

**Candidemia in Non-Neutropaenic Patients in a Tertiary Care Centre in South Kerala**Dr. Lancy. J<sup>1</sup>, Dr. Jyothi. R<sup>2</sup><sup>1</sup>Addl. Prof. of Microbiology, Govt. Medical College, Tvpm.<sup>2</sup>Associate Prof. of Microbiology, Govt. Medical College, Tvpm.**Correspondance Author:** Dr. Lancy. J, Addl. Prof. of Microbiology, Govt. Medical College, Tvpm.**Conflicts of interest:** None**Abstract:**

Blood stream infections due to candida species cause significant morbidity and mortality especially in the nosocomial setting. The infection is common among the Immuno compromised patients. But it is rare in healthy and non-neutropaenic patients. Systemic candidiasis is an opportune mycosis caused by candida species. Acute disseminated candidiasis usually presents as candidemia. Blood cultures positive for candida species must never be ignored. Surveillance for candidemia is necessary to detect the species distribution and antifungal resistance. A 2 year study was conducted in the department of Microbiology, Govt. Medical College, Thiruvananthapuram, Kerala to find out the prevalence of candidemia among non – neutropaenic patients admitted in the medical wards and intensive care units of the Govt. Medical College Hospital, Thiruvananthapuram. A total number of 4192 blood samples were screened for candida species of which 13 samples yielded candida species in culture. Among the isolates, candida albicans was the predominant species (53.84%) followed by candida tropicalis (15.38%) candida parapsilosis (15.38%) candida glabrata (7.69%) and candida krusei (7.69%). Patients were treated with 3 different antifungal agents – Amphotericin B, Fluconazole and voriconazole. The efficacy of voriconazole was found to be 100%. The

mortality rate was 23.08% in this study which is significantly reduced when compared to many other studies which may be due to prompt diagnosis and effective management with appropriate antifungal therapy.

**Keywords:** Candidemia, Voriconazole.**Introduction**

Candidemia is a fulminant fatal condition encountered with some other serious clinical diseases like leukaemia and other malignancies. Virtually all these patients might have received prolonged antibacterial therapy with broad spectrum antibiotics and corticosteroids. Candida albicans is responsible for more than half of such patients and mortality rate is very high. Candidemia can occur in a hospital setting as a primary central line associated blood stream infection (CLABSI) or secondary blood stream infection. Among the causes of blood stream infections, candida ranks fourth in United States and seventh in Europe. In India it is the third common cause of Blood stream infections in ICU. Candidemia occurs due to colonization of skin and mucous membranes by candida and disruption in the host's natural epithelial barrier due to burns, surgery, insertion of intravenous catheters etc. Transient Candidemia occurs as a result of prolonged intravenous catheters, peripheral plastic indwelling catheters and prolonged hyper alimentation especially in severely debilitated patients who require total parenteral

nutrition (TPN). Transient fungemia spontaneously resolves after removal of the infected catheter. Persistent Candidemia may occur as a complication of suppurative peripheral or central line thrombophlebitis. It should be treated with antifungal drugs. Initial therapy with Fluconazole is started usually. Later, therapy is adjusted according to clinical response, species involved and the antifungal susceptibility testing.

### **Aim of the Study**

The aim of the study was to find out the prevalence of Candidemia among non-neutropaenic patients admitted at Govt. Medical College Hospital, Thiruvananthapuram during the 2 year period and to evaluate the efficacy of the antifungal drugs – amphotericin B Fluconazole and Voriconazole in treating Candidemia and to know the outcome of the patients diagnosed and treated for Candidemia.

### **Materials and Methods**

Study design : Descriptive study.

Study period : 2 years (from January 2007 to December 2008).

Study population: Patients admitted with fever, non neutropaenic during the period.

Study setting : Department of Microbiology, Govt. Medical College and

Dept. of Internal Medicine, Govt. Medical College Hospital, Thiruvananthapuram, Kerala.

### **Collection of Blood Samples**

A total number of 4192 Blood samples were collected from non-neutropaenic patients admitted with fever in the medical wards and Intensive care units of the Govt. Medical College Hospital, Thiruvananthapuram during the above period. 2 samples were collected from each patient under sterile precaution. First sample of 5 ml of blood collected by venepuncture from cubital vein of one forearm after cleaning the site with 70% alcohol and the

second sample was collected from the other forearm after half an hour.

### **Laboratory Procedure**

Immediately after sample collection blood was directly inoculated into the blood culture bottle containing Brain Heart Infusion broth and Brain Heart Infusion Agar slant. After overnight incubation at 37<sup>0</sup>C, the broth was observed for turbidity. If there was no turbidity in the medium, the bottle was slightly tilted so that the broth can flow over the surface of the agar slant. If broth was turbid a smear was prepared from the broth and stained with gram's stain. If gram positive budding yeast cells were seen in the smear, the broth was sub cultured on SDA slope and incubated at RT and at 37<sup>0</sup>C in the incubator. The SDA slopes were examined daily for 3 – 4 days. If colonies appear on the slope, smear was prepared from 1 colony and wet mount preparation with Lacto phenol cotton blue was made and examined under the microscope for the presence of budding yeast to cells. Then germ tube test was done to differentiate *Candida albicans* and non *albicans*.

### **Germ Tube Test**

0.5 ml of human serum is taken in a sterile test tube and one colony of *Candida* species from SDA slope is inoculated in to the serum and incubated at 37<sup>0</sup>C for 2 – 3 hours. After 2 hours, one drop of the fluid is taken on a clean glass slide and examined under microscope. If germ tube is present, presumptive identification of *Candida albicans* is made and confirmed by other biochemical reactions. If it does not produce germ tube, then it is considered as non*albicans*.

### **Species Identification of Candida**

The speciation of *Candida* was done by conventional methods including morphology and chlamyospore formation on Cornmeal Agar and pigment production on CHROM AGAR and germ tube test. A commercially

available kit named Fungichrom-I was used to identify the species of Candida based on the sugar fermentation and assimilation reactions.

**Results**

Of the 4192 blood samples collected with different clinical diagnoses, only 142 samples were from suspected cases of Candidemia which accounts for 3.39%.

**Collection of Samples for Blood Culture**

Provisional diagnosis	No of samples Percentage
P.U.O	1620 (38.65%)
Septicemia	1390 (33.16%)
Infective endocarditic	380 (9.07%)
Meningitis	492 (11.74%)
Weil's disease	466 (11.12%)
Pneumonia	422 (10.07%)
Candidemia	142 (3.39%)
<b>Total</b>	<b>4192 (100%)</b>

Out of the 4192 samples collected, 2558 (61.2%) were collected from male patients and 1634 (38.97%) samples were collected from female patients.

**Gender Distribution**

Male	Female	Total
2558	1634	4192
61.02%	38.97%	100%

**Age Wise Distribution**

Age group	No & Percentage
18 – 20	436 (10.40%)
21 – 30	860 (20.51%)
31 – 40	794 (18.94%)

41 – 50	530 (12.64%)
51 – 60	680 (16.22%)
➤ 60	892 (21.28%)
<b>Total</b>	<b>4192 (100%)</b>

More no. of Blood samples were collected from patients with age group above 60 (21.28%) and also with age group before 21 – 30 (20.51%). Out of the 4192 blood samples collected from non-neutropaenic patients and screened for Candidemia, only 13 samples yielded Candida species. 5 species of Candida were isolated in this study.

Sl. No	Species	No. & Percentage
1	Candida albicans	7 (53.84%)
2	Candida tropicalis	2 (15.38%)
3	Candida parapsilosis	2 (15.38%)
4	Candida glabrata	1 (7.69%)
5	Candida krusei	1 (7.69%)

The predominant species isolated was Candida albicans (53.84%) followed by Candida tropicalis (15.38%), Candida parapsilosis (15.38%), Candida glabrata (7.69%) and Candida krusei (7.69%).

**Location at time of Candidemia**

Intensive care units	8	61.5%
Medical wards	5	38.5%

More number of Candidemia cases with positive blood cultures were obtained from intensive care units (61.5%) and culture positive cases in medical wards was 38.5%.

**Age wise distribution of culture positive cases**

Age group	Number & Percentage
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Below 20	1 (7.69%)
21 – 30	2 (15.38%)
31 – 40	3 (23.08%)
41 – 50	2 (15.38%)
51 – 60	1 (7.69%)
Above 60	4 (30.76%)

Most of the culture positive patients belong to the age group of above 60 years.

**Male: Female ratio of culture positive patients**

Male	Female
No %	No. %
9 (69.23%)	4 (30.77%)

Candidemia occurred more in males (69.23%) than females.

**Treatment for Candidemia Candida Species V/S Antifungal Drug.**

Sl. No	Age & Sex of the patient	Candida species isolated	Antifungal drug administered	Outcome
1	18 Years / Male	Candida albicans	Voriconazole	Survived
2	28 Years / Male	Candida albicans	Voriconazole	Survived
3	35 Years/ Female	Candida albicans	Voriconazole	Survived
4	45 Years / Male	Candida albicans	Voriconazole	Survived
5	32 Years / Male	Candida albicans	Fluconazole	Survived
6	47 Years / Male	Candida albicans	Fluconazole	Survived
7	65 Years/ Female	Candida albicans	Amphotericin B	Survived
8	32 Years / Male	C. parapsilosis	Voriconazole	Survived

9	25 Years / Male	C. parapsilosis	Amphotericin B	Survived
10	62 Years / Male	C. tropicalis	Amphotericin B	Survived
11	58 Years/ Female	C. tropicalis	Fluconazole	Expired
12	70 Years / Male	C. glabrata	Amphotericin B	Expired
13	68 Years/ Female	C. krusei	Fluconazole	Expired

Of the 13 culture positive cases of candidemia treated with the antifungal agents, 10 patients survived and 3 patients died. The mortality rate in this study is 23.08%. 5 patients were treated with Voriconazole and all of them survived. The 3 patients died because of the underlying diseases like diabetic nephropathy, abdominal surgery following road traffic accident and other risk factors like long term intra venous catheters etc.

**Treatment outcome in patients with Candidemia**

Antifungal drug	Total no. of posted	No. of patients survived	No. of patients died
Voriconazole	5	5 (100%)	NIL (0%)
Fluconazole	4	2 (50%)	2 (50%)
Amphotericin B	4	3 (75%)	1 (25.1%)

Of the 13 culture positive cases, 5 of them were treated with Voriconazole and all survived. 4 patients were treated with Fluconazole and 4 were treated with Amphotericin B. Mortality rate in patients treated with Fluconazole was 50% and Amphotericin B (25%). Voriconazole was proved to be better than the other two antifungal drugs used in this study for treating candidemia.

## **Discussion**

Candidemia is a major problem in health-care settings. Various studies conducted at different hospitals around the globe have found a higher incidence of candidemia in ICUS as compared to medical wards. In our study also candidemia cases from ICU were 61.5%. Majority of the patients belongs to age group >60 years (30.76%). More candidemia cases occurred in males (69.23%) candida albicans is the most common cause of candidemia accounting for 53.84%. This is consistent with the studies performed in United States by CDC, National Epidemiology of Mycoses Survey (NEMIS), Surveillance and Control of Pathogens of Epidemiological Importance (SCOPE). These studies were done in large tertiary care hospitals. The Emerging Infections and the Epidemiology of Iowa organisms (EIEIO) surveillance programme reported 58% of candidemia due to candida albicans. The EIEIO surveillance net work included 15 laboratories representing 17 medical centers in Iowa city. In India studies conducted by Department of Microbiology, JIPMER, Pondicherry and Sree Ramachandra Medical College and Research Institute, Chennai reported 57.8% of isolates being candida albicans. Candida tropicalis accounts for 15.38% of candidemia in this study. In Iowa study it was 20%. In a Brazilian tertiary care hospital it was reported as (15%) which is consistent with our study. In India Priyanka Gupta et al reported prevalence rate of 25% candidemia due to C. tropicalis. Candida parapsilosis isolated in our study was 15.38%. In an Italian tertiary care hospital, it was reported as 23% Indian studies reported 12.8% from Chennai and Pondicherry. Trauma centers in New Delhi and AIIMS, reported that candida tropicalis and candida parapsilosis are emerging causes of candidemia in India, which have contributed 59% of the total isolates in their study. Candida tropicalis is the predominant species causing candidemia in North India

and in Chile. Candida glabrata accounts for 7.69% of candidemia in our study which is consistent with the study conducted by an Italian tertiary care centre. It is an emerging pathogen causing candidemia in older adults. A study conducted at the tertiary care trauma centre of the all India Institute of Medical Sciences, New Delhi reported 11.3% prevalence of candida glabrata. A study from a tertiary care centre in North India reported 25% prevalence. Candida krusei isolated in our study was 7.69%. In a tertiary care hospital at Dehradun, in North India reported 16.6% of candida krusei isolated from candidemia cases in ICU.

The mortality rate in our study was 23.08% Active surveillance for candidemia in Australia in 2006 reported death rates associated with candidemia being 40 – 70%. In a study at New Delhi, it was 43%. Despite the availability of new antifungal therapies and publications of several guidelines for management of candidemia require a matter of concern in ICUs as it is associated with increase in mortality.

ESCMID (European Society of Clinical Microbiology and Infection Diseases) guidelines for the diagnosis and management of candidemia in non-neutropaenic patients published in 2012 recommends prophylactic use of Fluconazole followed by treatment with Amphotericin B and Vonicanazole. Treatment duration for candidemia should be a minimum of 14 days after the end of candidemia which can be determined by one blood culture per day until negativity. Switching over to oral treatment after 10 days of intravenous therapy has been safe in stable patients with susceptible candida species.

## **Conclusion**

The incident of candidemia has been on a rise worldwide. Candida albicans remains as the predominant species of Candida causing Candidemia among the non – neutropaenic patients admitted in the intensive care units

and in the medical wards with severe progressive illnesses. In our study, *Candida albicans* constitutes more than 50% of the clinical isolates. During the 2 years study, the prevalence of Candidemia in our institution was 3% and the culture positive candidemia was 0.3% only. Western studies reported 0.4% prevalence rate (average 0.2 to 0.67%). Most of the patients had transient Candidemia due to various underlying factors like prolonged presence of Central Venous Catheters peripheral plastic catheters and parentered hyper alimentation. Repeat blood culture was sterile after 48 hrs, after removing the catheter. Majority of the patients treated with Voriconazole responded well from whom *Candida albicans* and *Candida parapsilosis* were isolated from blood cultures. Fluconazole showed 50% resistance and Amphotericin B showed 25% resistance. *Candida glabrata* and *Candida krusei* isolated in this study were resistant to Amphotericin B and Fluconazole respectively. *Candida glabrata* causes serious illnesses in patients admitted in the hospitals especially in the old age. Even today, candidemia is a leading cause of morbidity and mortality among non-neutropenic patients admitted in ICU. These life threatening nosocomial infections require early diagnosis and prompt to treatment with appropriate anti fungal drugs.

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