JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.843796
J Contemp Med 2021;11(3):340-345

Orjinal Araştırma / Original Article

Candidemia in Non-neutropenic Patients in a Pediatric Intensive Care Unit

Bir Çocuk Yoğun Bakım Ünitesinde Nötropenik Olmayan Hastalarda Kandidemi

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Abstract

Aim: Candidemia has high morbidity and mortality rate in critically ill patients hospitalized in intensive care units. Prompt initiation of accurate anti-fungal therapy is essential for survival. In this study, a 6-year retrospective candidemia analysis of pediatric intensive care unit (PICU) was performed to review candida species distribution, risk factors for candidemia and change in the antifungal resistance in years.

Material and Method: The candidemia episodes of children older than 1 month followed in the PICU of Diyarbakır Children's Hospital between January 2014 and January 2020 were analyzed. The demographic and clinical characteristics, laboratory findings, treatments and outcomes of the patients were obtained from the medical records.

Results: In six years, 59 candidemia episodes were observed in 48 pediatric patients. Twenty-six of them female, median age at diagnosis was 43 months (range 1-225), median hospital stay was 48 days (range 3-664). All patients had received broad-spectrum antibiotics, majority had comorbidities (89.8%), nasogastric tube (84.7), central venous catheter (78.0%), and on mechanic ventilation (76.3%). Type of candida species was identified in 36 episodes of candidemia; 47.2% of these episodes were caused by *C. parapsilosis*, 38,9% by *C. albicans*, 8.3% by *C. glabrata* (8.3%), 2.8% by *C. lusitaniae*, and 2.8% by *C. tropicalis*. Length of hospital stay was longer among patients with nonalbicans candidemia (p=0.02), whereas patients with albicans candidemia had higher leucocyte count at the diagnosis (0.006). The antifungal resistance was observed in the nonalbicans candidemia group, not in the albicans group (p=0.017). Overall, thirty-day mortality rate was 16.9%.

Conclusion: In the PICU when initiating empirical antifungal therapy for a critically ill patient, in the presence of a long hospital stay an agent has coverage for non-albicans candida that may have antifungal resistance should be selected.

Keywords: PICU, candida, candidemia, nonalbicans

Öz

Amaç: Kandidemi yoğun bakım ünitelerinde yatan kritik hastalarda yüksek morbidite ve mortalite oranına sahiptir. Sağ kalım için doğru anti-fungal tedavinin gecikmeden başlanmasının hayati önemi vardır. Bu çalışmada, kandida türlerinin dağılımını, kandidemi için risk faktörlerini ve yıllar içinde anti-fungal dirençteki değişimi görmek için bir çocuk yoğun bakım ünitesi (ÇYBÜ)'inde gözlenen kandidemi ataklarının 6 yıllık retrospektif analizi yapıldı.

Gereç ve Yöntem: Ocak 2014- Ocak 2020 tarihleri arasında Diyarbakır Çocuk Hastalıkları Hastanesi ÇYBÜ'inde yatan 1 aydan büyük çocuk hastalarda gözlenen kandidemi atakları incelendi. Hastaların demografik ve klinik özellikleri, laboratuvar bulguları, tedavileri ve sonuçları tıbbi kayıtlarından elde edildi.

Bulgular: Altı yılda 48 çocuk hastada 59 kandidemi atağı izlendi. Hastaların 26'sı kız, tanı anındaki medyan yaş 43 ay (aralık 1-225), medyan hastanede kalış süresi 48 gün (aralık 3-664) idi. Hastaların tümü antibiyotik tedavisi almış, çoğunun komorbiditesi mevcut (%89,8), nazogastrik tüp (84,7), santral venöz kateter (%78,0) kullanılmış ve mekanik ventilasyonda (%76,3) izlenmişlerdi. Kandida türü 36 kandidemi epizodunda tanımlandı; %47,2'sinde *C. parapsilosis*, %38,9'unda *C. albicans*, %8,3'ünde *C. glabrata*, %2,8'inde *C. lusitaniae* ve %2,8'inde *C. tropicalis* etkendi. Albicans kandidemili hastalarda tanı anında lökosit sayısı daha yüksek (p=0,006), non-albicans kandidemili hastalarda ise hastanede kalış süresi daha uzun idi (p=0,02). Non-albicans candidemia grubunda anti-fungal direnç gözlenirken, albicans grubunda gözlenmedi (p=0,017). Genel olarak, otuz günlük ölüm oranı %16,9 idi.

Sonuç: ÇYBÜ'deki kritik hasta için ampirik antifungal tedavi başlarken, hastanın hastanede kalış süresi uzun ise antifungal direnci olabilen nonalbican kandidaları kapsayacak bir ajan seçilmelidir.

Anahtar Kelimeler: ÇYBÜ, kandida, kandidemi, nonalbikans

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Received *(Geliş Tarihi)*: 20.12.2020 **Accepted *(Kabul Tarihi)*:** 17.03.2021

INTRODUCTION

Candida species are significant pathogens for critically ill patients.[1] It is the fourth most common cause of healthcare related bloodstream infections.[2] Candidemia incidence was reported as 7 per 100,000 in infants under 1 year of age and 0.3 per 100,000 in children aged between 1 to 18 years by the 2017 United States' surveillance.[3] In a study from our country, Turkey, the pediatric candidemia incidence was estimated as 2.9 per 1,000 admissions between 2013-2014.[4]

Candida albicans (*C. albicans*) is the most frequently isolated species, whereas nonalbicans species are increasingly isolated in recent years.[1,5,6] The well-known factors that increase the risk for candidemia are prolonged hospital stay, broad-spectrum antibiotic usage, presence of comorbidities, immune suppression, mechanical ventilation, central venous catheter, parenteral nutrition, gastrointestinal perforation or operation, and renal failure which require hemodialysis.[5,7-9] Mortality rate was reported as over 60 % in untreated patients, in children with appropriate treatment this rate decreased to approximately 9 to 40 %.[10,11] In cases of high suspicion of invasive candidiasis, waiting for laboratory identification of candidemia is the time consuming and can increase mortality, early initiation of antifungal treatment will improve survival.[12,13]

Here, we retrospectively evaluated children with candidemia in term of clinical and laboratory characteristics to increase the awareness of physicians about disease and its management.

MATERIAL AND METHOD

This retrospective study included the patients with candidemia hospitalized in Diyarbakır Children's Hospital pediatric intensive care unit (PICU) between January 2014 and January 2020. The unit was working with its full capacity of 24 beds. Data about demographic and clinic characteristics of patients were collected from medical records and compared between patients with albicans candidemia and non-albicans candidemia, and also between patients followed before and after 2018.

The diagnosis of candidemia was made according to CDC/NHSN surveillance definitions.[14] If the blood culture from a patient was positive for same candida species in 30 days of first positive blood culture, this episode was not included to the study.

Blood specimens were incubated in BACTEC 9120 blood culture system (Becton Dickinson, USA). The media monitored for 5 days, when the automatic alert system signaled growth in any of the bottles, passages were performed from blood culture bottles to 5% sheep blood agar, chocolate agar Eosin Methylene-blue Lactose Sucrose (EMB) medium, and Sabouraud dextrose agar (SDA, Oxoid, United Kingdom) and incubated at 37 for 18 to 24 hours. In addition, for identification and antifungal susceptibility tests, VITEK 2 Compact® (bioMeriéux, France) system and identification cards (YST) were used. Antifungal susceptibility cards (AST-YST01) were used to investigate susceptibility to fluconazole, amphotericin B, voriconazole, caspofungin, micafungin and flucytosine. The results were made taking into account the EUCAST (European Committee on Antimicrobial Susceptibility Testing) recommendations.[15]

The statistical analyses were performed using SPSS Version 21.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY). Characteristics of patients, are described as n (percent) for categorical or median (min-max) for continuous variables, and were compared among test groups by using chi-square or Mann-Whitney tests, as appropriate. P values equal to or less than 5% were considered significant.

RESULTS

Fifty-nine candidemia episodes of 48 patients was included in study. Two patients had 3 episodes, 7 patients had 2 episodes, 39 patients had 1 episode of candidemia. The median time between two consecutive episodes in the same patient was 5,3 months (range 1.7-36.7). The median age at the diagnosis was 43 months (range 1-225). The median hospitalization time before candidemia was 48 days (range 3-664), all patients had used broad-spectrum antibiotics, %89.8 had comorbidities, 84.7% had nasogastric tube, 78.0% had central venous catheters, 76.3% were on mechanic ventilation support (**Table 1**).

The number of candidemia episodes was 8, 4, 4, 5, 18, 20 for 2014, 2015, 2016, 2017, 2018, and 2019 respectively. The increase in the number of candidemia episodes was striking in last two years. When demographic and clinical characteristic of patients with candidemia before and after 2018 were compared, no statistically significant difference was found (**Table 2**).

Candida species identification was not performed in hospital until end of 2017, so in only 36 episodes identification was done; 47.2% of these episodes were caused by *C. parapsilosis*, 38,9% by *C. albicans*, 8.3% by *C. glabrata* (8.3%), 2.8% by *C. lusitaniae*, and 2.8% by *C. tropicalis* (**Figure 1**). We compared the characteristics of patient with *C. albicans* candidemia and patients with nonalbicans candidemia. In nonalbicans group hospitalization duration before candidemia was significantly longer, and in albicans group leucocyte count was higher at diagnosis, p=0.02, p=0.006 respectively (**Table 1**).

Antifungal susceptibility test was begun after half of 2018; in 26 episodes antifungal susceptibility tests were performed, all resistant candida species were non-albicans (p=0.017); in 2017 one *C. glabrata* had resistance to fluconazole (intrinsic resistance), in 2018 no resistance was reported in 6 tests (0.0%), in 2019 3 *C. parapsilosis* had resistance to voriconazole, 2 *C. glabrata* had resistance to caspofungin (27.8%).

Table 1. The demographic and clinical features of pediatric patients with candidemia in PICU of Diyarbakır Children's Hospital between 2014 and 2020

Variables	Candidemia episodes n=59	Candidemia due to C Albicans n=14	Candidemia due to nonalbican candidas n =22	p-value
Median age months (min-max)	43 (1-225)	20 (4-225)	50 (3-219)	0.127
Sex f/m	32/27	8/6	12/10	1.000
Risk factors,				
Hospitalization days, median (min-max)	48 (3-664)	13 (6-490)	113 (7-664)	0.020
Broad-spectrum antibiotic usage, n (%) Presence of	59 (100%)	14 (100%)	22(100%)	1.000
comorbidities, n (%)	53 (89.8)	13 (92.9)	20 (90.9)	00.599
Enteral feeding, n (%)	55 (93.2)	13 (92.9)	21 (95.5)	1.00
Nasogastric, n (%)	50 (84.7)	10 (71.4)	20 (90.9)	0.181
Presence of central venous catheter, n (%)	46 (78.0)	8 (57.1)	18 (81.8)	0.140
Parenteral nutrition, n (%)	17 (28.8)	3 (21.4)	5 (22.7)	1.000
Proton-pump inhibitor usage, n (%)	11 (18.6)	1 (7.1)	7 (31.8)	0.115
Mechanic ventilation, n (%)	45 (76.3)	10 (71.4)	19 (86.4)	0.394
Choice of anti-fungal drug				
Fluconazole	20 (33.9)	6 (42.9)	3 (13.6)	0.111
Echinocandin	23 (39.0)	6 (42.9)	9 (40.9)	1.000
Amphotericin B	16 (27.1)	2 (14.3)	10 (45.5)	0.076
Anti-fungal resistance, n (%)	6/26 (23.1)	0/12 (0.00)	6/14 (42.9)	0.017
30-day mortality, n (%)	10 (16.9)	2 (14.3)	5 (22.7)	0.599
Laboratory findings, median (min-max)				
WBC $\times 10^9$/L	11.05 (0.03-81.60)	17.25 (2.50-81.6)	7.85 (0.03-26.11)	0.006
Neutrophil $\times 10^9$/L	4.7 (0.6-22.1)	7.8 (2.9-22.1)	4.1 (1.8-17.5)	0.186
Platelets $\times 10^9$/L	268.5 (12.0-752.0)	405.5 (36.0-752.0)	253.0(12.0-657.0)	0.086
C-reactive protein, mg/dl (>5 mg/dl)	90.4 (6.8-262.0)	68.3 (6.8-219.4)	93.0 (7.6-262.0)	0.466

Table 2. The comparison of demographic and clinical features of pediatric patients with candidemia before and after 2018

Variables	2014-2017 n=21	2018-2019 n=38	p-value
Median age months (min-max)	83 (1-196)	41 (1-225)	0.311
Sex f/m	10/11	22/16	0.586
Risk factors			
Hospitalization days, median (min-max)	37 (3-279)	73 (6-664)	0.322
Broad spectrum antibiotic usage, n (%)	21 (100)	38 (100)	1.00
Presence of comorbidities, n (%)	19 (90.5)	34 (89.5)	0.660
Enteral feeding, n (%)	19 (90.5)	36 (94.7)	0.611
Nasogastric, n (%)	19 (90.5)	31 (81.6)	0.469
Presence of central venous catheter, n (%)	19 (90.5)	27 (71.1)	0.109
Mechanic ventilation, n (%)	14 (66.7)	31 (81.6)	0.218
Parenteral nutrition, n (%)	6 (28.6)	11 (28.98	1.00
Proton-pump inhibitor usage, n (%)	3(14.3)	(21.1)	0.730
Choice of anti-fungal drug			
Fluconazole	10 (47.6)	10 (26.3)	0.151
Echinocandin	7 (33.3)	16 (42.1)	0.585
Amphotericin B	4 (19.0)	12 (31.6)	0.370
Anti-fungal resistance, n (%)	1/2 (50.0)	5/24 (20.8)	0.415
30-day mortality, n (%)	3 (15.0)	7 (22.6)	0.721
Laboratory findings, median (min-max)			
WBC x 10^9/L	10.65 (3.90-41.5)	11.15 (0.03-81.6)	0.952
Neutrophil x 10^9/L	3.3 (0.6-22.0)	4.9 (1.3-22.1)	0.704
Platelets x 10^9/L	253.5 (24.0-475.0)	270.5 (12.0-752.0)	0.439
C-reactive protein, mg/dl (>5 mg/dl)	89.2 (14.0-217.0)	68.3 (2.0-262.0)	0.079

Invasive candidiasis was investigated with echocardiography (ECO), ophthalmic examination, and abdominal ultrasonography in 38 candidemia episodes of last two years and BOS examination was additionally performed in 8 of these episodes, but no any visceral involvement was detected. There were no data for patient diagnosed before 2018. The overall mortality rate of candidemia was 16.9% in this study, there was no statistically significant difference in mortality rate between the *C. albicans* and nonalbicans groups, and between candidemia episodes diagnosed before and after 2018.

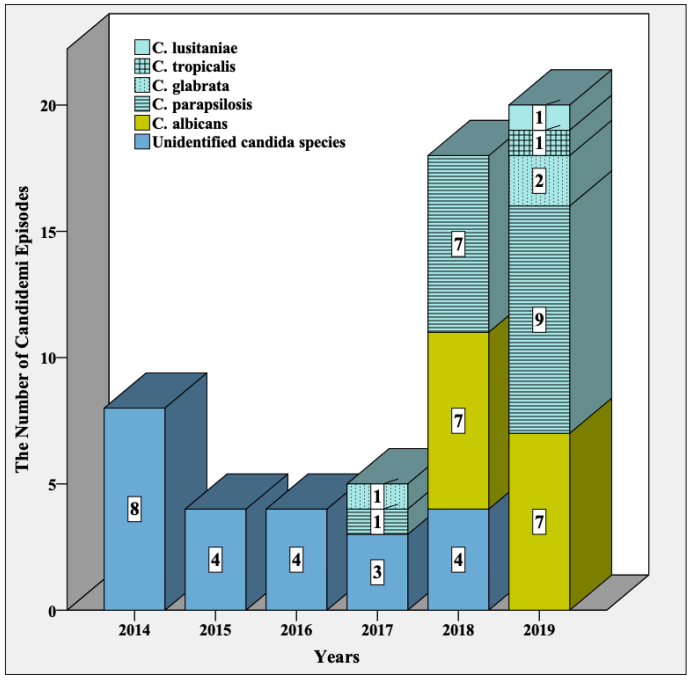

Figure 1. The candida species distribution in PICU of Diyarbakır Children's Hospital between 2014 and 2020

DISCUSSION

Candidemia has high morbidity and mortality rate in critically ill patients, timely initiation of accurate treatment is vital. Therefore, it is necessary to be aware of characteristic of disease, candida species distribution in unit and their antifungal resistance rate.

Incidence of fungal infections are increasing due to prolonged hospitalization and extensive use of broad-spectrum antibiotics, immune suppressant agents, and chemotherapeutics. In our study the number of candidemia episodes were found significantly higher in last two years than previous years. Since we had no a control group without candidemia, we could not fully analyze reasons for this increase. Ulu Kilic et al. also found an increase in the annual incidence of candidemia in their study involving patients aged 0-88 years, and attributed this increase to worsening of patient profile, use of broad-spectrum antibiotic, increased frequency of major surgery, and severe underlying comorbidities of the patients.[16] On the other hand, Mantadakis et al. reported decline in incidence of pediatric candidemia in United State and some other countries due to skin preparation with chlorhexidine before central catheter insertion, maintenance of bundles, meticulous catheter care and daily discussion of catheter necessity.[17] They advise taking additional interventions aiming to reduce gut associated candidemia. Hovewer it is challenging to make comparison as the rates of candidemia in the units affected by characteristics of patients, infection control measures taken, the frequency of invasive procedures, and the principle of antibiotic administration.

The median age of our patients at the diagnosis was 43 months. Sutcu et al. evaluated epidemiologic characteristics of healthcare associated candida infections in children, including newborns, and reported mean age as 11 months, 13.4% ≤1 month, 50.7% between 1-24 months, 35.9% >24 months old.[4] An 11-year retrospective study analyzed 1395 candidemia episodes in children in Europe reported that of the 36.4% of episodes occurred in neonates, 13.8% in infants, and 49.8% in children and adolescents.[1]

Risk factors for candidemia are well defined in children, compatible with this our all patients had used broad-spectrum antibiotics, the majority were on mechanic ventilation support, had nasogastric tube and central venous catheter. Even though we think these risk factors have increased gradually over the years, we could not prove this due to absence of a control patient group without candidemia.

The distribution of Candida species varies geographically and temporally. Even tough *C. albicans* is the most commonly isolated species, nonalbicans species isolation is increasing.[1,5,6] *C. parapsilosis* is reported as the dominant nonalbicans species in children.[1,5,18] In our PICU *C. parapsilosis* was the most frequently isolated candida species, and this appears to be related to the prolongation of hospital stay. Ulu Kılıç et al. reported same relation in adult patients, additionally they found high frequency of central venous catheter usage in nonalbicans candidemia.[16] Two other studies from Turkey stated higher use of central venous catheters and total parenteral nutrition (TPN) in *C. parapsilosis* candidemia.[19,20] In adults, the predominant nonalbicans candida is *C. parapsilosis* in Asia, Southern Europe, and South America, whereas it is the *C. glabrata* in northern Europe, Canada and United States.[21]

Positive blood culture is the gold-standard test for diagnosing of candidemia, but its overall sensitivity is about 50%.[22] So, non-culture methods like antigen, antibody, β-D-glucan detection assays, and polymerase chain reaction (PCR) are increasingly used. None of these tests were available in our institution. We compare non-specific laboratory test results between albicans and nonalbicans candidemia groups, leucocyte count was found higher in albicans group. Actually, clinical value of this finding is not well established, it may demonstrate acute septic clinic in C albicans candidemia. There are few studies compared leucocyte count between two groups. Cheng et al. reported that the leukocyte count was high, ≥15,000 /mm^3, in the albicans group, and neutropenia was more common in the non-albicans group.[25] It has been reported in many studies that non-albicans candidemia is more common in neutropenic patients.[23,24] After clinical value of this finding supported with the large-scale studies, leukocytosis can be used as a sign of albicans candidemia in suspicion of candidemia or if candida type is not yet been identified.

Besides being aware of candida species distribution in unit, knowing anti-fungal resistance rate can help to choose accurate antifungal treatment. In our institution antifungal

resistance tests begun to be performed in the second half of 2018. While there was no resistance in 2018, in 2019 estimated resistance rate for voriconazole was 16.7%, for echinocandins was 11,1%. Previous studies from Turkey reported no resistance for echinocandins and 7.5% for fluconazole.[16,19] The high antifungal resistance rate of our PICU may be related to widespread usage of echinocandins. In fact, in our institution generally the 2012 European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and 2016 Infectious Diseases Society of America (IDSA) guidelines were followed for treatment of candidiasis in children.[26,27] Empiric antifungal therapy was initiated when critically ill children had risk factors for candidiasis and if the fever persist despite the use of appropriate antibiotics. Echinocandins were the drugs of choice for those with moderate to severe disease. Although culture antibiogram revealed fluconazole susceptibility, hesitating to switch to step down therapy with fluconazole may be one of the reasons for high echinocandins resistance in ours PICU. So, use of stepdown antifungal treatment in susceptible type of candida seems essential.

Data about the investigation of candidemia complications, such as deep-seated infection, were reached for the last two years. Absence of complications in our patients may be due to small size of our study or due to rarity of these complications such as ocular involvement reported as 3.2%.[28]

Mortality rate of candidemia was roughly 47%.[26] In this study it was 16.9%, there was no statistical difference between *C. albicans* and non-albicans group, and between candidemia episodes diagnosed before and after 2018.

Even though sample size of study is small, candida species identification and anti-fungal resistance tests have begun to performed lately in a limited number of cases, it is still valuable, because it evaluates candidemia in pediatric age group.

CONCLUSION

Antifungal treatment should not be delayed in critically ill patients who have risk factors for candidiasis and with ongoing fever despite appropriate antibiotic use. For patients with long hospital stay empiric antifungal treatment should cover non-albicans candida which may have antifungal resistance. Patients should be monitored for clinical response to antifungals, if antibiogram show susceptibility switching to step down antifungal treatment should be considered. This may prevent antifungal resistance in institution.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the decision of Clinical Research Ethics Committee of Health Sciences University Diyarbakır Gazi Yaşargil Training and Research Hospital with the number of 283, Jun 14, 2019,

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Financial Disclosure: The authors declared that this study has received no financial support.

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