

## Frequency, Clinical Presentation and Microbiological Spectrum of Candidemia in a Tertiary Care Center in Karachi, Pakistan

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### Abstract

**Objective:** To document the frequency, clinical presentation, outcome and spectrum of species in Candida blood stream infection.

**Methods:** A prospective, descriptive cohort study was conducted from June 1st till November 30th 2012 at the Sindh Institute of Urology and Transplantation in Karachi, Pakistan. All patients  $\geq 15$  years of age from nephrology, urology, gastroenterology, oncology or intensive care units with candidemia were included.

**Results:** Of 2457 positive blood cultures, 145 (6%) were positive for Candida species in 121 patients. Seventy seven patients were included for further analysis as clinical data was available for these. The majority of patients had renal failure (89.6%) and 44% had femoral line. Non- albicans species were isolated in 70 (90.9%) patients; Candida parapsilosis in 28 (36.4%), C. lusitaniae in 23 (29.9%), C. tropicalis in 16 (20.8%), C. glabrata in 3 (3.9%) with only 7 (9.1%) with C. albicans. Mortality was 23.4% (18 patients).

**Conclusion:** Frequency of candidemia and species distribution with predominantly non-albicans candida in our study is similar to that reported from other developing countries. Mortality is high. The majority of our patients had line related candidemia. Therefore prevention of line infection must be our top priority.

**Keywords:** Candida, Candidemia, Central line associated blood stream infection, Non Albicans candida, C. Albicans, Blood stream infection. (JPMA 64: 281; 2014)

### Introduction

Candida species are the most common cause of fungal infections worldwide. The incidence of Candida infection has risen greatly since the 1940s, when widespread use of antibiotics was introduced. Candida infections can range from localized mucocutaneous involvement to disseminated candidiasis involving virtually any organ.

Candida species are the fourth most common cause of bloodstream infections (BSI) in the United States, often associated with a high mortality.<sup>1</sup> A study in Switzerland found Candida species to be the seventh most common cause of BSI in hospitals.<sup>2</sup> The burden of this illness in terms of morbidity, mortality and expense is enormous.<sup>3,4</sup> Attributable mortality has been reported in the range of 5%-71%.<sup>4</sup>

Developing countries are increasingly reporting trends in Candida infection that are similar to those of countries with advanced medical care. Brazil has reported an overall incidence of 2.49 cases of candidemia per 1000 admissions. Verma et al. from India ranked Candida species as eighth among all isolates from BSI.<sup>5</sup>

The most important predisposing factors for candida infection are the use of antibiotics and indwelling intravenous catheters.<sup>6,7</sup> Neutropenia, surgical procedures and total parenteral nutrition are also significant risk factors for invasive candida infection.<sup>6</sup>

There are more than 150 species of Candida but only 9 are regarded as pathogenic for humans: C. albicans, C. guilliermondii, C. krusei, C. parapsilosis, C. tropicalis, C. pseudotropicalis, C. lusitaniae, C. dubliniensis and C. glabrata. Recently, there has been an increase in the frequency of non-albicans species as etiological agents of candidemia.<sup>3</sup>

Increasing antifungal resistance in Candida species is emerging. Candida glabrata is often resistant to fluconazole, C. krusei is intrinsically resistant to azoles,<sup>8</sup> while C. lusitaniae can be resistant to amphotericin B deoxycholate.<sup>9</sup> As yet, antifungal susceptibility testing of candida is not widely available in Pakistan.

Data from Pakistan on candidemia is limited and there are no prospective studies. Studies have reported the leading causative agents to be C. albicans in neonatal candidemia and C. tropicalis in invasive candidiasis in two separate studies from Karachi.<sup>10,11</sup> Our study aims to document the frequency of Candida amongst blood stream infections, its clinical presentation and outcome at a tertiary care center in Karachi. We also wanted to

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determine which species of *Candida* are most commonly isolated in blood stream infections at our institution.

### Patients and Methods

This prospective study was conducted at the Sindh Institute of Urology and Transplantation (SIUT) in Karachi, Pakistan from June 1st till November 30th 2012. SIUT is a 500-bed urban tertiary care hospital.

All inpatients above the age of 15 years who were admitted in nephrology, urology, gastroenterology, oncology and intensive care units and had *Candida* species isolated in blood cultures, whether in monomicrobial or polymicrobial growth, either on admission or during the course of their hospitalization were included.

Patients on outpatient haemodialysis and renal transplant recipients with candidemia were excluded from the study. We did not include patients who fulfilled the eligibility criteria but had died or were transferred or discharged by the primary team prior to blood culture positivity for *Candida* species.

Patients were included only once with only their first episode of candidemia recorded. Demographic, clinical and microbiological data was documented in a proforma which included age, sex, diagnosis, co-morbidities, duration of hospitalization and antibiotic exposure prior to candidemia, ICU stay, presence of indwelling venous catheters, recent surgeries, steroids and parenteral nutrition. The most likely source of candidemia was evaluated and documented. The primary team was informed and referred to standard guidelines for the management of candidemia.<sup>12</sup> We sought to follow the patient for the duration of the hospitalization for a maximum of 2 weeks from our initial visit and in-hospital mortality within this 2 week period was recorded.

### Microbiology

Blood samples were inoculated in BACTEC 9240 system (Beckton, Dickinson, INC, Sparks, MD) and subsequently on blood agar. All *Candida* isolates, characterized by smooth, creamy white appearance of colonies on blood agar, underwent species identification using standard tests such as production of a germ tube test, morphology on cornmeal/Tween 80 agar, urease production, and the identification profile generated using API 20C Aux (bioMerieux). Antimicrobial sensitivity testing is not available at SIUT.

Candidemia was defined as the isolation of *Candida* species from at least 1 blood culture in the presence of signs and symptoms of systemic fungal infection.

Software SPSS, version 19, was used for statistical analysis. Continuous variables were dealt with mean and standard deviation. Categorical variables were analyzed as frequencies and percentages.

Approval for conducting the study was obtained from the Ethical Review Board of SIUT.

### Results

Over the 6 month study period, 8210 blood cultures were sent from inpatients that met the eligibility criteria. Of these, 2457(29.9%) blood cultures had microbial growth of which 145(6%) were positive for *Candida* species in 121 patients.

Of 121 patients, clinical data was available for 77 patients who were included for final analysis.. Of these, 57 (74%) had *Candida* species in monomicrobial, and 20 (26%) in polymicrobial cultures.

The mean age of participants was 35.87±13.27 years. Females were 40 (51.95%). The majority of patients had

**Table-1:** Demographics, clinical characteristics and outcome in 77 hospitalized patients with candidemia.

Demographic and Clinical Characteristics	Candidemia (n= 77) (%)
Age	35.87 ± 13.27
Females	40(51.9)
Rural residence	34(44.1)
Prior hospitalization <sup>a</sup>	54(70.1)
Empirical Antibiotics <sup>b</sup>	62(80.5)
Fever	72(93.5)
Septic shock	12(15.6)
ICU Stay > 7 days	12 (15.6)
Complications <sup>c</sup>	5(6.4)
Renal Failure	69 (89.6)
Associated Co-morbidities <sup>d</sup>	6(7.8)
Immunosuppressant medications <sup>e</sup>	5 (6.5)
Prior Antibiotic Exposure <sup>f</sup>	52(67.5)
Surgeries	17(22.1)
TPN <sup>g</sup>	9 (11.7)
<b>Site of Central Line</b>	
◆ Femoral	34 (44.2)
◆ Intra-Jugular	20 (26)
◆ Subclavian	14 (18.2)
<b>Source of candidemia</b>	
◆ Central line >48 hours	65(84.4)
◆ Urinary tract	3(3.9)
◆ Post Surgical	9(11.6)
◆ Died	18 (23.4)

a. Hospitalization within 4 weeks prior to current admission. b. Does not include antifungal antimicrobials. c. Endocarditis, pulmonary emboli, stroke. d. Diabetes, neutropenia or malignancy. e. Steroids or antineoplastic medications. f. Antibiotic exposure within prior 4 weeks. g. Total parenteral nutrition.

**Table-2:** Microbiological spectrum in 77 hospitalized patients with candidemia.

Species of Candida	Frequency	Percentage
<i>Candida parapsilosis</i>	28	36.4
<i>Candida lusitanae</i>	23	29.9
<i>Candida tropicalis</i>	16	20.8
<i>Candida albicans</i>	7	9.1
<i>Candida glabrata</i>	3	3.9

renal failure 69 (89.6%) whereas 52 (67.5%) patients received antibiotics in prior 1 month before Candidemia. Thirty-four (44.2%) patients had femoral line in situ. Overall mortality was 18 (23.4%) patients. The details of the clinical and demographic features of patients with Candidemia are shown in Table-1.

None of the patients had received empirical antifungal therapy.

### Species Distribution

Predominantly, non-*albicans* species were isolated (91%). The most prevalent species was *Candida parapsilosis* (36.4%) followed by *C. lusitanae* (29.9%). Only 7 (9.1%) patients had bloodstream infection with *C. albicans* (Table-2).

### Discussion

Our study has demonstrated a frequency of 6% *Candida* as a cause of bloodstream infection. This is similar to the prevalence of 6.14% for *Candida* species reported among blood culture isolates in Thailand.<sup>7</sup> A study from India found a comparable prevalence rate of 6% for *Candida* species in blood stream infections.<sup>7</sup>

Most patients in our study had a central line. *Candida* species adhere to materials used in intravascular catheters which provide a nidus for infection.<sup>7</sup> Our study found subclavian lines to be the least commonly infected, which is considered to be the preferred site for non-tunneled catheters in terms of risk for infection.<sup>13</sup>

Two-thirds of our patients had prior exposure to antibiotics, known to be an independent risk factor for candidemia.<sup>14</sup> One-tenth of our patients were receiving total parenteral nutrition (TPN), identified in many multivariate studies to be an independent risk factor for invasive candidiasis and candidemia.<sup>14</sup> Diabetic patients, of which we had 6, have been observed to have a greater degree of colonization with *Candida* species compared to control subjects.<sup>15</sup>

The majority of invasive infections due to *Candida* species have been attributed to five species; *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis*

and *Candida krusei*. However, the epidemiology of candidemia is different in various parts of the world and follows specific patterns.<sup>7</sup>

Hospital studies have found *C. albicans* to be the dominant species in candidemic patients in Europe and the USA, with prevalence ranging between 61.3% to 81.7% in European studies.<sup>17</sup> *C. Albicans* is less common in Asia and we report a prevalence of 9.1% which is even lower than the 17-33% reported from India.<sup>17</sup> It is the non-*albicans* species that predominate in Asia, Southern Europe and South America, as supported by our study (91%).

*C. parapsilosis* accounted for the highest proportion of *Candida* species in our study. In hospital based studies of candidemia, the frequency of *C. parapsilosis* was highest in Saudi Arabia (44%), Italy (35.5%), and Portugal (32%) whereas in India it varies from 9.5% to 20%.<sup>17</sup> It is especially known for causing BSI in infants and neonates. *C. parapsilosis* is found commonly on the skin surface and has been associated with formation of biofilms in central catheters and other implanted devices, and the use of TPN solutions. *C. parapsilosis* has therefore been increasingly implicated in BSI after placement of intravascular devices.<sup>6</sup> A study of invasive candidiasis from Pakistan also found that isolation of *C. parapsilosis* was higher with established central line associated blood stream infection (CLABSI)<sup>11</sup> Since most of our patients had central lines, it is not surprising that we found *C. parapsilosis* to be the dominant species.

We report the highest prevalence worldwide of 29.9% of *C. lusitanae* in patients with candidemia, and was the second most prevalent species in our study. In Europe, reported prevalence of *C. lusitanae* in bloodstream infections was found to be highest in Greece, where its relative frequency was 5% in the neonatal ICU. USA reported a prevalence of 2.2%, Turkey 3.9%, whereas India has reported 4.8%.<sup>17</sup> Another study from Australia in 2009 reported the prevalence of *C. lusitanae* to be as high as 12%.<sup>18</sup> High prevalence of *C. lusitanae* in our institution may be attributable to its propensity to form biofilm<sup>19</sup> which makes it a likely pathogen in CLABSI. Further studies are required.

Epidemiological studies have implicated *C. tropicalis* in as many as 33-60% of cases of candidemia, mainly in patients with haematological malignancies and neutropenia.<sup>20</sup> *C. tropicalis* was the third most prevalent species in our study (20.8%) whereas in India it is now the most common cause of nosocomial candidemia. *C. tropicalis* was also the most prevalent *Candida* species in a study of invasive candidiasis from Karachi, particularly in

patients with chronic liver disease. Increased *C. tropicalis* gastrointestinal carriage, has been proposed as a factor predisposing to candidemia with this species.

*C. glabrata* was the least prevalent species in our study whereas it was found to be the most prevalent in studies from Europe where proportions of 19.6-27% have been reported. Prevalence of *C. glabrata* in candidemic patients in studies from India ranges from 9.5-17%, 3% from Saudi Arabia and 5% from the United Arab Emirates.<sup>17</sup> *C. glabrata* fungemia occurs more often in older adults and among patients with haematological malignancies.

Almost all our patients with candidemia, except 3 cases of *C. glabrata*, had isolation of species which are known to be sensitive to fluconazole. *C. krusei* was not isolated in any patient. In a study from Karachi, no resistance to fluconazole was found for *C. parapsilosis*, *C. lusitanae*, *C. tropicalis* and *C. albicans*, whereas 15% of *C. glabrata* were resistant.<sup>11</sup> Therefore, fluconazole is an appropriate antifungal for empirical and directed therapy in the majority of candidemic patients. However, since *C. glabrata* can be resistant to fluconazole, whereas *C. lusitanae* can be resistant to amphotericin B deoxycholate, species identification is very important.

The species of *Candida* isolated has been seen in several studies to be an important determinant of the patient outcome. *C. parapsilosis*, which was the most common isolate in our study, was proved in other studies to have the lowest mortality rate.<sup>4</sup> Our mortality rate of 23.4% is high but comparable or lower than those reported from other countries such as 27% in Australia,<sup>21</sup> 36.7% in Taiwan<sup>22</sup> and 47% in Saudi Arabia.<sup>23</sup> Delay in administering systemic antifungal therapy for the treatment of *Candida* bloodstream infection >12 hours after the first positive blood culture is drawn, is a potential risk factor for mortality.<sup>24</sup> Our patients received antifungal therapy only after blood cultures were reported positive for candidemia. To minimize delay in starting antifungal therapy and reduce mortality, physicians should be able to identify subsets of patients who are at high risk for candidemia so that prophylactic, preemptive and early empirical therapy strategies may be implemented.<sup>6</sup> Removal of vascular catheters and at least 5 days of antifungal therapy have been found to be independently associated with a reduction in mortality.

More importantly than administering antifungal therapy, emphasis on prevention of candidemia can decrease mortality more effectively.<sup>25</sup> Compliance with hand hygiene recommendations is mandatory. Guidelines for prevention of CLABSI have recommended

implementation of the Central Line bundle.<sup>13</sup> Educational programmes must emphasize essential components of these guidelines. Judicious use of antibiotics is another important strategy in the prevention of nosocomial candidemia.

Although this is a prospective study, one of the major limitations of our study is that it is a single institution's experience so results cannot be generalized. Therefore, multicentric studies are required to identify risk factors. Also, since treatment decisions were made by the attending physician and not based on a controlled protocol, conclusions regarding outcome should be interpreted with caution.

## Conclusion

Frequency of candidemia in our population is similar to that reported from other developing countries as is the finding that non-*albicans* species are more common in this part of the world. None of the patients had received empirical antifungal therapy and mortality was high. Therefore, further studies are required to identify subsets of patients most at risk for candidemia so that early empirical antifungal therapy can be instituted. Fluconazole remains a good choice for antifungal therapy. Most importantly, since the majority of our patients had line related candidemia, one must focus on the prevention of CLABSI as its foremost priority.

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