ORIGINAL ARTICLE

# Incidence, Risk Factors and Susceptibility Profile of *Candida* species Isolated from Blood of Non-Neutropenic Medical Intensive Care Unit Patients in a Tertiary Care Centre

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**Abstract:**

*Background:* The critically ill patients are particularly susceptible to rapid colonization by endemic pathogens or hospital flora. Both immunocompetent and immunocompromised patients are particularly exposed to various risk factors. Bloodstream infection due to *Candida* species is now recognized as an important public health problem especially in intensive care unit patients with considerable morbidity, mortality and health care costs. *Aim*: The aim was to study the incidence, risk factors and antifungal susceptibility of the *Candida* species isolated from blood of Medical Intensive Care Unit (MICU) patients in our hospital. *Material and Methods*: The blood samples collected from MICU patients were processed as per standard protocol and antifungal susceptibility testing was done by broth microdilution method. *Results*: Out of total 111 samples, 22 (19.81%) yielded *Candida* species of which non-*albicans Candida* species predominated. In MICU, the risk factors associated with candidemia showing statistical significance were length of intensive care unitstay > 7 days, use of steroids, mechanical ventilation, central venous catheters and uncontrolled diabetes mellitus. *C. albicans, C. parapsilosis* and *C. guillermondii* have showed 100% susceptibility to Amphotericin B, 5-Flurocytosine, Fluconazole, Itraconazole and Voriconazole. *C. krusei* showed 100% resistance to fluconazole. *C. glabrata* showed 100% resistance to Itraconazole and Voriconazole. The mortality rate among MICU patients with candidemia was 59.09%. *Conclusion*: Although the patients in the ICU are at risk for candidemia, rapid diagnosis of aetiologic agent will reduce the delay in initiating the appropriate therapy with adequate dosage of anti-fungal agents along with effective correction of underlying risk factors which may actually improve their outcome.

**Keywords:** Candidemia, Medical Intensive Care Unit, Broth Microdilution Method

## Introduction:

The critically ill patients are those who are at risk for actual and potential life-threatening health problems [1]. Due to advances in supportive medical care, the intensive care unit plays a major role in keeping such critically ill patients stable and alive. The increased use of invasive monitoring and aggressive therapeutic and surgical technologies in the intensive care unit has not only improved the survival but also increased the risk of invasive fungal infections in these patients [2].

Several other identified risk factors such as indwelling catheters, use of broad spectrum antibiotics and corticosteroids, parenteral nutrition, prolonged uncontrolled diabetes mellitus, assisted ventilation, prior abdominal surgery, etc. also contribute [3].

The patients hospitalized in Intensive Care Units (ICUs) are 5 to 10 times more likely to acquire hospital acquired infections than other hospitalized patients because of severity of illness [4]. Colonization with *Candida* species further leads these patients to nosocomial fungal infections mainly blood stream infections [3]. Between 1995 and 2002, the frequency of nosocomial candidemia rose significantly from 8% to 12% of all reported bloodstream infections [5].

*Candida* is one of the most frequent cause of Bloodstream Infections (BSIs) leading to significant morbidity and mortality, especially in non-neutropenic critically ill patients which in turn lead to prolonged ICU stay thus increasing the health care cost [6].

One of the most challenging aspects of treating invasive fungal infections involves appropriate diagnosis. However, delay in identification can prolong the initiation of appropriate treatment ultimately leading to poor outcome. Antifungal therapy includes use of azoles, lipid formulations of amphotericin B and newly introduced echinocandins. Echinocandins are expensive, so its use in Indian hospitals is limited [7].

Antifungal prophylaxis with agents like fluconazole has been proven to be effective in neutropenic patients but less compelling for non-neutropenic ICU patients, hence its use in non-neutropenic ICU patients is controversial [8].

Most of the studies on candidemia have been carried out in Western countries and there is paucity of data from India [9]. Recently India is emerging as an important health care provider with many hospitals having specialized set ups and ICUs. Hence, this study was undertaken to know the incidence, risk factors, species distribution and antifungal susceptibility profile of *Candida* species isolated from BSIs in Medical Intensive Care Unit (MICU) patients of a tertiary care hospital.

**Material and Methods:**

**Study design and patients:**

This longitudinal hospital based observational study was carried out in the Department of Microbiology, Krishna Institute of Medical Sciences, Karad during a period of two years from January 2011 to December 2012. The statement of approval for the study was taken from the ethical committee. After taking informed consent, the blood samples were collected from patients admitted in MICU of Krishna Hospital and Medical Research Centre, Karad.

**Inclusion and Exclusion criteria:**

The patients included in this study were all clinically suspected non-neutropenic critically ill patients after 48 hours of admission in MICU. The complete blood count reports of the patients were referred to rule out neutropenia. The patients having known candidemia or diagnosed as candidemia before 48 hours of ICU admission were excluded from the study.

**Clinical data:**

Patients with candidemia were followed up clinically and microbiologically until their discharge or death. The clinical data was recorded from their medical records and bedside charts. Detailed history of any intervention within 2 weeks before initial positive culture, viz. use of broad spectrum antibiotic therapy, steroids, Central Venous Catheter (CVC), mechanical ventilation, total parenteral nutrition, indwelling catheters, and antifungal prophylaxis; history of duration of ICU stay, previous diabetes mellitus with blood glucose level > 180 mg/dl before the onset of candidemia were recorded.

**Mycological data:**

Five to ten ml venous blood was collected under strict aseptic precautions in biphasic medium containing brain heart infusion agar and brain heart infusion broth with blood-broth ratio 1:10. The biphasic culture bottle was kept vented and was tilted after 48 hours, 5 days and 7 days incubation to allow broth to flow over the whole agar surface and kept in that position for 1 hour. These cultures were carefully checked daily for growth. Culture bottles were incubated until growth appeared or for 6 weeks before discarding them as negative. The growth was confirmed to be yeast by Gram stain and was further inoculated on Sabouraud Dextrose Agar. As per the standard methods for identification of *Candida* species further tests like germ tube test, corn meal agar for chlamydospore formation, sugar assimilation and fermentation tests were done [10]. Antifungal susceptibility testing of the isolates was carried out by broth microdilution method as per Clinical and Laboratory Standards Institute (CLSI) M27-A3, USA, 2008 guidelines [11]. Antifungal agents used were amphotericin B, fluconazole, itraconazole, voriconazole and 5-flurocytosine. The antifungal powders were obtained in the form of pure salts from Sigma-Aldrich. Antifungal stock solutions were prepared at concentration of at least 1280 µg/mL, or ten times the highest concentration to be tested, whichever is greater. Antifungal agents like amphotericin B, itraconazole, voriconazole were dissolved in Dimethyl Sulfoxide (DMSO) (HiMedia) and series of dilutions at 100 times the final concentration was prepared from antifungal stock solution in the same solvent. Each intermediate solution was further diluted to final strength in the test medium. The drug concentration ranges used were 0.0313 to 16 µg/mL for amphotericin B, itraconazole and voriconazole and 0.125 to 64 µg/mL for flucytosine and fluconazole.

**Statistical Analysis:**

To determine the significant association between risk factors and candidemia, chi-square test and p value were calculated. P value < 0.05 was considered statistically significant. Analysis of risk factor was calculated by SPSS software package.

**Results:**

Out of total 111 blood samples collected, 22 (19.81%) showed growth of *Candida* species. Among the 22 candidemia patients, maximum i.e. 54.54% was between the age group 61-70 years with male preponderance of 63.63%.

Out of 22 candidemia cases, 17 (77.27%) were due non-*albicans Candida* species. *C. tropicalis* was the most common species isolated in 31.81% cases followed by *C. albicans* in 22.72% and *C. krusei* in 18.18% cases. The other species isolated are shown in Fig. 1.

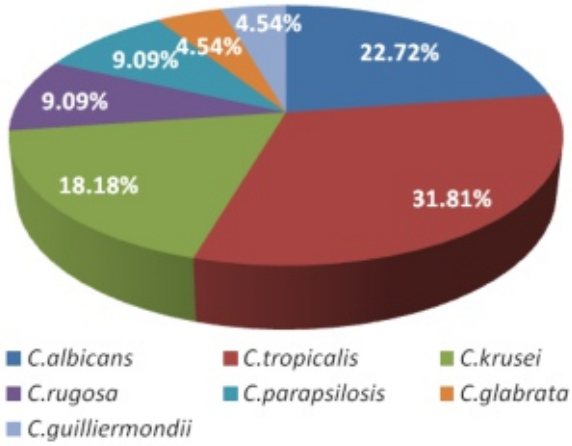


**Fig. 1: Graphic Representation of Distribution of *Candida Species* in Blood Cultures of Medical ICU Patients**

In the present study, the risk factors significantly associated with candidemia were length of ICU stay > 7 days, use of steroids, mechanical ventilation, central venous catheters and uncontrolled diabetes mellitus (Table 1).

**Table 1: Various Risk Factors Associated with Candidemia in MICU Patients**

| Sr. No. | Risk Factors | With Candidemia (n=22) | Without Candidemia (n=89) | Odds ratio | Chi-square ($\chi^2$) | P value |
|---|---|---|---|---|---|---|
| 1 | **Length of ICU stay (LOS)(>7days)** | 21 | 61 | 9.639 | 5.300 | **0.0213** |
| 2 | **Use of broad spectrum antibiotics** | 22 | 88 | 0.762 | 0.2494 | 0.6175 |
| 3 | **Use of steroids** | 16 | 41 | 3.122 | 4.008 | **0.0453** |
| 4 | **Total Parenteral Nutrition (TPN)** | 22 | 88 | 0.762 | 0.2494 | 0.6175 |
| 5 | **Mechanical Ventilation (MV)** | 18 | 50 | 3.510 | 3.865 | **0.0493** |
| 6 | **Central Venous Catheter (CVC)** | 19 | 54 | 4.105 | 4.093 | **0.0431** |
| 7 | **Urinary Catheter** | 21 | 80 | 2.363 | 0.1607 | 0.6886 |
| 8 | **Uncontrolled Diabetes Mellitus (DM)** | 10 | 19 | 3.070 | 4.136 | **0.0420** |
| 9 | **Use of prophylactic Fluconazole** | 3 | 4 | 3.355 | 1.188 | 0.2758 |

*P value < 0.05 = statistically significant*

**Table 2: Association of Candidemia with patients with multiple Risk Factors in MICU**

| Sr. No. | Presence of Number of Risk Factors | Candidemia (n=22) | Non-Candidemia (n=89) | Chi-square ($\chi^2$) | P value |
|---|---|---|---|---|---|
| 1 | **6 Risk factors (LOS>7days, CVC, MV, TPN, Urinary Catheter, Use of antibiotics)** | 14 | 30 | 5.412 | **0.020** |
| 2 | **5 Risk factors (LOS>7days, CVC, TPN, Urinary Catheter, Use of antibiotics)** | 17 | 43 | 4.847 | **0.027** |
| 3 | **3 Risk factors (Uncontrolled DM, Use of steroids and prophylactic fluconazole)** | 3 | 9 | 0.008 | 0.925 |

*P value < 0.05 = statistically significant*

In this study the mortality rate among MICU patients with candidemia was 59.09% (Fig. 2).


**Fig. 2: Graphic Representation of Percentage of Mortality among MICU patients with Candidemia**

The Minimum Inhibitory Concentrations (MICs) of the isolates were recorded after BMD test. All the isolates of *C. albicans*, *C. parapsilosis* and *C. guilliermondii* showed 100% susceptibility to amphotericin B, flucytosine, fluconazole, itraconazole and voriconazole. Among other isolates, 50% of *C. rugosa* and 57.14% isolates of *C. tropicalis* were resistant to all these five drugs.

Resistance to amphotericin B was noted among 50% of *C. rugosa* and 28.57% of *C. tropicalis.* Dose dependent susceptibility to fluconazole was seen in 100% of *C. glabrata*, 50% of *C. rugosa* and 28.57% of *C. tropicalis*. As *C. krusei* shows intrinsic resistance to fluconazole, all 4 isolates were considered as resistant to this drug even though they showed susceptible or dose dependent susceptibility after antifungal susceptibility test. 14.28% of *C. tropicalis* showed dose dependent susceptibility to itraconazole while *C. glabrata* was 100% resistant to this drug. Voriconazole susceptibility was high and detected in all isolates except 1(100%) isolate of *C. glabrata.*

**Discussion:**

In recent years, the risk of candidemia has been focused in non-neutropenic patients with multiple risk factors admitted in ICUs.

The present study compromising of 111 critically ill patients admitted in MICU of which 22 were diagnosed as cases of candidemia. Among the 22 candidemia patients, maximum cases (54.54%) were between the age group 61-70 years with male preponderance of 63.63%. These results were consistent with previous studies [12-13] which reported maximum cases in males within age group 50-70 years.

In our study, the incidence of candidemia was 19.81% which was consistent with a study carried out by Kothari *et al* [9] who reported incidence of 18% cases which is notably high. Few studies showed the incidence of candidemia ranging from 5-7% which is comparatively low [12, 14-16]. This low incidence may be due to preventive measures taken during the ICU stay like early recognition and treatment of risk factors, prophylactic antifungal drugs etc.

Out of 22 candidemia cases, 17 (77.27%) were due to non-*albicans Candida* species while *C. albicans* was isolated in 22.72% cases. Blumberg *et al* [17] and few studies carried out in India [7, 9, 13, 18,] reported non-*albicans Candida* species to be the predominant species which is in consistent with the present study. However, other authors [19, 20] reported *C. albicans* to be the predominant species. In the past few decades,

there is a changing trend from *C. albicans* to non-*albicans Candida* spp. which is correlated with an increasing use of azoles for prophylaxis or empirical treatment [10, 21].

Among the NAC species, our study shows *C. tropicalis* to be the most predominant species accounting for 31.81% which are parallel to the findings of studies carried out in India [13,18] and Asian countries [15]. *C. tropicalis* shows increased virulence in those patients with disrupted mucosal integrity. However, studies carried out by Wisplinghoff *et al* [19] and Germain *et al* [20] found *C. glabrata* as predominant species among non-*albicans Candida* spp which is inconsistent with the present study which shows only 4.54% isolates of *C. glabrata*. It is the second most common leading cause of candidemia in United States [22] seen more often in older adults [21].

The present study shows 18.18% isolates of *C. krusei* which is very high in contrast to a study carried out by Chakrabarti *et al* [18] among ICUs in India who reported only 5.8% of *C. krusei* causing candidemia. *C. krusei* accounts for 2-4% of all *Candida*-associated BSIs and is best known to emerge in settings where fluconazole is used for prophylaxis and possesses innate resistance to fluconazole [3, 8]. *C. rugosa* which is emerging as a distinctive cause of candidemia in recent years was isolated in 9.09% cases in contrast to Singh et al [7] who reported 18.4% isolates which is very high.

The report showing *C. parapsilosis* as the leading cause of *Candida* BSIs in North America and second cause of candidemia in Europe [22] is totally inconsistent with the present study which shows only 9.09% isolates of *C. parapsilosis*. This species is mostly found on the hands of health care workers which cause skin contamination near the insertion site of venous catheter leading to venous catheter colonization, biofilm production and subsequent fungemia [3, 8].

*C. glabrata* which is an emerging and potentially resistant species is found in only 4.54% of cases in the present study. This is in contrast to the reports from United States [22] which show *C. glabrata* to be the second most leading cause of candidemia. This species has emerged in patients with terminal stages of haematological malignancies and in intensive care units [21].

In the present study, duration of ICU stay more than 7 days is a major risk factor associated with candidemia which is due to the underlying medical conditions and immunosuppressed state of the patients. This finding parallels the study conducted by Deorukhkar *et al* [13]. The use of steroids and presence of uncontrolled diabetes mellitus among patients of MICU in the present study were significantly associated with candidemia which was in contrast to the findings of Singh et al [7]. However, Goldani *et al* [23] also found use of corticosteroids to be significant risk factor for candidemia. Diabetes mellitus cause increased colonization of *Candida* species and immunosuppression which ultimately leads to dissemination and invasion of *Candida* species deep into the tissues and organs.

Candida cause skin colonization, hence any break in the epithelial barrier due to intravascular catheters lead to invasive candidiasis. The use of

CVC catheter and mechanical ventilation is significantly associated with the development of candidemia which parallels the findings of few other authors [16, 24]. There are few studies which found association between administration of fluconazole and increased risk of BSI due to non-*albicans Candida* species [6, 10] but this was not the case in the present study.

The indiscriminate use of broad spectrum antibiotics suppresses the growth of normal intestinal flora resulting in fungal overgrowth [21]. In the present study this factor was not significantly associated with candidemia which was consistent with the study carried out by Yap *et al* [25]. On the contrary, Xess *et al* [16] have reported the use of antibiotics as a major risk factor for candidemia.

As shown in Table 2, the presence of multiple risk factors have increased the chances of getting candidemia, thus timely identification of these risk factors can predict the frequency of acquiring candidemia early during the hospital stay.

The need for reproducible and clinically relevant antifungal susceptibility testing has been encouraged due to increasing number of IFIs, extended use of new and established antifungal agents and increased antifungal resistance. In the present study, 100% susceptibility to amphotericin B was seen among *C. albicans*, *C. krusei*, *C. parapsilosis*, *C. glabrata* and *C. guillermondii* and resistance was seen in 50% and 28.57% isolates of *C. rugosa* and *C. tropicalis* respectively. These findings were consistent with studies carried out by Antunes *et al* [26] who reported not a single isolate of *Candida* species from BSIs showed resistance to amphotericin B. On contrary, Estrella *et al* [27] noted higher MICs for non-*albicans Candida* species to amphotericin B.

All 22 isolates in the present study were susceptible to flucytosine which was also reported by Singh et al [7]. We noted dose dependent susceptibility to fluconazole in 28.57% isolates of *C. tropicalis*, 50% of *C. rugosa* and 100% among *C. glabrata*. *C. krusei* showed 100% resistance to fluconazole in the present study. Similar study [27] conducted earlier also noted decreased susceptibility to fluconazole among *C. glabrata* and *C. tropicalis*; and resistance *C. krusei*. *C. krusei* is known to show intrinsic resistance to fluconazole. In our study, dose dependent susceptibility to itraconazole was seen in 14.28% of *C. tropicalis* and resistance was seen in 100% of *C. glabrata* isolates. A previous study [28] also reported maximum number of *C. glabrata* isolates showing resistance to itraconazole.

In our study, among 22 *Candida* isolates, 21 (95.45%) were susceptible to voriconazole while 1 isolate of *C. glabrata* showed resistance with MIC > 4μg/ml which was in agreement with Pfaller *et al* [29] who have reported 6.4% isolates of *C. glabrata* to be resistant to voriconazole.

Candidemia is associated with significant morbidity and mortality especially in non-neutropenic critically ill patients. In our study, the crude mortality rate was 59.09% which paralleled the findings of a previous study[19] who observed the crude mortality rate ranging between 45-60%.

**Limitations:**

Our study being a hospital based study; the findings cannot be applied to the general population or different patient groups at risk for candidemia. Secondly, the source of infection was not studied which could have been applied for epidemiological purpose. Finally, we have not used echinocandins drug which play a major role in treatment of candidemia. Echinocandins were not available in pure powder form so could not be used for antifungal susceptibility testing.

**Conclusions:**

Although patients in ICU are at risk of candidemia, early diagnosis and timely initiation of appropriate antifungal drug can definitely increase the survival of the patients. The species distribution as well as susceptibility patterns show geographical differences, hence it is important to establish continuous surveillance and knowledge of the local epidemiological trends in *Candida* species. It is the responsibility of the clinical microbiologists and the ICU clinicians to come together and develop local guidelines for treatment of invasive candidiasis considering the epidemiological data in their region. Newer technologies such as β-D-glucan, PCR-based assays and molecular typing should be carried out wherever facilities are available which support early diagnosis of candidemia as well as for epidemiological purpose.

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