

Candidemia in adult intensive care units: Analysis of a 4 year process in a tertiary hospital in Turkey

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Abstract

Aim: Candidemia are one of the most important causes of mortality and morbidity in inpatients, and their importance is increasing with the increasing number of immunosuppressive patients and the widespread use of invasive procedures and broad spectrum antibiotics in recent years. In our study, we aimed to identify *Candida* species isolated from blood cultures and to determine the antifungal susceptibility rates of adult patients who were hospitalized in Malatya Education and Research Hospital Intensive Care Units between July 2015 and July 2019, and had *Candida* growth in at least one of their blood cultures.

Materials and Methods: The blood cultures isolated from adult intensive care units patients and sent to the Microbiology Laboratory of our hospital over the four years, were examined retrospectively. Species distribution and antifungal susceptibility were determined using VITEK 2 Compact System (BioMerieux, France).

Results: Of the 123 clinical samples, 59 (48%) were *C. albicans*, 21 (17.1%) were *C. parapsilosis*, 18 (14.6%) were *C. tropicalis*, 12 (9.8%) were *C. glabrata*, 5 (4.1%) were *C. kefyr*, 2 (1.6%) were *C. krusei*, 2 (1.6%) were *C. lipolytica*, 2 (1.6%) were *C. lusitaniae*, 1 (0.8%) was *C. dubliniensis* and 1 (0.8%) was *C. pelliculosa*. 96.5% of *C. glabrata* strains were found to be susceptible to amphotericin-B, 93.1% to fluconazole, 98.3% to voriconazole, 93.5% to caspofungin, 91.4% to micafungin and 96.7% to flucytosine. 98.1% of non-*albicans Candida* (NAC) strains were found to be susceptible to amphotericin-B, 74.6% to fluconazole, 90.7% to voriconazole, 78.4% to caspofungin, 80% to micafungin and 100% to flucytosine.

Conclusion: The highest resistance to antifungals was found in *C. glabrata* and the highest susceptibility was observed in *C. tropicalis*. In order to develop effective and accurate infection control strategies and reduce mortality and morbidity, it is important to know the distribution and susceptibility of infectious agents, especially in critical patients in intensive care units.

Keywords: *Candida albicans*; Non-*albicans Candida* (NAC); candidemia; intensive care unit; antifungal resistance

INTRODUCTION

Although 5 million species of fungi have been identified in nature, only about 300 are responsible for fungal infections in mammals. In most cases, *Candida* is opportunistic pathogens found as common organisms in the endogenous microbiome of the body. It is estimated that fungal infections cause 1.5 million deaths each year in the world. Nosocomial infections due to fungi are always important due to their high mortality and morbidity, prolonged hospital stay and serious economic burden. Infections due to *Candida* species are reported to be 80% among all nosocomial fungal infections (1-3).

While *Candida albicans* is the most important causative agent of invasive *Candida* infections, infections caused by non-*albicans Candida* (NAC) species have also been increasing rapidly in recent years. *C. albicans*, *C. glabrata*,

C. parapsilosis, *C. tropicalis* and *C. krusei* are the five most common causative agents in 90% of cases. However, the incidence of these agents varies depending on the concerned population, geographical region, previous antifungal exposure, and age of the patient. The increase in NAC brings antifungal resistance and increased complications and mortality with it, and the most important reason for this increase is the previously used antifungals (2,4-7).

Nosocomial candidemia is more commonly observed in patients with severe chronic disease, intensive invasive intervention exposure, long-term and broad-spectrum antimicrobial usage, immunosuppression due to diseases such as cancer or AIDS, a long stay in intensive care, abdominal or transplant surgery, and in the elderly. Candidemia is a clinical condition with difficult diagnosis and treatment and it is more severe than sepsis due to

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other agents. Therefore, rapid diagnosis and treatment is important (8-10).

Especially, due to prolonged hospital stay and increased invasive interventions in intensive care units (ICUs) of patients, natural barriers are broken thereby providing a basis for infection formation. In candidemia, inappropriate diagnosis and treatment increases mortality and morbidity and leads to serious economic losses. Due to the differences in antifungal use and infection control strategies, the distribution of *Candida spp.* and their antifungal susceptibility varies according to years, countries and centers. For these infections to be detected and treated correctly, the centers must conduct surveillance studies at regular intervals and review the given treatment and prophylaxis preferences (4, 8, 11).

Resistance rates need to be known before effective treatments can be started. Therefore, comprehensive studies are needed. The aim of our study was to explore the epidemiologic data about distribution of *Candida spp.* isolated from blood cultures at the species level, to find their in vitro susceptibility to antifungal agents and to shed light on empirical and specific treatment plans in our hospital and region.

MATERIALS and METHODS

Between July 2015 and July 2019, 123 candidemia agents isolated over the 4 years from blood culture samples sent from adult intensive care unit to Education and Research Hospital Microbiology Laboratory with a capacity of 1040 beds located in Malatya, which is a city in eastern Turkey, were retrospectively included in the study. All blood cultures sent to the hospital laboratory were incubated in the BACTEC (Becton Dickinson, Maryland, USA) automated system. After identification of yeast isolates at species level, Vitek 2.0 Compact automated system (BioMérieux, France) was used for in-vitro antifungal susceptibility to fluconazole, voriconazole, caspofungin, micafungin, amphotericin-B and flucytosine drugs.

The study was started on July 30, 2019 with the permission of the Scientific Committee of our hospital. All necessary data were obtained from hospital information system. In blood samples, in the presence of clinical findings, *Candida spp.* growth in at least one blood culture was defined as candidemia. However, samples isolated from the same patient in a single hospitalization period and having the same antifungal resistance profile were excluded from the study.

RESULTS

Candida spp. was detected in 123 patients from blood cultures in the ICUs of our hospital over the four years. 110 (89.4%) patients out of 123 candidemia strains were isolated in reanimation ICUs, 12 (9.8%) in internal ICUs and 1 (0.8%) in coronary ICU respectively. Approximately six thousands patients have been followed in intensive care units of our hospital annually (Beginning with second half of the year 2015, including entire 2016, 2017, 2018

and first half of the year 2019, 3143, 5695, 6074, 5996 and 3158 patients have been monitored).

Candidemia patients with an average age of 71 years were adults aged between 18 and 101. 71 (57.7%) of the patients in candidemia cases were male and 52 (42.3%) were female. Gender distribution of patients with candidemia was made according to the age groups. And, the rates of patients were seen to be increased with age in both genders (Table 1).

Table 1. Gender distribution of patients with candidemia according to age groups

Age range	Female	Male	Total
0-20	0	3	3
21-40	5	6	11
41-60	7	7	14
61-70	10	16	26
71 and above	30	39	69
Total n (%)	52 (42.30%)	71 (57.70%)	123 (100%)

Of the 123 clinical samples, 59 (48%) were *C. albicans*, 21 (17.1%) were *C. parapsilosis*, 18 (14.6%) were *C. tropicalis*, 12 (9.8%) were *C. glabrata*, 5 (4.1%) were *C. kefyr*, 2 (1.6%) were *C. krusei*, 2 (1.6%) were *C. lipolytica*, 2 (1.6%) were *C. lusitanae*, 1 (0.8%) was *C. dubliniensis* and 1 (0.8%) was *C. pelliculosa*.

The distribution of *Candida* species isolated from blood culture was examined by years. When each year was evaluated separately, *C. albicans* was found to be the most frequently isolated species. In addition, although the number of patients admitted to our hospital was increased each year, the number of candidemia patients associated with ICUs did not increase over the years (Table 2).

The distribution of *Candida spp.* isolated from blood cultures, in different age groups was examined in Table 3. When *Candida* isolated in different age groups were evaluated, *C. albicans* were found to be prominent in each age distribution.

In our study 96.5% of *C. albicans* strains were found to be susceptible to amphotericin-B, 93.1% to fluconazole, 98.3% to voriconazole, 93.5% to caspofungin, 91.4% to micafungin and 96.7% to flucytosine. 98.1% of NAC strains were found to be susceptible to amphotericin-B, 74.6% to fluconazole, 90.7% to voriconazole, 78.4% to caspofungin, 80% to micafungin and 100% to flucytosine. Antifungal susceptibility rates of all isolates were determined as; amphotericin-B 97.3%, fluconazole 83.7%, voriconazole 95%, caspofungin 85.3%, micafungin 86.4% and flucytosine 98.5%. In vitro antifungal susceptibility was detected to be the highest in flucytosine and lowest in fluconazole (Table 4).

Among the five most common species of *Candida* which are *C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata* and *C. kefyr*, the highest resistance to antifungals was found in *C. glabrata* and the highest susceptibility was observed in *C. tropicalis*. In our study, flucytosine, amphotericin-B,

voriconazole, micafungin, caspofungin and fluconazole were determined to be the most effective antifungal drugs, respectively. The effect of fluconazole against *C. glabrata* is known to be limited. In our study, *C. glabrata* was found to have the lowest susceptibility against fluconazole.

Table 2. *Candida* species isolated from blood culture and their distribution by years (n/%)

Year	<i>C. albicans</i>	<i>C. parapsilosis</i>	<i>C. tropicalis</i>	<i>C. glabrata</i>	<i>C. kefyr</i>	Total NAC
2015 (13)	7/53.8	3/23.1	2/15.4	0	0	6/46.2
2016 (25)	11/44	3/12	6/24	2/8	2/8	14/56
2017 (40)	21/52.5	6/15	6/15	2/5	1/2.5	19/47.5
2018 (27)	12/44.4	5/18.5	2/7.4	6/22.2	1/3.7	15/55.6
2019 (18)	8/44.4	4/22.2	2/11.1	2/11.1	1/5.5	10/55.6
Total	59/48	21/17.1	18/14.6	12/9.8	5/4.1	64/52

Table 3. Distribution of *Candida* species isolated from blood cultures in different age groups (%)

AGE (n/%)	<i>C. albicans</i>	<i>C. parapsilosis</i>	<i>C. tropicalis</i>	<i>C. glabrata</i>	<i>C. kefyr</i>	Total NAC
0-20 (3)	1 (33.3%)	1 (33.3%)	1 (33.3%)	0	0	2 (66.6%)
21-40 (11)	8 (72.7%)	1 (9.1%)	0	0	0	3 (27.3%)
41-60 (14)	7 (50%)	4 (28.6%)	1 (4.2%)	1 (4.2%)	1 (4.2%)	7 (50%)
61-70 (26)	9 (34.6%)	7 (26.9%)	5 (19.2%)	0	2 (7.7%)	17 (65.4%)
70 and above (69)	34 (49.3%)	8 (11.6%)	11 (15.9%)	11 (15.9%)	2 (2.9%)	35 (50.7%)
Total (123)	59 (48%)	21 (17.1%)	18 (14.6%)	12 (9.8%)	5 (4.1%)	64 (52%)

Table 4. Antifungal susceptibility of *Candida* strains isolated from blood cultures according to species

	Amphotericin-B	Fluconazole	Voriconazole	Caspofungin	Micafungin	Flucytosine
<i>C. albicans</i> (59)	58/56 (96.5%)	58/54 (93.1%)	58/57 (98.3%)	31/29 (93.5%)	58/53 (91.4%)	30/29 (96.7%)
<i>C. parapsilosis</i> (21)	20/19 (95%)	21/15 (71.4%)	20/16 (80%)	12/11 (91.6%)	21/12 (57.1%)	12/12 (100%)
<i>C. tropicalis</i> (18)	17/17 (100%)	18/18 (100%)	17/17 (100%)	9/7 (77.8%)	7/7 (100%)	8/8 (100%)
<i>C. glabrata</i> (12)	11/11 (100%)	9/1 (11.1%)	1/1 (100%)	9/4 (44.4%)	12/12 (100%)	9/9 (100%)
Total Candidemia (123)	111/56 (97.3%)	117/98 (83.7%)	101/96 (95%)	68/58 (85.3%)	103/89 (86.4%)	65/64 (98.5%)
Total (123)	59 (48%)	21 (17.1%)	18 (14.6%)	12 (9.8%)	5 (4.1%)	64 (52%)

DISCUSSION

In recent years, along with the increase in infections caused by *Candida* spp., there are also changes observed in the diversity of the species causing these infections. *Candida* species are one of the most important causes of invasive fungal infections in inpatients. There are at least

15 different types of *Candida* that cause human disease. However, more than 90% of invasive diseases are caused by the 5 most common pathogens known as *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis* and *C. krusei*. Each of these *Candida* species has its own virulence potential, antifungal susceptibility and epidemiology (11, 12).

Antifungal susceptibility tests are used to determine regional resistance, in the follow-up of empirically initiated treatment of patients to be treated for a long time such as candidemia and other invasive fungal infections, in cases of non-responsiveness to treatment, and to determine the resistance in individuals with the recurrent mucosal disease and to select an alternative treatment. The main goal of antifungal susceptibility test is to predict the clinical success rate of the drug that is used to treat the infection.

The frequency of *Candida* infections, isolated species and antifungal resistance patterns vary according to years, hospitals and different study periods.

In a multicenter study conducted in Europe, *C. albicans* species are reported to be the most common isolate in candidemias with 49.5%. In our study, when all age groups and years were evaluated, it was found that the most frequently isolated *Candida spp.* was *C. albicans*. In addition, *C. parapsilosis* (17.1%) was the most frequently isolated agent after *C. albicans*. The results that we had obtained were consistent with the results of surveillance studies conducted in Europe (6).

In a study conducted by Xiao et al. in China in 2019, it was found that *C. albicans* was the most common causative agent and all *Candida spp.* were susceptible to amphotericin-B. The susceptibility of fluconazole for *C. albicans*, *C. parapsilosis*, *C. glabrata* and *C. tropicalis* was 100%, 75%, 69.2% and 83.3%, respectively. In our study, although *C. tropicalis* strains were found to be 100% susceptible to other drugs except caspofungin, fluconazole susceptibility rates were found to be lower in our other *Candida* isolates. Similar to our study, resistance rates for flucytosine were quite low and antifungal efficacy was high (13).

In a 12-year national fungemia surveillance study conducted in Denmark, it was observed that the rate of *C. albicans* decreased over the years and that *C. glabrata* was isolated more frequently. According to the antifungal susceptibility results, fluconazole susceptibility rates decreased over the years and amphotericin-B susceptibility remained to be high (14). In our study, amphotericin-B susceptibility was found to be high.

Within the scope of the international SENTRY Antimicrobial Surveillance Program, in which 135 health centers and 39 countries participated and 20-year data were evaluated, the micafungin resistance rate was reported to be 2.8% in *C. glabrata* strains and 1.3% in *C. tropicalis* strains in 15,308 *Candida* isolates. In the United States, a steady increase was observed in the isolation of *C. glabrata* and the resistance of fluconazole for 20 years (15). In our study, there was no significant increase found in NAC species and resistance levels over the years.

Antifungal susceptibility rates of all isolates in our study were; amphotericin-B 97.3%, fluconazole 83.7%, voriconazole 95%, caspofungin 85.3%, micafungin 86.4% and flucytosine 98.5%. The highest susceptibility

was found to be in flucytosine, whereas the lowest susceptibility was found to be in fluconazole. Among the most common species of *Candida*, which are *C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata* and *C. kefyr*, the highest resistance to antifungals was found to be in *C. glabrata* and the highest susceptibility was observed to be in *C. tropicalis*.

In a study conducted in our province by Akdogan et al. in the reanimation intensive care units of Malatya Turgut Ozal Medical Center in 2013, unlike our study 91.6% of the causative agents of candidemia were found to be NAC (16). In our study, *C. albicans* was found to be the most common causative agent of candidemia.

In a study conducted by Hanci et al. with *Candida* isolates isolated from blood cultures of cases over 65 years of age in Izmir Tepecik Education and Research Hospital in 2015, it was reported that the frequency of *C. parapsilosis* increased in blood cultures with age. They found the susceptibility rates to be 95.8% for amphotericin-B, 82.5% for fluconazole, 77.5% for voriconazole, 97.5% for flucytosine and 91.7% for itraconazole. In this study conducted with geriatric patients, antifungal susceptibilities were found to be lower compared to our study. This condition was an indication that antifungal susceptibility decreased with increasing age in elderly patients (17).

In a study conducted in Kahramanmaraş in 2016, Ozkaya et al. found 93 *Candida spp.*, and that *C. parapsilosis* constituted 62% of candidemia isolates. The second most common causative agent was detected to be *C. albicans* (34.0%). Antifungal susceptibility tests showed no resistance to flucytosine. The lowest susceptibility rate (74.2%) was observed against voriconazole in *C. parapsilosis* isolates. Susceptibility rate observed in *C. albicans* isolates to amphotericin-B was 94.1%, whereas there was no resistance found to other tested antifungal agents (18). In our study, the lowest susceptibility was observed in *C. glabrata* isolates against fluconazole. The susceptibility of *C. albicans* to amphotericin-B was calculated as 96.5%.

In a study conducted by Hazirolan et al. in Ankara in 2014, 30.4% of the 187 isolates obtained were identified as *C. glabrata* and 29.9% as *C. albicans*. In all *Candida* species, the susceptibility rates obtained for fluconazole, voriconazole, amphotericin-B, flucytosine, and caspofungin were 92.52%, 98.85%, 95.97%, 91.95% and 100%, respectively (19). Compared to this study, in-vitro susceptibility rates were higher to amphotericin-B and flucytosine drugs in our study. The susceptibilities of fluconazole and caspofungin determined in our study were considerably lower than the susceptibility rates in this study.

In a retrospective study conducted in Ankara, Yesilkaya et al. investigated the distribution of *Candida* isolates isolated from blood cultures between January 2007 and August 2014, and similar to our study, *C. albicans* was

found to be the leading cause of candidemia (20).

In a multicenter study conducted across Turkey, Arikan-Akdagli et al. investigated the antifungal resistance rates of *Candida* isolates isolated from patients with candidemia. They generally found low resistance rates in all drug groups as compared to our study. They found different rates of azole resistance in different *Candida* isolates in different centers, but they did not determine the echinocandin resistance (21). *Candida* species isolated over 4 years showed a low susceptibility to caspofungin and micafungin, which are the echinocandins that we used in our study. In our study, especially susceptibility to caspofungin was found to be quite low against the four most common *Candida* species.

In the study of distribution and antifungal susceptibility of yeast species isolated from various postmortem samples conducted by Ziyade et al, *C. albicans* was the most frequently isolated species among 176 strains in all sample groups. The in vitro (84.6%) susceptibility of fluconazole to *C. tropicalis* isolates was found. No resistance to amphotericin-B was observed (22). In our study, fluconazole resistance was not detected in *C. tropicalis* strains.

In our study, flucytosine, amphotericin-B, voriconazole, micafungin, caspofungin and fluconazole were found to be the most effective drugs in terms of in-vitro susceptibility rates. Among the antifungal drugs, the use of amphotericin-B is limited due to its frequency of toxicity and side effects, and azole group drugs are frequently preferred due to their high bioavailability and good safety profiles. However, widespread and repeated use of fluconazole has led to the resistance problem resulting in clinical unresponsiveness.

Although candidemia treatment has been greatly facilitated by the discovery of azoles, frequent use of fluconazole has led to the development of resistance. There are multi-factor complex mechanisms related to host, agent and drug in the development of resistance. The high fluconazole resistance that we found in our study, can be considered as an indicator of the inappropriate use of azoles in the clinic. Also, high resistance rates may occur since we made the patient selection among adult patients in intensive care unit and the average age of our patients was high.

CONCLUSION

As a result, *C. albicans* was the most frequently isolated species in blood culture samples. NAC isolation rates were also extremely high. Isolated *Candida* species were found to be resistant to many antifungals. This condition has shown that identification of the *Candida* at the species level and reporting their antifungal susceptibility is critical in the diagnosis and planning of appropriate treatment, especially in critical patients receiving ICUs treatment. It is, therefore, important periodically to determine the distribution of *Candida* spp. in each institution, especially when empirical therapy is common practice.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: On 30/07/2019, the study was initiated with the permission number 23536505-604.02 received from the Scientific Committee Commission of our hospital.

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