of patients was found in the 60-69 year age group (22.6 %), followed by patients in the age groups of 40-49 and 20-29 years. Similar findings have been reported in studies by Leon *et al.* who reported a mean age of 60 (±17) years and Laupland *et al.* reported a mean age of 57.8 years in their 5-year study of invasive *Candida* infections.[24, 25] Gonzalez de Molina *et al.* reported a mean age of 59 (±17.9) years in their study of mortality attributable to candidemia in critically ill patients.[26] Candidemia is well-known for affecting the extremes of age, possibly due to the immaturity of the immune system in children, and the waning of the immune response in the elderly. But the majority of patients in our study were middle-aged, possible reasons for this might be the over-representation of middle-aged people among patients admitted to our ICU.

Male patients outnumbered females in our study with a male to female ratio of 3.2:1; similar findings have been seen in other studies across the world. Leroy *et al.* reported a male to female ratio of 3.08:1 in their evaluation of the *Candida*-score in critically ill patients.[27] Ylipalosaari *et al.* reported a male to female ratio of 2.4:1 in their study of the epidemiology and risk factors for candidemia in an ICU setting.[28] The male to female ratio among culture-positive patients in our study was 1.4:1, which is similar to the corresponding figure of 1.7:1 reported by Gonzalez de Molina *et al.*[26] Another study by Leon *et al.* reported a male to female ratio 1.89:1 in culture-positive.[24] The male preponderance seen among culture-positive patients in all these studies was corroborated by the findings of our study.

Geographical variation is recognized to be an important feature in the species distribution of *Candida*. In sync with trends observed in the majority of studies from around the globe, a shift in the species distribution of *Candida* from *albicans* to non albicans has been noted in several major Indian hospitals.[29] The authors all over the world have noted a strong correlation of the rise in non-albicans species with the use of fluconazole.[30]. However in our study, *C. albicans* with six isolates was the commonest species (50%) isolated from candidemic patients (n=12), followed by *C. glabrata* with three isolates (25%), *C. krusei* with two (16.6%) and the least common species being *C. tropicalis* (8.3%) with only one isolate. This could be accounted for by the fact that prophylactic use of fluconazole is not a standard practice in our ICU and none of the patients recruited in this study were receiving antifungal prophylaxis.[31] Similar findings have been reported by many authors across the world. In the SENTRY surveillance programme conducted between 1997- 2000, *C. albicans* accounted for 50% of isolates, while the same species comprised 71% of all *Candida* isolates in a study by Yamamura *et al* from Canada.[32] The percentages of *albicans* and non-albicans species *Candida* were equal (50%) in our study. Leroy *et al* reported similar findings with 53% of *C. albicans* and 47 % of non-albicans species in their study.[27]. In contrast, Dimopoulos *et al* reported a higher percentage (64.3%) of *C. albicans* than non *albicans* species.[33] Kett *et al* reported regional variations in the relative abundance of *C. albicans* and other *Candida* species. According to their study on Candida blood stream infections in ICUs, *C. albicans* accounted for 72.7%, 100%, and 68.8% of Candida isolates in Asia, Russia & Pacific, and North America respectively.[34] Our study also reiterates the regional variation in distribution of *Candida* species in ICUs of different tertiary care hospitals.

In our study, 33.3% of *C. albicans* were resistant to fluconazole and ketoconazole, 16.7% to voriconazole and none to amphotericin B. Similar high level of resistance had been reported by Kotwal *et al.*[29] Another study by Kothari et al reported resistance to fluconazole among 42% of isolates of *C. albicans*. This is in contrast to low rate of resistance (5%) to fluconazole among isolates of *C. albicans* reported by Pfaller *et al*, in their study on ICU patients.[35] Similarly the ARTEMIS DISK global antifungal susceptibility surveillance study conducted over a period of 10.5 years reported only 2% resistance to fluconazole among *C albicans* isolates.[36] The reason for this difference remains unknown; this could be an interesting regional characteristic if this finding is validated in future studies. The intrinsic and emerging resistance to azoles actually represents a major challenge for empirical, therapeutic and prophylactic strategies.[37]

Among non-albicans *Candida* species isolated in our study, *C. glabrata* showed a very high rate (66.6%) of resistance to fluconazole and ketoconazole.

Table.1 Gender wise distribution of patients with and without Candidemia

Gender	Candidemia present (n=12)	Candidemia absent (n=63)
Males (n=57)	7	50
Females (n=18)	5	13

Table.2 Distribution of Candida species isolates recovered from blood

Candida species	No of cases (n=12)	Percentage (%)
Candida albicans	6	50
Candida glabrata	3	25
Candida krusei	2	16.67
Candida tropicalis	1	8.33

Table.3 Antifungal resistance pattern of culture positive isolates

Candida species	No of cases (n=12)	Resistance (%)			
		Fluconazole	**Ketoconazole**	**Voriconazole**	**Amphotericin B**
C. albicans	6	2 (33.33 %)	2 (33.33 %)	1 (16.67%)	0 (0%)
C. glabrata	3	2 (66.66%)	2 (66.66%)	1 (33.33 %)	0 (0%)
C. tropicalis	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)
C. krusei	2	-	1 (50 %)	1 (50 %)	0 (0%)
Total	12	6 (50 %)	5 (41.7 %)	3 (25%)	0 (0%)

Table.4 Comparison of Antifungal susceptibility of albicans and non-albicans *Candida*

Isolates	Resistance (%)				
	Number (%)	**Fluconazole**	**Ketoconazole**	**Voriconazole**	**Amphotericin B**
Candida albicans	6 (50 %)	2 (33.33 %)	2 (33.33 %)	1 (16.67%)	0 (0%)
Non-albicans *Candida*	6 (50 %)	4 (66.67 %)	3 (50 %)	2 (33.33 %)	0 (0%)
p value		0.24	0.24	0.18	1

This is similar to data published in recent years in which azole resistance has been found to be higher among *C. glabrata*. In a Scottish study, among the isolates of candidemia, 55% of *C. glabrata* isolates showed reduced susceptibility to fluconazole, but azole resistance among other species of *Candida* was extremely low.[38, 39] Similarly, Tan *et al* observed relatively higher fluconazole resistance among *C. glabrata* isolates.[40] Our lone isolate of *C. tropicalis* was sensitive to all drugs tested. In contrast, Chakrabarti *et al* reported resistance rates of 10.2 to 13.6 % to azoles in *C tropicalis.*[41] This discrepancy in sensitivity pattern can be explained by the fact that only one isolate of *C. tropicalis* recovered in our study. The overall prevalence of resistance to voriconazole, ketoconazole and fluconazole was 25 %, 42 % and 50 % respectively among our *Candida* isolates. No isolate of ours was resistant to amphotericin B. Kothari *et al* also found the smallest percentage of their isolates (8%) to be resistant to amphotericin B, followed by 44% to voriconazole and 64% to fluconazole.[21] Resistance to amphotericin B is attributable to the reduction in ergosterol in resistant mutants of Candida. Such cases have been reported from immunocompromised patients who have received extensive antifungal agents and broadspectrum antimicrobials.

In the ICU, there is usually a failure of host defense mechanisms and also complications associated with the patient's underlying disease. Therefore, mortality is not solely related to the pathogenicity of the *Candida* species. In this study, mortality in patients presenting with candidemia was high (75%), but direct correlation of candidemia and mortality could not be ascertained. Barberino *et al*. suggest that invasive candidiasis is a better marker for disease severity than an independent risk factor for mortality during the course of infection.[42]

Candidemia is emerging as a significant problem in hospitalized patients especially in ICU setup. A gradual but significant epidemiological shift to higher isolation of non-albicans *Candida* species is being noticed, with high rates of azole resistance. Based on the present results, it is clear that routine screening of *Candida* isolates to the species level followed by confirmation of resistant strains by antifungal susceptibility testing is essential, and could assist clinicians in promoting adoption of important prophylactic and treatment guidelines for its improved management. Moreover, continued surveillance of candidemia is important to document changes in its epidemiological features and antifungal susceptibilities.

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