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PREVALENCE AND ANTIFUNGAL SUSCEPTIBILITY OF *CANDIDA* SPECIES IN BLOODSTREAM INFECTIONS AMONG PEDIATRIC PATIENTS IN A TERTIARY CARE HOSPITAL

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Abstract

Introduction: Candidemia, a severe and potentially life-threatening bloodstream infection caused by *Candida* species, remains a significant concern in pediatric populations, especially in developing countries such as India. The increasing prevalence of non-*albicans Candida* (NAC) species, which often exhibit reduced susceptibility to commonly used antifungal agents, has further complicated clinical management and therapeutic outcomes.

Aim: The present study aimed to evaluate the prevalence of *Candida* species in bloodstream infections among pediatric patients and to characterize their antifungal resistance patterns.

Material and methods: Blood samples from patients with suspected candidemia were collected in automated blood culture bottles. Identification of *Candida* species was performed using standard microbiological techniques, including the VITEK 2 Compact system. Antifungal susceptibility was assessed using the AST-YS09 card, which determines the minimum inhibitory concentration (MIC) for six antifungal agents i.e., voriconazole, caspofungin, flucytosine, micafungin, fluconazole, and amphotericin B.

Results: A total of 97 (6.2%) *Candida* isolates were identified, with *Candida albicans* (32%) being the most prevalent species, followed by *Candida tropicalis* (22.6%), *Candida parapsilosis* (19.5%), *Candida pelliculosa* (12.3%), *Candida glabrata* (7.2%), *Candida krusei* (4.1%), and *Candida guilliermondii* (2%). Antifungal resistance was notable, with 36% of isolates resistant to flucytosine, 32% to fluconazole, 26% to amphotericin B, 21.6% to voriconazole, 14.4% to micafungin and 12.3% to caspofungin.

Conclusion: Our study highlights a higher incidence of non-*albicans Candida* species compared to *Candida albicans*, with a notable resistance to various antifungal agents. These findings underscore the urgent need for antifungal stewardship programs and stringent preventive control measures to mitigate the further spread of antifungal resistance.

Keywords: *Candida albicans;* Non-albicans *Candida;* Candidemia; Antifungals; Candidemia; Resistance; VITEK

Introduction:

Candidemia is a leading cause of invasive fungal infections in hospitalized patients [1,2]. *Candida* species have now emerged as the fourth most common causative agent of nosocomial sepsis [3]. Pediatric patients diagnosed with candidemia experience higher mortality rates, prolonged hospital stays, and a significant increase in total hospital costs per patient [4].

According to data from the Centers for Disease Control and Prevention (CDC) and the National Healthcare Safety Network (NHSN), *Candida* species rank as the fourth most common pathogens causing bloodstream infections (BSIs) and the fifth most prevalent hospital-acquired pathogens [5–7]. While *Candida albicans* was historically the predominant cause of candidemia, non-*albicans Candida* (NAC) species, such as *C. tropicalis* and *C. parapsilosis* in developing countries and *C. glabrata* in developed nations, are increasingly recognized as significant contributors to nosocomial infections [8,9]

Pediatric patients with *Candida* bloodstream infections (BSIs) remain at risk for other nosocomial infections, including recurrent candidemia or secondary bacterial infections [10,11]. The rising antifungal resistance among *Candida* species significantly contributes to morbidity and mortality in neonates and children. Fluconazole remains the most commonly used antifungal for treating candidemia; however, *Candida krusei* exhibits intrinsic resistance to fluconazole, while other non-*albicans Candida* (NAC) species, such as *Candida guilliermondii*, *Candida glabrata*, and *Candida inconspicua*, demonstrate reduced susceptibility to azoles. Although echinocandin resistance has traditionally been considered rare, its incidence is increasing. Both intrinsic and acquired resistance to antifungal agents pose significant challenges in the management of candidemia [12]. Therefore, accurate identification of *Candida* species and determination of their antifungal susceptibility patterns are crucial for selecting the most effective treatment and ensuring appropriate antifungal coverage.

Unfortunately, data on antifungal susceptibility patterns in pediatric patients with candidemia remain limited. As a result, empirical treatment for suspected invasive candidiasis in children is often based on extrapolated data from adult populations. Given this gap in pediatric-specific data, the present study aims to evaluate the prevalence of *Candida* species in bloodstream infections among pediatric patients and to characterize their antifungal resistance patterns.

Methodology

This retrospective study was conducted over a period of two years in the Department of Microbiology at the Government Institute of Medical Sciences (GIMS), Greater Noida, India.

Blood cultures received from all suspected cases of septicemia and various locations, such as neonatal intensive care units (NICU), Pediatric intensive care units (PICU), Sick intensive care unit (SNCU), outpatient departments (OPDs), and wards during this period were processed using the Becton Dickinson BACTEC TM FX40 automated culture systems. Blood samples were collected under strict aseptic conditions in BacT/ALERT (bioMérieux) culture bottles for aerobic bacterial and fungal growth and incubated at 37°C for up to seven days. Upon a positive signal from the BacT/ALERT system, the culture bottles were unloaded, and a preliminary Gram stain was performed. The samples were then subcultured on Sabouraud dextrose agar (SDA) supplemented with chloramphenicol (0.5 g/L) (Oxoid, UK) and incubated at 37°C for 24–48 hours.

Colonies were identified using standard microbiological methods, including colony morphology, Gram staining, and germ tube testing. Further confirmation was performed using the VITEK 2 Compact system (bioMérieux, USA) with YST ID REF21343 (yeast identification cards), following the manufacturer's instructions.

Antifungal Susceptibility Testing

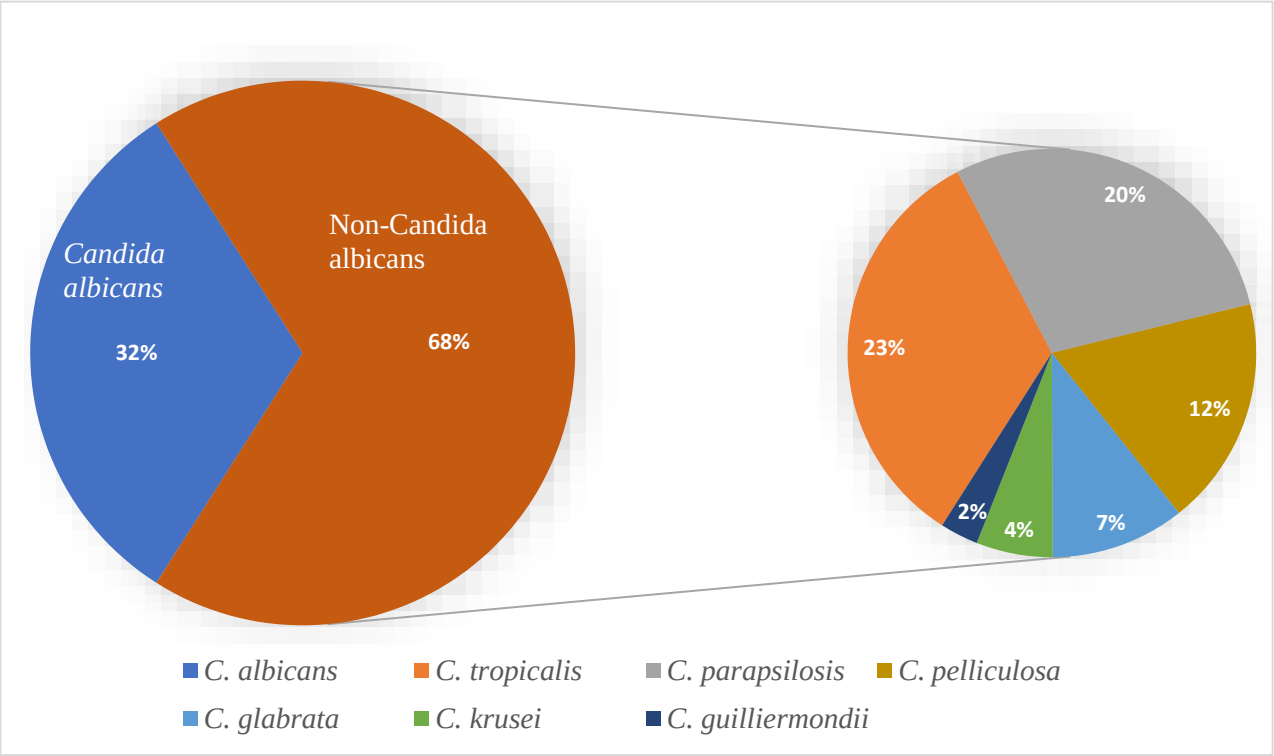
Antifungal susceptibility testing of *Candida* isolates was conducted using the VITEK 2 system, following Clinical and Laboratory Standards Institute (CLSI) guidelines [13]. The AST-YS08 card was used to determine the minimum inhibitory concentration (MIC) of six antifungal agents: voriconazole, caspofungin, flucytosine, micafungin, fluconazole, and amphotericin B.

Data obtained from this study were analyzed using various descriptive statistics like percentage and proportion. The Chi-square test was used to determine the association of various parameters with *C. albicans* and NAC. All the data analysis was performed using the SPSS software (version 28.0).

Results

Among all 1542 the blood samples processed, a total of 97 (6.2%) samples tested positive for *Candida* species. Of these, *Candida albicans* accounted for 31 (32%) isolates, while the majority, 66 (68%), were non-*albicans Candida* (NAC) species (Graph 1). Among NAC species, *Candida tropicalis* was the most prevalent, with 22 (22.6%) isolates, followed by *Candida parapsilosis* 19 (19.5%), *Candida pelliculosa* 12 (12.3%), *Candida glabrata* 7 (7.2%), *Candida krusei* 4 (4.1%) and *Candida guilliermondii* 2 (2.1%) (Graph 2).

Graph 1: Distribution of *Candida* Species Isolated from Bloodstream Infections

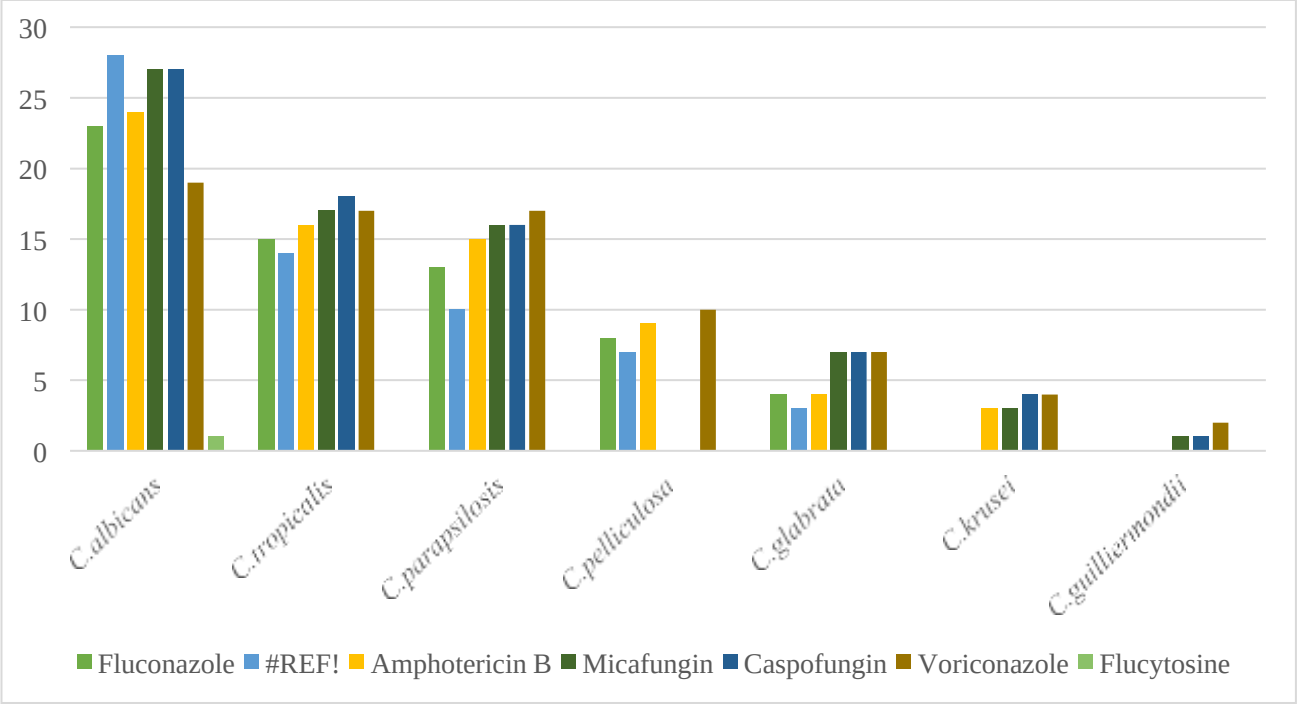


Among these, 97 samples yielded *Candida* species. The highest incidence of candidemia was observed in infants (41.2%), followed by neonates (37.1) (Table 1).

Table 1: Distribution of Candidemia Cases by *Candida* Species and Age Group

Species	Neonate (birth to <1 month)	Infant (1 month to <1 years)	Children (1 to <12 years	Adolescent (12–14 years)	Total No. (%)
C. albicans	13 (36%)	11 (27%)	5 (33%)	2 (33%)	31 (28.6%)
C. tropicalis	8 (22%)	9 (22%)	3 (20%)	2 (33%)	22 (23.5%)
C. parapsilosis	7 (19%)	9 (22%)	2 (13%)	1 (17%)	19 (17.6%)
C. pelliculosa	4 (11%)	7 (17%)	1 (7%)	0	12 (12.5%)
C. glabrata	2 (5%)	2 (5%)	2 (13%)	1 (17%)	7 (8.8%)
C. krusei	2 (5%)	1 (2.5%)	1 (7%)	0	4 (6.6%)
C. guilliermondii	0	1 (2.5%)	1 (7%)	0	2 (2.2%)
Total	36 (37.1%)	40 (41.2%)	15 (15.4%)	6 (6.5%)	97

Graph 2: Antifungal Susceptibility Patterns of *Candida albicans* and Non-*Candida albicans* Species



Antifungal susceptibility testing (AFST) results revealed *C.pelliculosa* read fluconazole, voriconazole, amphotericin B and flucytosine. *C.krusei* is intrinsic resistant to fluconazole and read caspofungin, flucytosine, micafungin, fluconazole and amphotericin B.

Among *Candida* isolates voriconazole (78.3%) and caspofungin (75.2%) exhibited the highest efficacy against *Candida* species, followed by micafungin (73.1%) and amphotericin B (73%). Fluconazole and flucytosine demonstrated the lowest efficacy, with a susceptibility rate of 65% and 64%.

Among individual species, *Candida albicans* showed the highest resistance to voriconazole (38.7%) and fluconazole (29%). *Candida tropicalis* exhibited maximum resistance to flucytosine (37%) and fluconazole (32%), while *Candida parapsilosis* displayed the highest resistance to flucytosine (47%) and fluconazole (31%). *Candida glabrata* showed notable resistance to flucytosine (57%). *Candida krusei* was intrinsically resistant to fluconazole, whereas *Candida guilliermondii* demonstrated the highest resistance to amphotericin B (100%) and flucytosine (100%).

Discussion

The overall prevalence of *Candida* species in our study is 6.2% distribution of *Candida* species in this study revealed that *Candida albicans* accounted for 32%% of cases, while non-*albicans Candida* (NAC) species constituted 68%. This finding is consistent with a study conducted in Haryana, India, which reported a higher prevalence of NAC species (77%) compared to *C. albicans* (33%) [14]. Similar trends have been observed in recent studies from various Indian healthcare settings, where NAC isolation rates have ranged from 66% to 90% [15–18].

In recent years, *Candida* has emerged as a major causative agent of bloodstream infections. In the United States, *Candida* species rank as the fourth most common cause of bloodstream infections [19] and are among the top ten pathogens responsible for hospital-acquired bloodstream infections [12]. Additionally, a study by Chakrabarti A. reported that the incidence of candidemia in developing countries is 4–15 times higher than in developed nations [20].

In this study, *Candida albicans* accounted for 32% of cases, while non-*albicans Candida* (NAC) species constituted 68%. This finding aligns with a study conducted in Haryana, India, which reported a higher prevalence of NAC species (77%) compared to *C. albicans* (33%) [14]. Similar trends have

been observed across various Indian healthcare settings, with NAC isolation rates ranging from 66% to 90% [15–18]. Over the years, *Candida* has emerged as a major cause of bloodstream infections. In the United States, *Candida* species are the fourth most common cause of bloodstream infections [19] and rank among the top ten pathogens responsible for hospital-acquired bloodstream infections [12]. Furthermore, a study by Chakrabarti A. reported that the incidence of candidemia in developing countries is 4–15 times higher than in developed nations. [20]

In the present study, among 97 *Candida* isolates, the most common species identified was *C. albicans* (32%), followed by *C. tropicalis* (23%), *C. parapsilosis* (19.5%), *C. pelliculosa* (12.3%), *C. glabrata* (7.2%), *C. krusei* (4.1%), and *C. guilliermondii* (2%). These findings are consistent with studies conducted by Capoor Malini et al. [21] and Naseem Shaikh et al. [31]. Additionally, *C. tropicalis* was reported as the most common species by Jyoti Pal et al. [32]. Similarly, a study from North India identified *C. tropicalis* (39%) as the most frequently isolated species, followed by *C. parapsilosis* (18%) [33]. In contrast, a study from South India found *C. parapsilosis* to be the predominant pathogen among pediatric patients [34].

The pediatric population is particularly vulnerable to *Candida* bloodstream infections (BSI). In the present study, the prevalence of candidemia was highest among infants (41.2%), followed by neonates (3%). A declining trend in infection rates was observed with increasing age, suggesting an inverse relationship between age and candidemia prevalence. This pattern aligns with findings from other studies, which reported a high prevalence of candidemia among neonates (35%) [35–36]. The increased susceptibility in neonates and young children is primarily attributed to their underdeveloped immune system, which is not yet fully equipped to mount an effective defense against infections. Consequently, *Candida* can proliferate and invade the bloodstream, leading to BSI. Significant variations in *Candida* species distribution were observed across different pediatric age groups. In our study, *C. albicans* (36%) and *C. tropicalis* (22%) were the predominant species among neonates. Similarly, a study from Chile reported that neonates had the highest proportion of *C. albicans* cases (60%) [37]. Among infants, *C. albicans* (27%) was the most frequently isolated species, followed by *C. tropicalis* (22%).

Regarding antifungal resistance, the highest resistance was observed against flucytosine (36%), followed by fluconazole (32%) and amphotericin B (26%). Previous studies have also reported fluconazole resistance rates of 10% in Ethiopia (Seyoum E et al., 2020), 15% in China (Bilal H et al., 2022), 5% in Italy (Bedini A et al., 2006), and 34.8% in India (Bhattacharjee P et al., 2016) [38, 24–26]. Many *Candida* species exhibit intrinsic resistance to antifungal agents, with *C. krusei* being inherently resistant to fluconazole. As fluconazole remains one of the most commonly used antifungal agents, its resistance is rising in various parts of the world, posing a significant challenge in treatment [39].

Most *Candida* isolates in our study were susceptible to caspofungin based on the revised CLSI breakpoints. However, resistance was observed against fluconazole, amphotericin B, micafungin, voriconazole, and caspofungin. This resistance may be attributed to reduced susceptibility to fluconazole and cross-resistance among azole antifungals. Consistent with previous studies, we found higher mortality rates among patients infected with non-*albicans Candida* (NAC) species compared to those infected with *C. albicans* (68% vs. 32 respectively), highlighting the clinical significance of NAC infections and the need for effective antifungal stewardship.

CONCLUSION

In the present study, candidemia accounted for 6.2% of all bloodstream infections (BSIs) among pediatric patients, with a predominance of non-*albicans Candida* (NAC) species. The most commonly isolated species were *Candida tropicalis* and *Candida parapsilosis*. Among the antifungal agents tested, voriconazole exhibited the highest activity, whereas fluconazole showed the lowest efficacy. Early diagnosis of *Candida* BSI and determination of its resistance profile are crucial for optimizing treatment strategies and improving clinical outcomes, particularly in critically ill neonates and young children.

Conflicts of Interest

The authors declare no conflicts of interests.

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