Prevalence of Candidemia with Susceptibility Pattern in a Tertiary Care Hospital in North India

Ashish William[1], Aroma Oberoi[2], Divya Dsouza[3], Arpit Oberoi[4]

[1,2] Department of Microbiology, Christian Medical College & Hospital, Ludhiana, Punjab, India.
[3,4] Christian Medical College & Hospital, Ludhiana, Punjab, India.

ABSTRACT

BACKGROUND

Blood stream infections (BSI) caused by various candida species have been reported from many countries worldwide and are a significant cause of morbidity and mortality in hospitalised patients. The alarming increase in infections with multidrug resistant bacteria is due to overuse of broad-spectrum antimicrobials, which leads to over growth of candida species; thus, enhancing its opportunity to cause the disease. During recent decades, there has been a change in the epidemiology of candida infections, characterised by a progressive shift from a predominance of *Candida albicans* to non-albicans candida species. This study was conducted to determine the prevalence of candidemia in blood stream and the susceptibility pattern in a tertiary care hospital in North India.

METHODS

This is retrospective study which has been conducted for a period of 1.5 years form April 2015 to October 2016. All blood cultures received during this period by BACTEC automated culture system and Becton Dickinson were included in the study. The culture was done on positive blood culture bottles and were cultured on Sabouraud dextrose agar. Recovered candida isolates were speciated and antifungal susceptibility testing was performed as per Clinical and Laboratory Standards Institute guidelines (CLSI).

RESULTS

A total of 80 out of 8020 blood cultures were culture positive for candida species. Therefore, the overall prevalence rate of isolation of candida species was 0.99 % in our study. The incidence of blood stream infection caused by non albicans candida species (73.8 %) was higher than *Candida albicans* (26.2 %). Among NAC species, *Candida tropicalis* (44 %) was the most common, followed by *Candida parapsilosis* (24 %), *Candida glabrata* (17 %), *Candida krusei* (8.5 %), *Candida guilliermondii* (5 %) and *Candida dubliniensis* (1.5 %). Candidemia was predominantly observed in ICU patients. Resistance was significantly higher among non-albicans candida species (NAC), amphotericin B, fluconazole, ketoconazole, itraconazole and clotrimazole - 96.72 %, 59.84 %, 51.23 %, 19.44 %, and 56.15 % respectively.

CONCLUSIONS

With an ever-expanding array of non-candida species-related infections in highly compromised and terminally ill patients, understanding the activity of the antifungal agents used against both *C. albicans* and nonalbicans species becomes mandatory. Continued surveillance of candida infections will be required to document changes in epidemiology and antifungal susceptibilities.

KEYWORDS

Bloodstream Infections, Candidemia, Non Albicans Candida (NAC)

Corresponding Author:
Dr. Ashish William,
22/108, First Floor,
West Patel Nagar - 110008,
New Delhi, India.
E-mail: ashudon.william@gmail.com

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BACKGROUND

Over the last few years, the incidence of fungal infections caused by opportunistic fungal pathogens, such as yeasts and yeast-like species, has witnessed a dramatic increase. The most important yeasts isolated from clinical specimens are candida species. These species infect hospitalised patients, especially those admitted to intensive care units or oncology wards. Invasive candida infection has been associated with high mortality.[1-2]

The importance of candida species as a cause of BSI has been highlighted in many studies in the past few years. In the hospital set up in United States, candida species has been considered as one of most common cause of blood stream infections.[3]

Among patients admitted in intensive care units (ICUs), those admitted in surgical ICUs (SICUs) are considered to be at a greater risk for developing candidemia.[4] There are many risk factors which can lead to the development of candidemia in surgical ICU, along with wide variation in infection rates between institutions with the highest rates of candidemia seen in urban hospitals caring for trauma patients.[4] The risk factors independently associated with development of candidemia includes prior surgery, acute renal failure and parenteral nutrition. An elevated acute physiology and chronic health evaluation II (APACHE) score can help identify ICU patients who can have a higher risk of developing candidemia which may help in diagnosis[4]. SICU patients had a longer duration of antibiotic therapy and received a larger number of antibiotics than patients admitted in MICU. SICU patients also have other risk factors like total parenteral nutrition (TPN) and central venous catheters (CVCs).[5]

More than 90 % of the invasive infections due to candida are attributed to five species; *C. albicans, C. glabrata, C. parapsilosis, C. tropicalis* and *C. krusei*. However, the list of new species of candida isolated from clinical specimens continues to grow every year.[6]

In contrast to the United States (US) scenario, in many other countries, *C. tropicalis* and *C. parapsilosis* have become the most common candida species to cause BSI.[6] In India, *C. tropicalis* is now the most common cause of nosocomial candidemia. *C. tropicalis* has been seen to be covering around 67 - 90 % of cases of candidemia.[7-8] The increased use of fluconazole has been determined to be the major cause of predominance of non-albicans candida, especially *C. tropicalis* over *C. albicans*.[9] Among the non-albicans candida species, *C. glabrata* has emerged as an important opportunistic pathogen worldwide. It is the second most common yeast isolated as part of normal flora and its role as a pathogen has only been recognised in the past few decades. In today's era, there has been a considerable increase in the isolation rate of *C. glabrata* from BSI in ICUs.[10]

Apart from resistance to antifungal agents which is one of the most important causes of antifungal treatment failure, many other factors also play important roles in this. Host factors like severity of the illness or immunosuppression can lead to treatment failure. Decreased bioavailability and decreased concentration of the drug at the target site due to various pharmacokinetic and pharmacodynamic variables also lead to antifungal treatment failure.

Antifungal prophylaxis is commonly used in patients with specific risk factors like malignancies, transplant patients and patients with neutropenia. Whereas guidelines for the treatment of candidemia are available, the role of prophylactic or empirical therapy in preventing candidemia or decreasing the mortality rate associated with it is not very clear.

Empirical therapy is instituted before the diagnosis of candidemia. Because of the high mortality associated with delayed therapy in candidemia especially in neutropenic patients, empirical therapy with anti-fungal drugs is usually advocated for such patients.[11] This study was conducted to know the prevalence of candidemia in blood stream and the susceptibility pattern in a tertiary care hospital in North India.

METHODS

This retrospective study was conducted for a period of 1.5 years. Blood cultures received during this period by Becton Dickinson BACTEC 9120 and 9050 automated culture system; were included in the study. Blood sample was collected in automated blood culture bottle under proper aseptic conditions. Then blood culture bottle was put in automated microbial detection system based on the colorimetric detection of carbon dioxide (CO2) produced by microorganisms. After signalling positive for blood culture bottle, samples were inoculated on routine culture media and further tests were performed. The isolates of candida were identified to the species level. Primary identification was done by direct smear examination of blood samples by Gram stain. Sample was inoculated on Sabouraud dextrose agar (SDA) and incubated at 37° C and 25° C for 48 - 72 hours. Typical candida colonies, characterised by smooth, creamy and pasty appearance on SDA were speciated using standard tests such as germ tube test, sugar assimilation test, sugar fermentation test, microscopic morphology on corn meal agar and color production on CHROMagar media (Himedia Laboratories Pvt. Ltd. Mumbai, India).

The candida isolates were also subjected to antifungal susceptibility testing using the disk diffusion method on Müller–Hinton agar with 2 % glucose and 0.5 lg / ml methylene blue, according to the standard Clinical and Laboratory Standards Institute (CLSI) guidelines. Antifungal drugs like amphotericin B (100 units / disc), fluconazole (10 mcg / disc), itraconazole (30 mcg / disc), ketoconazole (10 mcg / disc) and clotrimazole (10 mcg / disc) were used for antifungal susceptibility. For interpretation of sensitivity, zone sizes recommended by the CLSI guidelines corresponding to year were referred to.[12] American Type Culture Collection (ATCC) strains *C. albicans* 90028, *Candida parapsilosis* 22019 and *Candida krusei* 6258 were used as controls.

The study protocol was reviewed and approved by the institutional ethics committee and written informed consent was recorded from each of the recruited patients.

Statistical Analysis

Descriptive statistics was used to summarise demographic and other clinical features of patients. Qualitative and quantitative data values were expressed as frequency along with percentage.

RESULTS

During this period of 1.5 years, a total of 8020 blood culture samples were processed out of which total of 80 samples were positive for candida species. Therefore, the overall prevalence rate of isolation of candida species was 0.99 % in our study. Out of the 80 candida isolates, 21 (26.2 %) were *Candida albicans*, while majority 59 (73.8 %) were NAC species (Figure 1). Among NAC species *Candida tropicalis* 26 (44 %) was the most common, followed by *Candida parapsilosis* 14 (24 %), *Candida glabrata* 10 (17 %), *Candida krusei* 5 (8.5 %), and *Candida guilliermondii* 3 (5 %) and *Candida dubliniensis* 1 (1.5 %) (Figure 2).

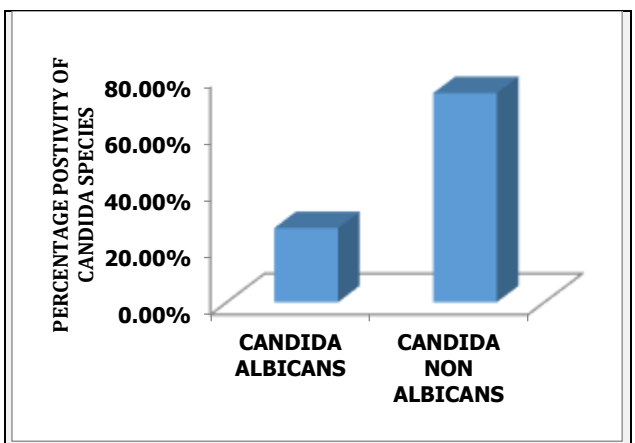

Figure 1. Distribution of Candida Isolates Percentage

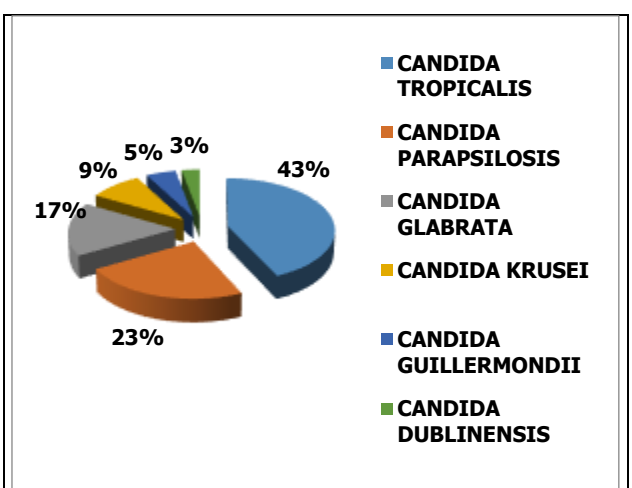

Figure 2. Distribution of Non Albicans Candida

Majority of candida species were isolated from adult patients (65 %) followed by patients of age group < 1 year (10 %) whereas 25 % strains were isolated from age group 1 - 18 years. We noted a predominance of male patients (65 %). The male to female ratio was 2:1.

Candidemia was observed in 44 patients from ICU from surgical ICU, medical ICU, paediatric ICU, high dependency unit (HDU) and 36 patients from ward (burn unit ward, haemato-oncology ward, medical ward, paediatric ward and surgical ward). Among ICUs, 25 (56.8 %) patients with candida infection were observed from paediatric ICU followed by 8 (18.1 %), 6 (13.6 %), 5 (11.5 %) from surgical ICU, medical ICU and ward respectively. The candida infection among wards is predominantly seen in haemato-oncology ward followed by paediatric ward, medical ward, surgical ward and burn unit ward with 15 (41.6 %), 8 (22.2 %), 6 (16.6 %), 4 (11.1 %), 3 (8.5 %) patients respectively (Table 2). All these patients who had candidemia have received broad spectrum antibiotics with presence of central venous catheter in 58 (72.6 %) patients and peripheral venous catheter in 17 (21.25 %) patients. There were 53 patients who were on total parenteral nutrition, 26 patients on corticosteroid therapy and 15 patients with diabetes (Table 3).

Candida Isolates	Fluconazole	Ketoconazole	Itraconazole	Clotrimazole	Amphotericin B
C. albicans (21)	21 (80 %)	16 (76 %)	16 (76 %)	15 (71 %)	21 (100 %)
NAC (59)	32 (54 %)	36 (61 %)	33 (55 %)	33 (55 %)	58 (98 %)
Total (80)	**53**	**52**	**49**	**48**	**79**

Table 1. Comparison of Antifungal Susceptibility between NAC and C. albicans

	Location of Candidemia	Positivity
ICU	Paediatric ICU	25 (56.8 %)
	Surgical ICU	8 (18.1 %)
	Medical ICU	6 (13.6 %)
	HDU	5 (11.5 %)
WARD	Haemato-oncology ward	15 (41.6 %)
	Paediatric ward	8 (22.2 %)
	Medical ward	6 (16.6 %)
	Surgical ward	4 (11.1 %)
	Burn unit	3 (8.5 %)

Table 2. Distribution of Candidemia According to Location (N = 80)

Predisposing Factor	Positivity
Broad spectrum antibiotics	80 (100 %)
Central venous catheter	58 (72.6 %)
Total parenteral nutrition	53 (66.25 %)
Corticosteroids	26 (32.5 %)
Peripheral venous catheter	17 (21.25 %)
Diabetes	15 (18.75 %)
Previous surgeries	10 (12.5 %)
Haemodialysis	3 (3.75 %)

Table 3. Predisposing Factors in Candidaemia Patients (N = 80)

Antifungal susceptibility profile of Candida species is shown in Table 4. As compared to amphotericin B, *Candida albicans* demonstrated higher resistance to azole group of antifungal agents. Among azoles, *C. albicans*, demonstrated good sensitivity against fluconazole (80 %) and ketoconazole (76 %). Azole resistance was significantly higher among NAC species. like *Candida tropicalis*, *Candida glabrata* and *Candida parapsilosis*.

Because *Candida krusei* is intrinsically resistant to azoles. It was not analysed for sensitivity to the azole group of drugs. Amphotericin B was sensitive in 100 % isolates of

Candida albicans, *C. parapsilosis*, *C. guilliermondii*, *C. glabrata, C. krusei*, followed by *Candida tropicalis* (96 %). *Candida dubliniensis* isolate was resistant to amphotericin B. For NAC species, resistance to amphotericin B, fluconazole, ketoconazole, itraconazole and clotrimazole was found in 98 %, 54 %, 61 %, 55 %, and 55 % of the cases, respectively.

Non albicans Candida Species (59)	Fluconazole	Ketoconazole	Itraconazole	Clotrimazole	Amphotericin B
C. tropicalis (26)	17 (65 %)	20 (76 %)	17 (65 %)	18 (69 %)	25 (96 %)
C. parapsilosis (14)	10 (71.4 %)	12 (85.7 %)	8 (57 %)	9 (64.2 %)	14 (100 %)
C. glabrata (10)	6 (60 %)	5 (50 %)	4 (40 %)	6 (60 %)	10 (100 %)
C. krusei (5)	0	0	0	0	5 (100 %)
C. guilliermondii (3)	2 (66.6 %)	2 (66.6 %)	2 (66.6 %)	1 (33 %)	3 (100 %)
C. dubliniensis (1)	1 (100 %)	0	0	1 (100 %)	0

Table 4. Antifungal Susceptibility Patterns of Non-Candida albicans

DISCUSSION

Both albicans and NAC cause invasive candidiasis, and the antifungal resistance of invasive candida aggravates the situation. Increasing number of treatment failures, associated mortality, and shift to more resistant isolates advocate the need for species identification in candida.[13]

Candidemia is reported as the fourth common cause of BSIs in the intensive care units (ICUs) and account for 10 % of all BSIs. In the present study, candidemia accounted for 0.99 %. There are studies done in India with variable prevalence rate of candidemia which ranges from 0.65 % to 6.9 % (Giri et al. 2013, Verma et al. 2003, Sanhi et al. 2005 and Deorukhkhar et al. 2012).[14-16] Majority of candida species were isolated from adult male patients followed by patients of age group < 1 year (12 %) whereas 16 % strains were isolated from age group 1 - 15 years. These findings were similar to a number of reports from all around the Indian suncontinent.[17,18]

In the present study, the predominance of NAC species (73 %) was observed over *C. albicans* (27 %). It was similar to another study conducted in Haryana, India which had shown 77 % NAC as compared to *C. albicans* (33 %).[21] Recent epidemiological data also revealed a mycological shift from *Candida albicans* to the nonalbicans candida (NAC) species such as *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, and *Candida krusei*. It is considered that frequent use of fluconazole as antifungal prophylaxis has played a major role in the emergence of NAC species. Some of these species have been correlated with increased virulence and sometimes with increased mortality.[19]

More than 90 % of the invasive infections due to candida are attributed to five species; *C. albicans, C. glabrata, C. parapsilosis, C. tropicalis* and *C. krusei*. However, the list of new species of candida isolated from clinical specimens continues to grow every year.[20] In the present study also, among NAC *C. tropicalis* was the most common isolate (44 %), *Candida parapsilosis* (24 %), *Candida glabrata* (17 %), *Candida krusei* (8.5 %), *Candida guilliermondii* (5 %) and *Candida dubliniensis* (1.5 %). This was similar to other findings done in India.[19,21]

It was observed in various studies about greater incidence of candidemia in ICUs than wards.[22] Also in our country, according to one multicentric study, early colonisation was seen by candida species in Indian ICUs. Lack in healthcare is considered as the important cause of early acquisition of candidaemia post admission in ICU.[23] Colonisation in > 70 % neonates has been noticed within a week after delivery in one study in India, the reason of higher incidence of candidemia than developed countries in paediatric ICU is probably due to the higher colonisation.[24] Even in our study, the results were similar predominantly paediatric ICU with maximum cases (Table 2).

In a study conducted by Yapar et al*.* it was found that there are some predisposing factors independently associated with candidemia like catheter, antibiotics usage and total parenteral nutrition.[25] According to one Indian study, there is also increased risk of developing candida infection with the increase in usage of broad spectrum antibiotics due to increased duration of stay in hospital.[22] Indwelling vascular catheters is considered to be an important risk factor in patients with candidemia. The probable cause of infection is due to strong adherence to materials which is used in intravascular devices.[26] In a study done in Uttar Pradesh, India, central venous catheter was seen in 66.7 % of candidemia patients.[26] In our study, the similar factors (central venous catheter, antibiotic usage, neutropenia, transfusions and total parenteral nutrition) was seen with 72.6 % candidemia patients with central venous catheter. The results were also similar to one study done by Chow et al*.* in which central venous catheter was found to be associated with maximum candidemia patients (90 %) as predominant risk factor.[27]

Many researchers have confirmed that decreased susceptibility to candida is significantly associated with previous antifungal exposure and an inappropriate prior course of antifungal therapy.[28,29] In fact, fluconazole exposure was found to be a risk factor for gene mutation and overexposure that leads to future fluconazole-resistant *C. parapsilosis*.[30] It is conceivable that the selective pressure of fluconazole, due to the increased use of this antifungal in some hospitals,[31] may be responsible for both the emergence of *C. glabrata* and fluconazole resistance, with the latter being related to the ability of the microorganism to rapidly develop secondary antifungal resistance due to its haploid state.[32] In our study, it was observed that NAC species has significantly high resistance to azoles as compared to *C. albicans*. These findings are similar to the studies done in northern India and Maharashrta.[33,34] It was also observed in our study that *C. glabrata* has shown highest resistance to azoles. *C. glabrata* has the highest incidence of azole resistance among candida clinical isolates and exhibits intrinsic decreased susceptibility to the azole class of antifungals.[35]

Also, we noticed that among *Candida tropicalis* isolates fluconazole resistance was 35 %. This is similar to the study results (31 %) from China.[36] According to some previous studies indicated that invasive infections caused by *C.*

tropicalis have higher mortality compared to those caused by other non-tropicalis candida species.[37]

Reports of resistance to amphotericin B among isolates of candida are limited. However, some species like *C. lusitaniae*, *C. lipolytica* and *C. guilliermondii* can show intrinsic resistance to amphotericin B. There have been a few reports of strains of *C. albicans* showing resistance to amphotericin B.[38] In our study, it has been observed that all *Candida albicans* isolates were sensitive to amphotericin. These findings remained in concordance with a study done by Kaur et al. who quoted that resistance rate was lower for amphotericin B (7.8 %) with candida isolates studied, and Monda et al. reported that all the candida isolates remained sensitive to amphotericin B.[39,40]

High resistance to antifungal agents is an alarming sign to the healthcare professionals. Therefore, early and accurate diagnosis of candida infection is essential.

CONCLUSIONS

With an ever-expanding array of non-candida species-related infections in highly compromised and terminally ill patients, understanding the activity of the antifungal agents used against both *C. albicans* and nonalbicans species becomes mandatory. This study demonstrates significant association of broad spectrum antibiotics and central venous catheters as predominant risk factors for candidemia. It is comforting to know that amphotericin B remains efficacious against both albicans and nonalbicans species. However, fluconazole has exhibited reduced activity, especially among NAC species, and resistance to other azoles has also been encountered among those with acquired resistance to fluconazole. There is a need for continuous surveillance and complete understanding of the important differences among resistance mechanisms employed by these species to combat with this important clinical problem.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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