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Original Research Article

Candidemia in a tertiary care hospital: Changing trends

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ABSTRACT

Background: Candida has emerged as a major cause of blood stream infections and ranks among the top ten pathogens responsible for hospital acquired infections. It is more common in children and adults admitted in critical care units. Though *Candida albicans* was the most commonly isolated species there has been a shift to Non-albicans species of Candida (NAC) as the major causative agent in the recent years. Many NAC are also intrinsically resistant to azoles.

Materials and Methods: Blood samples from patients with suspected candidemia were received in automated blood culture bottles. *Candida* species were identified using standard microbiological techniques, including CHROM agar and VITEK 2 compact. Patient's demographic and clinical details were collected. Data was analyzed using Microsoft excel.

Results: Out of the 4367 blood culture samples received, 131 (2.99%) grew *candida* species. Most frequently isolated species was *Candida parapsilosis* (32%) followed by *C.tropicalis* (29%). Antifungal resistance was notable: 26.8% of isolates were resistant to fluconazole , 11.5% to voriconazole,10% to caspofungin,7.7% to micafungin and 18.4% to amphotericin B. Mortality due to candidemia was 16.79%, with C.parapsilosis being the most prevalent species among deceased patients

Conclusions: With the emergence of drug-resistant *Candida* species, the treatment of candidemia is becoming increasingly challenging. Rapid diagnosis, early treatment, adherence to proper infection control and antimicrobial stewardship practices are essential to reduce the burden of candidemia in developing countries like India. Effective management strategies are crucial to improve patient outcomes and combat the rising threat of antifungal resistance.

1. Introduction

Candida species are normal inhabitants of skin and mucosa.[1] It can become pathogenic in situations where the host defences are disturbed. Risk factors include immunocompromised conditions like diabetes mellitus, prolonged use of steroids, long term use of antibiotics, old age, presence of indwelling devices and recent gastrointestinal surgery[1,2]*Candida* can cause various clinical manifestations like oropharyngeal candidiasis, vulvovaginal candidiasis, genitourinary candidiasis and blood stream infections.[3] Over the past two decades, blood stream infections (BSI) caused by *Candida* species are increasing. Prevalence of candidemia in India (2020) ranges from 1.31%- 3.41%.[4,5] Although *Candida albicans* was considered as the most common species causing candidemia, BSI caused by Non-albicans *Candida*(NAC) species like *C. tropicalis* & *C. parapsilosis* (in developing countries) and *C. glabrata* (in developed nations)are emerging as a major cause of nosocomial infections.[5,6] Increased morbidity and prolonged hospital stay are

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associated with invasive candidiasis resulting in mortality. Mortality associated with candidemia is estimated to be 19–24% by CDC.[7]

Fluconazole is the most commonly used antifungal for the treatment of candidemia. *Candida* krusei is intrinically resistant to fluconazole. Other NAC species like, *Candida* guilliermondii, *C.glabrata C. inconspicua* are less susceptible to azoles. Though resistance to echinocandins is considered rare, it is also on the rise. Intrinsic and acquired resistance to various antifungals is becoming a major problem in treatment of candidemia.[2] Therefore it is important to identify the *Candida* species causing sepsis and determine their antifungal susceptibility pattern to select the right antifungal giving appropriate coverage. This will help in effective management of these patients, thus reducing mortality caused by *Candida* and also to control outbreaks.[8] This study was undertaken to find out prevalence of *candida* species causing sepsis and its outcome in a tertiary care hospital.

2. Materials and Methods

2.1. Study design

Descriptive cross-sectional study.

2.2. Study period

July 2021 to June 2023.

2.3. Place of study

Department of Microbiology, tertiary care hospital, Pune

2.4. Methodology

All the blood samples received during the study period and which grew *Candida* species were included in the study. Blood cultures which grew organisms other than *Candida* species were excluded from the study. Blood samples of patients with suspected candidemia were received in automated blood culture bottles (BD BACTECFX 40) and were incubated in the automated BD BACTEC TM FX (Becton, Dickinson and Company, NJ, and USA). Once the bottle flagged positive, Gram stain was done and presence of gram positive budding yeast cells was recorded. Gram's staining findings were immediately communicated to clinician for early start of antifungal therapy. *Candida* species were identified by routine conventional methods like growth on blood agar (Figure 1), SDA (Sabouraud Dextrose Agar), germ tube test, CHROM agar *Candida* (HiMedia, Mumbai, India) (Figure 2) and automated identification system (VITEK 2 compact - BioMérieux, France). In vitro antifungal susceptibility profile was determined by the automated antifungal susceptibility system (VITEK 2 BioMérieux, France). Demographic and clinical details of the patients were collected.

2.5. Statistical analysis

The collected data was entered in Microsoft excel sheet and analysed. Data presented as numbers and percentages.

3. Results

A total of 4367 blood cultures were received during the study period. Of this, 131(2.99%) grew *Candida* species. 36 (out of the 131) isolates were obtained from children below one year of age (Table 1). Majority {91 of 131 (69.4%)} of the patients were admitted in critical care units (ICUs) (Figure 3), out of which (45) 34.35% were adults, while (46)35.1% were children below 10 years. Male and female patients were equally affected. Majority of the patients had associated co-morbidities like diabetes mellitus, malignancy, chronic kidney disease (Table 2). *C. parapsilosis* was isolated from 42 samples (32%), followed by *C. tropicalis* 38 (29%) , C. albicans 30 (22.9%), C.guilliermondi 07 (5.34%), *C.glabrata* 06 (4.58%), C.krusei 05 (3.8) and C.lusitaniae 01 (0.78) (Figure 4). Antifungal susceptibility pattern of the *Candida* isolates showed that 73.2% were susceptible to fluconazole, 88.5% to voriconazole, 90% to caspofungin, 92.3% to micafungin, 81.6% to amphotericin B and 100% to flucytosine (Figure 5). A total of 16.6% of C.parapsilosis strains were resistant to fluconazole, voriconazole and amphotericin B while 7.4% were resistant to caspofungin and micafungin. Seventeen (44.7%) *C.tropicalis* strains were resistant to fluconazole, 7 (18.4%) were resistant to amphotericin B and voriconazole while 4(10.5%) were resistant to caspofungin and micafungin each. C.albicans strains were fully susceptible to all antifungal agents except (n=4)13.3% of strains which were resistant to fluconazole (Table 3) Antifungal susceptibility testing of *Candida auris* isolates could not be performed.

3.1. Follow up

Twenty two (16.79%) patients succumbed to candidemia (Table 4). All others responded to azole group of drugs. Two patients infected with *Candida auris* were treated with echinocandins. Contact precautions were followed while handling these patients.

4. Discussion

Over the recent years, *Candida* has emerged as a major cause of blood stream infections. In the United States, *Candida* species have been found to be the fourth most common cause of blood stream infections.[9] *Candida* ranks among the top ten pathogens responsible for hospital acquired blood stream infections.[2] A study by Chakrabarti A has found that the rate of candidemia in developing countries is 4-15 times more than in developed countries.[10] The prevalence of candidemia was found to be 2.99 %

Table 1: Age wise distribution of patients

Age group (in years)	Number of patients
0-1	36
1-10	09
11-20	08
21-30	07
31-40	13
41-50	30
51-60	15
61-70	07
71-80	06
>80	0
Total	131

Table 2: Associated Co-morbidities

Co-morbidities associated	Number of patients with risk factors
Diabetes mellitus	40
Chronic kidney disease	20
Malignancy	25
Prolonged use of broad spectrum antibiotic	90
Prolonged stay in ICU/NICU (>1 month)	30
Total parenteral nutrition	20
Premature neonates with respiratory distress	25
Presence of CVC	28

Abbreviations used: NICU- Neonatal ICU, PICU- Paediatric ICU

Table 3: Antifungal resistance in different Candia species *100% susceptible to Flucytosine

Candida species	Fluconazole	Voriconazole	Caspofungin	Micafungin	Amphotericin B
C. albicans	4	0	0	0	0
C. parapsilosis	7	7	3	3	7
C. tropicalis	17	7	4	4	7
C. guilliermondi	3	1	2	2	2
C. krusei	5IR	0	0	0	5
C.glabrata	4	0	4	1	3
C. lusitaniae	0	0	0	0	0

Abbreviations used- IR: Intrinsic resistance

Table 4: *Candida* species isolated from patients who expired due to candidemia

Candida species isolated	Number of patients
C. parapsilosis	9
C.tropicalis	7
C.glabrata	4
C.albicans	1
C.guilliermondii	1

in our study. The prevalence of candidemia was found to be 3.4% by Ahmed S et al in Uttar Pradesh, 1.3% by Kaur H et al in Chandigarh (North India), 1.4% by Jain V et al in Rajasthan (Western India), 3.8% by Behera C et al in Bhubaneswar (Eastern India) and 0.65% by Giri S et al in Tamil Nadu (South India).[4,5,11–13] In our study, 27.4% of the population was below 1 year of age. As per Mantadakis E et al, candidemia is several times more common in infants and neonates than in adults .Main risk factors associated with candidemia in children were respiratory diseases, prematurity, ICU admission, mechanical ventilation, neutropenia, and malignancy.[14] In our study comorbidities associated with candidemia in neonates were prematurity and respiratory distress syndrome. All the children were admitted in critical care units. In the present study the risk factors in adults were diabetes mellitus, chronic kidney disease and malignancy. In the study of Blyth et al., renal disease, recent surgery, diabetes mellitus and haemodialysis were the frequent risk factors in adults.[15] Underlying conditions

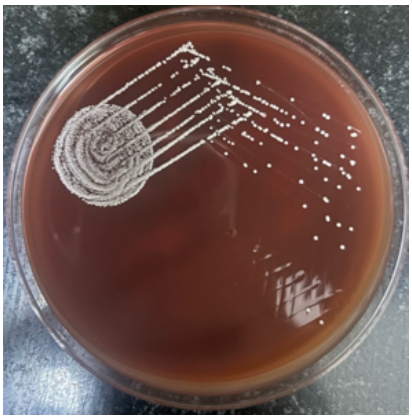

Figure 1: Growth of *Candida* on blood agar

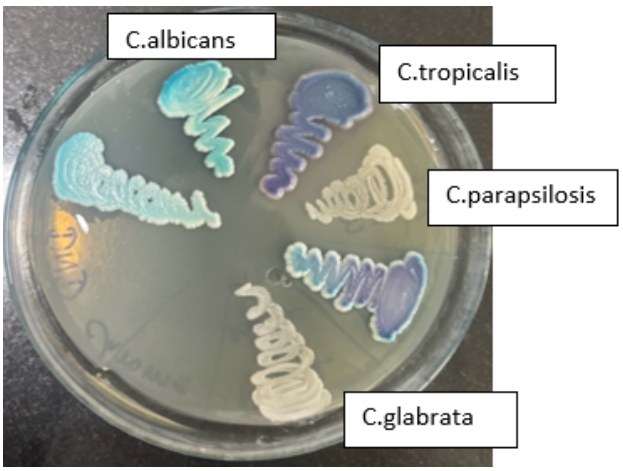

Figure 2: CHROM agar

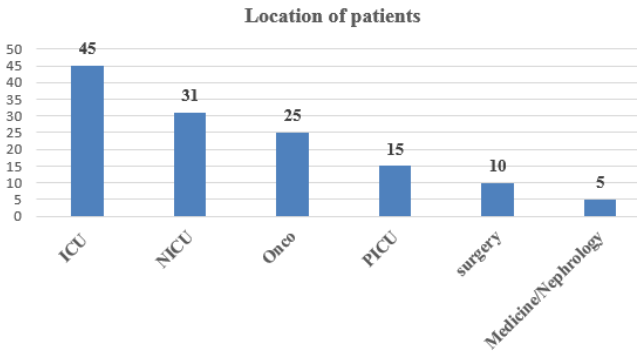

Figure 3: Location of patients

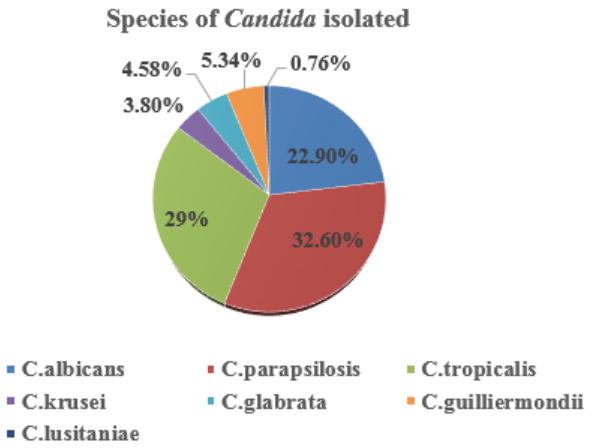

Figure 4: Isolated *candida* species

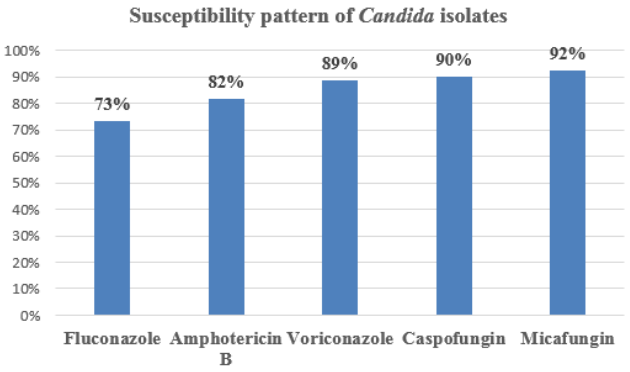

Figure 5: Antifungal susceptibility pattern of all *Candida* isolates

like renal insufficiency, trauma, gastrointestinal perforation, prolonged use of broad spectrum antibiotics, stay in ICU or use of central venous catheter were predisposing factors in a study done by Capoor MR et al.[16] It has been observed that candidemia is more common in diabetic patients because of the adhesion of yeast to host epithelium, high serum glucose levels as compared to healthy individuals, poor candidacidal activity of neutrophils and microvascular degeneration.[17] In present study, 19.0% (25) had history of malignancy. Presence of central venous catheter or parenteral nutrition were the reason for development of candidemia in patients with hematologic malignancies in a study by Girmenia C et al.[18]

In India, a change in trend of species causing candidemia in the recent years from C albicans to NAC[6] has been observed. Along with C albicans, other NAC species like *C. parapsilosis*, C.krusei, *C. tropicalis* and *C. glabrata* contribute to 92% of cases candidemia globally. *Candida* glabrata is common in elderly patients and *Candida albicans* is more common in children upto 18 years of age.[19] *Candida auris* which was considered a rare pathogen

previously is also becoming a prominent pathogen.[20] This shift could be due to better detection rate of NAC or as a result of rampant use of fluconazole for treatment of all fungal infections resulting in shift in the colonisation and infection with fluconazole resistant strains like *C. krusei.*[21–28] In our study, *Candida parapsilosis* was the commonest species (32%) which correlated with the studies undertaken by Shivprakash et al (28.8%) and Capoor et al. (27.4%).[6,16] Low prevalence of *C. parapsilosis* was reported in studies conducted by Sridharan et al (17%) and Bhattacharje et al(17%) and Amir et al (8%).[22,27,28]

Fluconazole is the preferred antifungal for treatment of less severe infections while echinocandins are preferred for moderate to severe infections or in systemic candidiasis as per the guidelines from the Infectious Diseases Society of America.[2] Fluconazole being the most frequently used antifungal, its resistance is on the rise in many parts of the world.[4] Various studies have reported resistance to fluconazole i.e 10% by Seyoum E et al in Ethiopia(2020),15% by Bilal H et al in China (2022), 5% by Bedini A et al in Italy(2006) and 34.8% by Bhattacharjee P et al in India(2016).[21–24] In the present study 26.7% of the isolates were resistant to fluconazole. This is slightly higher than other studies as candidemia caused by NAC was more common in this study. Many species of *candida* are intrinsically resistant to many antifungals. C. auris is intrinsically resistant to polyenes and fluconazole while *C. krusei* is intrinsically resistant to fluconazole. Empiric antifungal therapy is usually given in febrile neutropenia patients who do not respond to antibiotic therapy and in cases of perforated peritonitis. This has led to the development of acquired resistance to many antifungals especially the azoles. Mechanisms by which azoles develop resistance are over expression of membrane transporters, alteration of ergosterol biosynthesis, sterol import alteration and genome plasticity.[25]

Hand hygiene, isolation of patient, environmental disinfection and avoiding unnecessary use of broad spectrum antibiotics are measures by which candidemia can be controlled to an extent. If the patient is on central venous catheter, it must be regularly monitored for signs of infection.[26]

5. Conclusion

The prevalence of candidemia was found to be 2.99%, with an increasing trend of bloodstream infections caused by non-albicans *Candida* (NAC) species. Most cases occurred in patients admitted in critical care units. Commonly isolated species were *Candida parapsilosis* and *Candida* tropicalis, many of which showed resistance to the commonly used antifungal fluconazole. The recent emergence of *Candida auris* has further complicated the treatment of candidemia. Rapid diagnosis, early treatment, strict infection control measures, and robust antimicrobial stewardship practices are essential to reduce the burden of candidemia.

6. Ethical Approval

This study was approved by the institutional Ethical Committee (Approval number-BVDUMC/IEC/263).

7. Conflict of Interest

None.

8. Source of Funding

None.

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