Species Distribution and Antifungal Susceptibility of Candida Species Isolated From Blood Cultures (2012-2015)

Kan Kültürlerinden İzole Edilen Candida Türlerinin Dağılımı ve Antifungal Duyarlılığı (2012-2015)

Kandidemi / Candidemia

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Özet

Kandidemi önemli bir kan kaynaklı enfeksiyondur ve yüksek oranda mortalite ve morbidite ile ilişkilidir. Uygulanan kompleks medikal ve cerrahi prosedürlere paralel olarak insidansı artmaktadır. Bu çalışmada, Şubat 2012 ile Mart 2015 tarihleri arasında saptanan kandidemilerin tür dağılımı ve antifungal duyarlılıkları retrospektif olarak incelenmiştir. Hastanemizde, Şubat 2012 ile Mart 2015 tarihleri arasında 157 kandidemi olgusu saptanmıştır. Kandideminin toplam insidansı, 0.09/1,000 başvuru olarak bulunmuştur ve 3 yıllık analizde değişiklik saptanmamıştır (P=0,238). Candida albicans en sık izole edilen enfeksiyon ajanıdır (%39.5). C. albicans' ı, C. parapsilosis (%22.9), C. tropicalis (%14,1), C. famata (%7.6) ve C. glabrata (%5.7) izlemektedir. En sık kandidemi olgusu yoğun bakım ünitesinde (%50,3) saptanmış, bunu pediatri ve hematoloji onkoloji servisleri izlemektedir. Test edilen 157 izolatın %14.6 'sı flukonazole dirençli olarak saptanmıştır. CLSI ve EUCAST sınır değerleri kullanılarak, izolatların sırasıyla %12.7 ve %7.6' si varikonazole dirençli veya doza bağlı duyarlı olarak bulunmuştur. En yüksek MIK değerleri C. tropicalis suşlarında saptanmıştır (MIK90, 128 µg/ml). En düşük MIK değerleri Amfoterisin B için bulunmuştur.

Anahtar Kelimeler

Candida; Antifungal Duyarlılık

Abstract

Candidemia has become an important bloodstream infection that is frequently associated with high rates of mortality and morbidity, and its growing incidence is related to complex medical and surgical procedures. We conducted a retrospective study and evaluated the species distribution and antifungal susceptibility of candidemia episodes. In the period of January 2012 to May 2015, 157 episodes of candidemia were identified in the hospital. The overall incidence of candidemia was 0,09 cases per 1,000 admissions and remained stable during the 3- year analysis (P=0,238). Candida albicans was the leading agent of infection (39.5%), followed by C. parapsilosis (22.9%), C. tropicalis (14,1%), C. famata (7.6%) and C. glabrata (5.7%). The majority of the candidemia episodes were found in the intensive care units (50,3%), followed by the pediatric, and the hemato-oncology ward. Overall, 14.6% af the isolates tested were resistant to fluconazole and 12.7% and 7.6% of the 157 isolates tested were resistant or susceptible dose dependent (SDD) to voriconazole based on CLSI and EUCAST breakpoints respectively. Higher MICs for fluconazole were found, especially with C. tropicalis (MIC90, 128 µg/ml). Amphotericin B had the lowest MICs.

Keywords

Candida; Antifungal Susceptibility

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Introduction

Candida spp are an important cause of bloodstream infections (BSIs), leading to significant mortality and morbidity rates and with increased costs of patient care and duration of hospitalization. Despite the availability of effective antifungal therapy, mortality has remained high, ranging from 36% to 63% [1]. The incidence of Candidaemia is growing with the increasing complexity of surgical procedures, the existence of patient populations who are at higher risk of infection and increased use of broad-spectrum antimicrobial agents, advanced life-support and aggressive chemotherapy. Candida spp are currently the fourth [2] and sixth most common blood stream isolates found in studies done in the United States and Europe. Candidemia rates vary geographically. It seems that differences do exist in the epidemiology of candidemia between different countries as well as region to region, underscoring the need for continuous surveillance to monitor trends in the incidence, species distribution, and antifungal drug susceptibility profiles and thus are providing the information necessary for appropriate empirical antifungal therapy [3-7]

Although Candida albicans remains the most prevelant yeast isolated from blood cultures, a shift toward greater isolation of non-C. albicans Candida species has been reported, especially in hematological, transplanted, and intensive care units (ICU) patients [2,3,8].

A reduced antifungal susceptibility in non-C. albicans Candida species and a correlation with routine fluconazole prophylactic use has been suggested. Intrinsic and emerging resistance to azoles represents a major challenge for empirical therapeutic and prophylactic strategies [3].

This study was performed to evaluate the species distribution and antifungal susceptibilities of Candida spp growing in the blood cultures retrospectively in Baskent University Adana Practice and Researche Center between January 2012 and May 2015 from laboratory-based surveillance.

Material and Method

All consecutive patients who developed candidemia at Baskent University Adana Practice and Researche Center, a 576 beds tertiary care hospital with about 519,488 admissions per year were enrolled in the study during the period January 2012-May 2015. Patients with at least one positive blood culture for Candida spp. were identified through the microbiological laboratory database and all informations was recorded in an electronic database. For each patient, only the first episode of candidemia was recorded. The information with regard to candidemia episodes were analyzed, including the fungal species and resistance to antifungals. Patients whose cultures grew > 1 species of Candida were excluded from the analysis.

During the study period there were no changes in microbiological laboratory techniques. Candida species were isolated from blood using BACTEC 9240 system (Becton Dickinson) following the manufacturer' s instructions. Yeast isolates identification was based on germ tube production and sugar assimilation profiles by using the API-20C AUX system (bioMérieux, France). Antifungal susceptibility testing isolates of Candida spp. was performed using ATMTM FUNGUS 3 (bioMérieux, France). Yeast identification and antifungal susceptibility testing were repeated for azole resistant C. albicans species. The interpretive breakpoints used for tests were based on values recommended by the Clinical Laboratory Standards Institute (CLSI) [9] and European Committee on Antimicrobial Susceptibility Testing (EUCAST) [10]. The following antifungal drugs were tested: Amphotericin B, fluconazole, itraconazole and voriconazole.

The chi-square test was used to compare categorical variables. Differences between the groups were considered to be significant for variables yielding a P value of <0.05.

Results

A total of 157 episodes of candidaemia were identified during the study period (January 2012-May 2015) with an overall incidence of 0,09 episodes/1000 admissions and remained stable during the 3-year analysis (Table 1). The age-specific incidence rate was highest in infants (0.1 episodes/1,000 admissions). Children (≤ 18 years, 57.5 % younger than 1 year) comprised 86 (54,8%) of the patients, and adults comprised 71 (45.2%) of the patients. The median patient age of pediatric patients was 2.2 years (0-18 years) and the median patient age of adult patients was 58.7 years (19-92 years). In our study, males (54.8%) were more prevelant than females (44%). There were not important differences in the incidence of candidemia from 2012 to 2015 (P=0.238) (Table 1). The demographic and clinical chracteristics of the patients are summarized in table 1.

The distribution of isolated Candida species is shown in figure 1 and figure 3. C. albicans was the leading cause of infec-

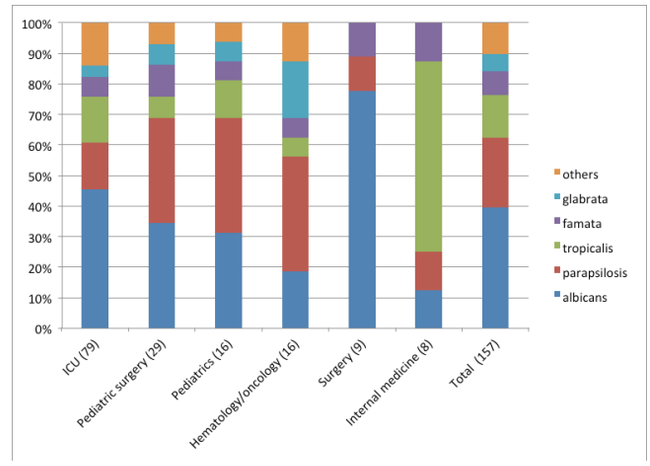

Figure 1. Distribution of the Candida species according to underlying pathology/ medical care (n)

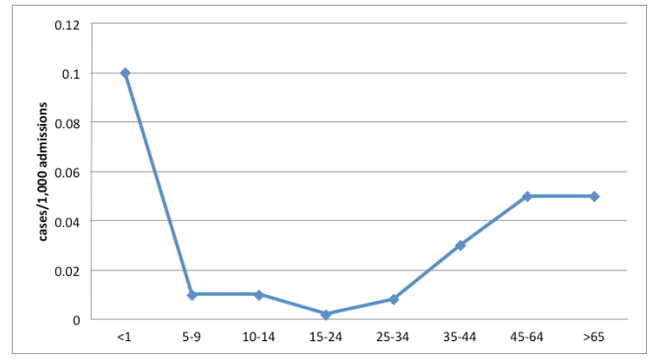

Figure 2. Age specific incidence of candidemia at Baskent University Adana Practice and Researche Center between January 2012 and May 2015. The incidence was low in people aged 5-40 years but started tor ise among people aged 41 to 50 years. Incidence subsequently increased with advancing age, peaking among patients aged 61 to 92 years (0.06 cases/1,000 admissions). With a high incidence occuring in the youngest age group (<1 year, 0.1 cases/1,000 admissions).

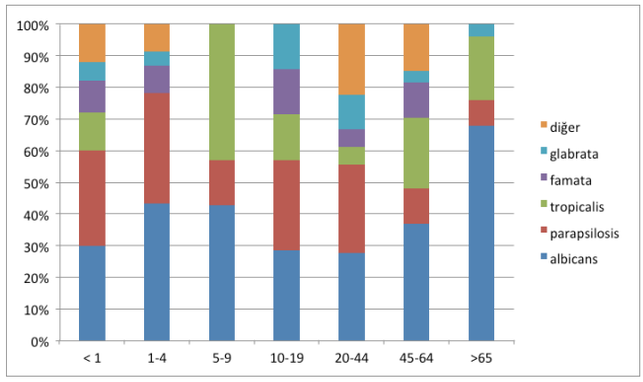

Figure 3. Age specific distribution of Candida spp at Baskent University Adana Practice and Researche Center between January 2012 and May 2015.

ity was seen with C. tropicalis (54,5%) and C. famata (75%). As, our MIC breakpoints did not contain 4 µg/ml, we did not evaluate SDD to fluconazole. Overall, 14.6% of the 157 isolates tested were resistant to fluconazole based on CLSI and EUCAST breakpoints. The rates of susceptibility to voriconazole were 100% for C. parapsilosis, 95.2% for C. albicans. Decreased susceptibility was seen with C. tropicalis (54.5% [CLSI] and 59.1% [EUCAST]). The six strains (1 C albicans, 4 C. krusei, and 1 C. tropicalis) were susceptible dose dependent (SDD) to voriconazole. Overall, 12.7 % and 7.6% of the 157 isolates tested were resistant or susceptible dose dependent (SDD) to voriconazole based on CLSI and EUCAST breakpoints respectively. Amphotericin B had lowest MIC values.

Table 1. Patient characteristics and incidence (episodes/1000 admissions)

	Candida species C. albicans (n=62)	C. parapsilosis (n=36)	C. tropicalis (n= 22)	C. famata (n= 12)	C. glabrata (n=9)	Other* (n=16)	Total (n=157)
	39.5%	22.9%	14.1%	7.6%	5.7%	10.2%	100.0%
Patients characteristic							
Female sex, n (%)	30 (42.3)	15 (21,1)	9 (12.7)	4 (5.6)	3 (4.2)	10 (14.1)	71 (45.2)
Male sex, n (%)	32 (37.2)	21 (24.4)	13 (15.1)	8 (9.3)	6 (7)	6 (7)	86 (54.8)
Underline diseases, n (%)							
Surgery	26 (41.3)	17 (26.9)	7 (11.1)	5 (7,9)	4 (6.4)	4 (6.4)	63 (40.1)
Hematologic malignancy	5 (22.7)	8 (36.4)	2 (9.1)	0 (0)	2 (9.1)	5 (22.7)	22 (14)
Solid tumour	18 (47.3)	6 (15.8)	2 (5.3)	5 (13.2)	3 (7.9)	4 (10.5)	38 (24.2)
Cardiovascular diseases	10 (55.6)	0 (0)	6 (33.3)	0 (0)	0 (0)	2 (11.1)	18 (11.4)
Diabetes mellitus	0 (0)	0 (0)	2 (66.7)	0 (0)	0 (0)	1 (33.3)	3 (1.9)
Congenital anomalies	1 (2.5)	3 (37.5)	3 (37.5)	1 (2.5)	0 (0)	0 (0)	8 (5.1)
Prematurity	2 (50)	1 (25)	0 (0)	1 (25)	0 (0)	0 (0)	4 (2.5)
Immunodefficiency	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)
Incidence (episodes/1000 admissions)							
2012	0,04	0,02	0,02	0,01	0,01	0,01	0,11
2013	0,02	0,02	0,01	0,01	0,01	0,01	0.07
2014	0,05	0,02	0,02	0,01	0	0,02	0.10
2015	0,04	0,01	0,01	0,001	0	0,01	0,07

*Candida krusei (6), Candida kefyr (3), Candida lusitaniae (2), Candida magnoliae (1), Candida norvegensis (1), Candida pelliculosa (3).

tion (39,5%). Globally, non-C. albicans Candida species caused around 60,5% of the cases each. Non-C. albicans Candida species included Candida parapsilosis (22.9%), Candida tropicalis (14.1%), Candida famata (7.6%) and Candida glabrata (5.7%). The distribution of albicans and non-C. albicans Candida strains differed according to the type of population, risk factors and age, as shown in Figure 1. In hemato-oncology patients, C. parapsilosis was isolated in 37,5% (6/16) of the cases, C. albicans in 19% (3/16), and C. glabrata in 19%(3/16); in the overall pediatric wards, C. parapsilosis accounted for 34.8% (16/45) and C. albicans accounted for 33.3% (15/45); in the ICU and the surgery ward, C. albicans was isolated 45,6%(36/79) and 77,8% (7/9) respectively. In the internal medicine wards, C. tropicalis was the leading cause of infection (62,5%) (5/8).

Table 2 shows the results of the in vitro activity of 4 systemically active antifungal agents tested against 157 BSI isolates of Candida spp. By appliying species-specific new clinical breakpoints (CBPs) of CLSI and EUCAST breakpoints. The rates of susceptibility to fluconazole were 100% for C. parapsilosis and C. glabrata and 93,5 % for C. albicans. Decreased susceptibil-

Discussion

Several studies have shown a substantial increase in the incidence of candidemia in the past two decades. Our data show that in our hospital the incidence of candidemia was stable in the past 3 years. Our rates (0,09 episodes/1000 admissions) are not higher than those reported for centers, including the United States (0.28 to 0.96 case per 1,000 admissions), Europe (0.20 to 0.53/1,000 admissions) [11,12], Latin America (1.18 cases per 1,000 admissins) [13] and Iceland (0. 55 case per 1,000 admissions) [14]. The differences in candidemia rates between countries may reflect differences in representativeness and age distributions of the study populations, variations in health care practices, patterns using blood cultures, and antibiotic usage as well as the resistance situation.

Over the past 10 years, some studies have reported a shift in the etiology of candidemia. While C. albicans still considered the most common species causing candidemia, increasing rate of candidemia caused by C. tropicalis, C. parapsilosis, C. glabrata, and C. krusei have been reported worldwide. The species

Table 2. Antifungal susceptibility test results for selected species of Candida isolated during the study period

Species (n)	Antifungal agent	MIC range (µg/ml)	MIC 50a (µg/ml)	MIC 90b (µg/ml)	No. (%) of resistant or susceptible dose dependent c	
					CLSI	EUCAST
C. albicans (62)	Amfotericin B	0,5-16	0,5	0,5	NA	0
	Fluconazole	1-128	1	1	4 (6.5)	4 (6.5)
	Itraconazole	0,125-4	0,125	0,125	NA	NA
	Voriconazole	0,06-8	0,06	0,06	3 (4.8)	3 (4.8)
C. parapsilosis (36)	Amfotericin B	0,5-16	0,5	0,5	NA	0 (0)
	Fluconazole	1-128	1	1	0 (0)	0 (0)
	Itraconazole	0,125-4	0,125	0,125	NA	NA
	Voriconazole	0,06-8	0,06	0,06	0 (0)	0 (0)
C. tropicalis (22)	Amfotericin B	0,5-16	0,5	0,5	NA	0 (0)
	Fluconazole	1-128	1	128	10 (45.5)	10 (45.5)
	Itraconazole	0,125-4	0,5	4	NA	NA
	Voriconazole	0,06-8	0,06	8	10 (45.5)	9 (40.9)
C. famata (12)	Amfotericin B	0,5-16	0,5	0,5	NA	0 (0)
	Fluconazole	1-128	1	1	3 (25)	3 (25)
	Itraconazole	0,125-4	0,125	0,25	NA	NA
	Voriconazole	0,06-8	0,06	0,06	3 (25)	NA
C. glabrata (9)	Amfotericin B	0,5-16	0,5	0,5	NA	0 (0)
	Fluconazole	1-128	1	8	0 (0)	0 (0)
	Itraconazole	0,125-4	0,25	0,5	NA	NA
	Voriconazole	0,06-8	0,06	0,25	NA	NA
All Candida spp (157)	Amfotericin B	0,5-16	0,5	0,5	NA	0
	Fluconazole	1-128	1	16	23 (14.6)	23 (14.6)
	Itraconazole	0,125-4	0,125	4	NA	NA
	Voriconazole	0,06-8	0,06	0,5	20 (12.7)	12 (7.6)

NA: breakpoint not available.
aMIC at which 50% of the isolates tested are inhibited.
bMIC at which 50% of the isolates tested are inhibited
c As, our MIC breakpoints did not contain 4 µg/ml, we did not evaluate SDD to fluconazole.

distribution in the our study is characterized by a predominance of C. albicans, C. parapsilosis and C. tropicalis consistent with other studies from Turkey [15-17]. We observed a predominance of non-C. albicans Candida species (60,5%), however C. albicans was the most frequently isolated species (39.5%). Traditionally, C. tropicalis has been the second and C. glabrata the third or fourth most common Candida species from blood [1,6]. In our study, C. parapsilosis (22.9%) surpassed the other non-C. albicans Candida species to become the most common species isolated after C. albicans. The high incidence of C. parapsilosis candidemia has been previously reported some studies from Turkey [15-17], France [18], Spain, Italy and Latin America [13]. The relative contribution of different Candida species varies between countries in Europe. C. albicans was identified in 56% of cases. C. glabrata, causing 12% of the episodes, was the second most common species recovered in all the countries, except in Italy and Spain where it ranked 3 and 4, respectively. C. topicalis occured in 7% of the cases, ranging from 2% to 10%. C. parapsilosis was the second most common species in Spain and Italy [11].

Several investigators postulated that the widespread use of fluconazole would have selected yeast species intrinsically resistant or less sensitive to fluconazole, such as C. krusei, C. glabrata or C. tropicalis. Some published reports confirmed this hypothesis, while others did not [8]. However, it be recognised that other events might have played a role in the selection of different species [1]. For example, in our study, the increased proportion of candidemias due to C. parapsilosis, a yeast species almost always susceptible to fluconazole, is not readily explained by increased fluconazole use. It is likely that changes in the proportion of fungemias due to C. parapsilosis reflect nosocomial acquisition of this species.

We identified that 50,3% of episode of fungemia occured in patients in ICU. Our findings was similar that some studies from Turkey identified that 45,7%-70,1% of episodes of nosocomial fungemia occured in patients in ICU [15,16,19]. C. albicans dominated in our study in surgery wards with 77,8% and ICU with 45,6% of the species isolated. Non-C. albicans Candida species occurs frequently among pediatric, haemato-oncological and internal medicine patients. In hemato-oncology patients, C. parapsilosis was isolated in 37,5%, C. albicans was isolated in 19% (3/16), and C. glabrata was isolated in 19%(3/16) of the cases; in the overall pediatric wards, C. parapsilosis accounted for 34.8% and C. albicans accounted for 33.3% (15/45); in the internal medicine wards, C. tropicalis was the leading cause of infection (62,5%)

Our findings of overall fluconazole-resistant (14.6 %) was higher than the rates observed in studies from Turkey (21.81-7.48%), European (6,3%), North American (6.6%) and Latin America (7.1%) [13, 15-17, 19-21]. Our proportion of voriconazole resistant (12.7 [CLSI] and 7.6 [EUCAST]) was higher than that studies from Turkey (0%-4.4%) [15-17, 19, 21]. Azole-resistant C. albicans strains and antifungal susceptibility testing were confirmed by repeating the reference method. CLSI recently developed new Candida species-specific clinical breakpoints (CBPs) for fluconazole and voriconazole as the EUCAST for three common Candida species. A recent report has shown that resistance to azoles of Candida species was increased using the new CLSI CBPs [8]. In our study when the old breakpoints applied for C. albicans strains, only two strains were found as resistant to fluconazole and voriconazole (2/62, 3.2%). We didn' t compare the results of new and old breakpoints. We hypothesed that using these species-specific CBPs may increase the resistance to fluconazole and voricoazole in this study. None of our Candida bloodstream isolates had MIC of >1 µg/ml for amphotericin B, some studies from Turkey and Europe reported the low level of amphotericin B resistance [15-17, 19].

In our study, the proportion of children in this study was very high (54,8%). C. albicans was the most prevelant yeast isolated from blood cultures in all age groups. The dominant causes of Candida BSI in the pediatric and adolescent age groups (0-19) were C. albicans (34.5%) and C. parapsilosis (29.9%) similar with previous studies [6]. The high incidence of Candida BSI among infants observed here is consistent with previous studies (Figure 2) [2]. We observed the most common species that recovered from neonates are C. albicans (15 of the 50 cases, 30%) and C. parapsilosis (15 of the 50 cases, 30%), consistent with previous studies [2,11], with increasing age, a reduction in the percentage of C. parapsilosis was seen (from 14,3-34.8% to

8%). A similar trend has been noted both in population-based and in sentinel surveilance studies conducted in the USA [11]. In contrast to other studies that reported the proportion of C. glabrata inreased with patient age [6,11,13], we found that the proportion of C. glabrata BSI did not increase with patient age and the lowest proportion (4%) was seen in the > 65 year age group. In our study, the proportion of C. albicans increased with patient age and the highest proportion (68%) was seen in the > 65 year age group.

Our study was subject to limitations. The major one is that this is a single center study, regional conditions such as features of the patient population and antimicrobial/infection control practices of this specific tertiary care centre may influence the results. As, the data we have reported are based on records from the microbiology laboratory, the lack of clinical data, severity of illness measures, risk factors and antifungal drug exposure data limit the clinical utility of the study.

It is well known that positive blood culture for Candida spp is a life threatening situation, requiring an empirical antifungal treatment which should started with the appropriate agents as soon as possible. Therefore, the knowledge of the local epidemiological trends in Candida species isolated in blood cultures is important to guide therapeutic choices.

Competing interests

The authors declare that they have no competing interests.

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