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Research Article

Candidemia - Species Distribution and Antifungal Resistance Patterns in Two Tertiary Care Centers in South India

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Abstract

Background: Bloodstream infections due to *Candida* species are a significant cause of morbidity and mortality in hospitalized patients worldwide. Epidemiology of Candidemia is dynamic with reports of non-albicans *Candida* species on a steady increase and the emergence of *C.auris* reported from many centers in India. This study was undertaken to analyze species distribution and antifungal susceptibility of *Candida* bloodstream infections in two tertiary care centers in Telangana, South India.

Material and Methods: In a retrospective analysis, *Candida* isolates from blood cultures of patients with suspected bloodstream infection over five years (2017-2021) were identified and tested for antifungal susceptibility by Vitek 2 Compact (Biomerieux, France).

Results: A total of 85,603 blood cultures were processed from two centers from January 2017 to December 2021. Among these, 270 (0.31%) *Candida* species were isolated. Of the total Candida isolates, *C. tropicalis* (49.2%) was the most common isolate, followed by *C. albicans* 55 (20.3%), *C. glabrata* 35 (12.9%), *C. parapsilosis 25* (9.2%), *C. auris* (5.5%), *C. guilliermondii* (1.4%) and *C. krusei* (1.1%). We have tested six antifungals and of the total isolates, resistance to fluconazole was highest (11.9%) followed by amphotericin B (7.0%), caspofungin (2.9%), voriconazole (2.3%), flucytosine (1.8%) and micafungin (0.7%). *C.auris* isolates were found to be resistant to two or three classes of antifungals tested and 13.3% were pandrug -resistant.

Conclusion: *C.tropicalis* was the most common isolate and each *Candida* species showed varied antifungal resistance rates. We emphasize the need for the identification of *Candida* species and antifungal susceptibility for every invasive isolate to tailor targeted preventive and therapeutic antifungal strategies in line with current evidence and guidelines.

Keywords: Candidemia; *Candida* species; Antifungal resistance

Introduction

Over the past decade, there has been a steady increase in the incidence of Invasive Fungal Infections (IFI), particularly candidemia. As a result of advances in medical care, there are more immunocompromised patients as well as critically ill patients who are prone to fungal infections in the hospital setting. Exposure to broad-spectrum antibiotics, the Central Venous Catheter (CVC), recent major surgery, necrotizing pancreatitis, total parenteral nutrition, and diabetes mellitus are common risk factors for candidemia [1].

Despite the availability of safe and effective choices of antifungal treatment, candidemia has an overall crude mortality rate of 40-60% [2,3], and early suspicion and prompt treatment with antifungals are critical to enhancing survival. There is considerable geographic variation in the range of *Candida* species isolated from hospitals. Non-*albicans Candida*. Has been almost universally prevalent over the last decade, accounting for more than 50% of all *Candida* isolates [3]. With the growing resistance to commonly used antifungals and the emergence of

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multidrug-resistant *C.auris*, it is essential to know the local epidemiology of *Candida* species and rates of antifungal resistance to make informed therapeutic decisions while awaiting culture and susceptibility data.

Data regarding the epidemiology of *Candida* is scarce from the south India. This study aims to describe the epidemiology of *Candida* species isolated from two tertiary care hospitals in South India over 5 years from January 2017 to December 2021 and compare the findings with other published studies from India. To our knowledge, this is the only study from South India reflecting data collected over more than 2 years duration.

Materials and Methods

A retrospective observational study was conducted in the Department of Clinical Microbiology in two tertiary care centers in Hyderabad, Telangana. All patients with suspected bloodstream infections admitted to the hospital from January 2017 to December 2021 were included in the study. Candidemia was defined as the isolation of Candida species from blood cultures in a patient with signs and symptoms of bloodstream infections. Demographic data of all patients such as age, gender, and location were derived from the hospital medical records system. *Candida* species were isolated from blood samples using BacT/Alert ((Biomereiux, France), and identification with antifungal susceptibility testing was done by Vitek 2 Compact (Biomereiux, France) using ID-YST and AST-YS08 cards respectively according to manufacturer's instructions. A total of six antifungals were tested including amphotericin B, fluconazole, voriconazole, caspofungin, micafungin, and flucytosine. For *Candida* species except for *C.auris,* MIC breakpoints were interpreted as per CLSI M27-A3 supplement for yeasts [4]. For *C. auris* breakpoints were defined based on expert opinion as released by the US Centers for Disease Control and Prevention (CDC) in October 2017 and modified in April 2019 [5,6]. Microsoft Excel Ver 16.16.17 (2018) was used to tabulate and statistically analyze the results.

Results

A total of 85,603 blood samples from patients with suspected bloodstream infection were processed during the five years study period (January 2017 to December 2022) with a prevalence of 0.31% candidemia. The age of the patients with candidemia ranged from 21 days to 80 years with a median age of 58 years among them 210(77.7%) were males and 60(22.2%) were females, of which 192(71.1%) were from ICU and 78(28.8%) were from wards. Among *Candida* species, *C. tropicalis* 133(49.2%) was the commonest isolate, followed by *C. albicans* 55(20.3%), *C.glabrata* 35(12.9%), *C. parapsilosis* 25(9.2%), *C.auris* 15(5.5%), *C. guilliermondii* 4(1.4%) and *C. krusei* 3(1.1%) (Figure 1). Of the total candida isolates resistance to fluconazole was highest (11.9%) followed by amphotericin B (7.0%), caspofungin (2.9%), voriconazole (2.3%) and (1.5%) flucytosine (1.8%) micafungin (0.7%) (Table 1). Among seven species of candida isolated, *C.auris* were (100%) resistant to amphotericin B and fluconazole, (23%) to flucytosine, (13.3%) to caspofungin, (13.3%) to micafungin. Of the total 15, *C.auris* isolate 2 (13.3%) were pandrug- resistant.

Discussion

Candidemia is an emerging problem in healthcare settings worldwide. In the present study, the incidence of Candida bloodstream infection was 0.31%. A great variation in the incidence of candidemia has been reported in India with isolation rates ranging from 0.65% to as high as 18.86% has been reported in various studies from the subcontinent [7-15]. It is interesting to note that most of these studies are from the northern part of the country and the occasional study we found reported from South India had lower isolation rates of Candidemia (0.65%, 1.05%) similar to our study [14,15]. In a nationwide, multicentric study performed at 27 Indian ICUs, Chakrabarti et al. reported an overall incidence of 6.51 cases per 1,000 ICU admissions [16].

The distribution of Candida species isolated from blood varies markedly between different geographical areas in the world. Studies from India's tertiary care centers have reported a steady rise in the incidence of candidemia caused by non-albicans Candida, with isolation rates varying from 50 to 96% [17]. In our study also, non-albicans Candida (79.6%) bloodstream infections were more common. This finding is consistent with other studies not only from the Indian subcontinent but also from Asia, Southern Europe, and South America [18]. In contrast, C. *albicans* is still reported to be the most common isolate in Northern Europe and the USA [19].

More than 90% of invasive infections are attributed to five species: *C. tropicalis, C. albicans, C. glabrata, C. parapsilosis, C. guilliermondii,* and *C. Krusei* [20]. In our study also, these five species were predominantly isolated and in addition, we isolated *C auris* accounting for 5.5% of the total 270 isolates. Similar to our study, in India, *C. tropicalis* ranks first as a cause of candidemia, reported in as many as 34.4-74.6% of cases [7,10-11,16,17,21,22]. These studies also underline the declining incidence of candidemia caused by *C. albicans*. Also, in line with other studies [11,23-25], *C. glabrata* was the third most isolated Candida species isolated at our center. The increased isolation of *C. glabrata* is believed to be a consequence of the increased use of fluconazole within the hospital set-up, especially as prophylaxis for immunosuppressed patients or patients of suspected sepsis with multiple invasive intravascular catheters. Due to the same reason, there has also been an increase in the incidence of *C.krusei.* Fluuconazole MICs are naturally high in *C.glabrata* isolates and *C.krusei* is considered to be intrinsically resistant to fluconazole [26].

Table 1: Antifungal resistance of each Candida species isolated.

Candida species	Amphotericin B n(%)	Fluconazole n(%)	Voriconazole n(%)	Caspofungin n(%)	Micafungin n(%)	Flucytosine n(%)
C tropicalis (n=133)	4(30.0%)	8(6.0%)	5(3.7%)	0(0%)	0(0%)	2(1.5%)
C albicans (n=55)	0(0%)	1(1.8%)	1(1.8%)	0(0%)	0(0%)	0(0%)
C.glabrata (n=35)	0(0%)	0(0%)	0(0%)	6(17.1%)	0(0%)	0(0%)
C.parapsilosis (n=25)	0(0%)	7(28%)	0(0%)	0(0%)	0(0%)	0(0%)
C.auris (n=15)	15(100%)	15(100%)	0(0%)	2(13.3%)	2(13.3%)	3(20.0%)
C.guilliermondii (n=4)	0(0%)	1(25%)	0(0%)	0(0%)	0(0%)	0(0%)
C.krusei (n=3)	0(0%)	*na	0(0%)	0(0%)	0(0%)	0(0%)
Total (n=270)	19(7.0%)	32(11.9%)	6(2.3%)	8(2.9%)	2(0.7%)	5(1.8%)

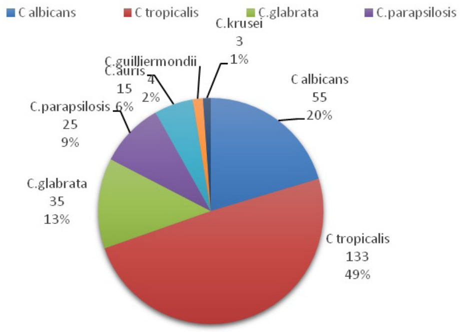

Figure 1: Species distribution of Candida isolates.

C.parapsilosis isolation has been associated with vascular catheters, prosthetic devices, and parenteral nutrition [27] and is an emerging cause of candidemia in India. In our study, we have isolated 9.2 % *of C.parapsilosis* similar to other studies from India [16,21,28]. Earlier, *C. guilliermondii* was thought to be an animal saprophyte with little or no involvement in human infection. Over the recent past, there is a rise in the infections caused by *C. guilliermondii*, with reported incidence ranging from 0.6 % in North America to 3.7 % in Latin America [29] and 0.95-10.1% from India [7,22,28] and there was an overall decline in isolation of *C. guilliermondii* and *C.krusei* during the study period.

C.auris at our institute was first isolated in 2017, confirmation of species identification was done at the Post Graduate Institute of Medical Education and Research, Chandigarh which is the Center for Advanced Research in Medical Mycology in India, and subsequent identification was done by Vitek 2 compact version 8.01. *C.auris* ranked 5th most predominant isolate causing candidemia at our institute and over the recent 5 years, 2017-2021, we isolated 15 *C.auris*. Other centers from India have also reported the recent isolation of *C. auris* indicating that this species is an emerging pathogen in this part of the world [8,22].

A range of antifungal drugs is available belonging to three major classes -polyenes, azoles, and echinocandins. Knowledge of local epidemiology is crucial to decide on the choice of empirical antifungal treatment along with patient co-morbidities and cost of treatment. The emergence of non-albicans Candida and the prevalence of antifungal-resistant strains mandates the identification of all invasive candida species along with its antifungal susceptibility testing for tailoring treatment.

Among the total 270, Candida isolates 11.9% were resistant to fluconazole, and 2.3% were resistant to voriconazole. Fluconazole resistance was not reported for *C.krusei* in our study as it is considered to be intrinsically resistant and *C.glabrata* isolates all of which are considered to have intermediate susceptibility to fluconazole [26]. The prevalence of azole resistance from other studies from India varied from 3.3% to 64% [7,13,17,22] for fluconazole and 2.4 to 8.82% for voriconazole [7,1].

The high bioavailability, the multitude of dosage forms, minimal side effects and the relatively low cost make fluconazole preferable antifungal for all types of yeast infections but, there is a growing incidence of its resistance. Further analysis of our study showed that all 15 isolates of *C.auris* (100%), 7(28%) *C.parapsilosis*, 1(25%) of *C. guilliermondii*, and 8(6%) of *C.tropicalis* isolates were resistant to fluconazole which were the major contributors and *C.albicans,* showed very low resistance of 1.8%.

In *C.auris*, a very high resistance to fluconazole of 90-100% has been reported in other studies from India [30,31]. Some authors have suggested that there might be a mechanism of intrinsic resistance to explain such high MICs of >32µg/ml [31-33]. However, in the landmark multicentre study by Chakraborti et al in 2014, [16] the resistance of fluconazole reported against *C.auris* strains was only 30.8%. A nationwide multicentre study is required to ascertain whether the high resistance is a recent phenomenon and the mechanisms contributing to the development of resistance.

There appears to be a dichotomy in reported resistance rates to fluconazole concerning *C. parapsilosis,* while Kaur et al [7] have reported low resistance (<10%) over the past 20 years, other studies have reported high resistance of 37.5% [34], 38.5% [21] like our findings of 28%. In a large, international antifungal surveillance program [35] the percentage of resistance is low (<10%) however, the authors have noticed resistance to fluconazole raised eventually in this isolate. Importantly, in our present study, no resistance to azoles among *C.glabrata* was observed which is similar to one Indian study [36] and other multi-centric studies from Peru [37], indicating the possibility of genetic strain variations in Indian *C. glabrata* isolates compared to other countries. Very few studies from India have reported resistance to echinocandins**.** In our study, we have reported resistance to caspofungin in *C. glabrata* and resistance to both caspofungin and micafungin in *C. auris* while other species did not show resistance to echinocandins. Other studies from India have reported echinocandin resistance [7,21,34] with higher resistance reported in *C. auris*, *C. glabrata,* and *C. krusei*. Resistance to amphotericin B in our study was also present in all 15(100%) *C. auris* isolates. This may be explained in part by recent studies which demonstrate that under stress conditions, a hypermutable state may lead to rapid acquisition of resistance to fluconazole, echinocandin, and amphotericin B [35] and it may be why, even though the drug targets and resistance mechanisms are vastly different, resistance too many antifungals develops after exposure to fluconazole.

Our study has certain limitations. It was a retrospective study conducted at two tertiary care hospitals. As such it reflects the epidemiology and antifungal practices within the patient population of our hospital only. Secondly, the antifungal susceptibility test was done by automated colorimetry. Confirmation of resistant strains was not done by a micro broth dilution method. However, in all cases, adequate precautions were taken to ensure that a pure isolate was processed as per the manufacturer's instructions.

Conclusion

C. tropicalis was the most common isolate causing candidemia. Fluconazole resistance was high with each Candida species showing different antifungal resistance rates. As there is a huge geographical variation in the distribution of candida species and their resistance patterns, it is important to monitor them from time to time. This will not only aid the clinician in the timely institution of directed therapy in the form of appropriate antifungal agents but also contribute to antifungal stewardship.

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