NON-ALBICANS SPECIES: MAIN ACTORS OF CANDIDEMIA? SEVEN-YEAR EXPERIENCE FROM A SINGLE CENTRE

KANDİDEMİLERİN BAŞ AKTÖRÜ ALBİCANS DIŞI TÜRLER MİDİR? YEDİ YILLIK TEK MERKEZ DENEYİMİ

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ABSTRACT

Objective: Candidemia is a major cause of mortality among healthcare-associated infections. Considering the increase in non-*albicans* species in recent years, it is important to define the treatment approach by identifying *Candida* at the species level. The aim of this study was to evaluate the epidemiological characterics, risk factors and mortality of patients with candidemia in our hospital.

Material and Method: Forty-four patients with *Candida* species isolated from at least one bottle of blood culture taken during hospitalization between January 2013 and October 2019 were included in the study. Patients' demographic information, comorbidities, duration of hospitalization and ward, neutropenia, total parenteral nutrition (TPN), steroid administration and invasive device use, antimicrobial treatments used in the last month, source of candidemia, acute phase indicators, *Candida* species and antifungal resistance, antifungal treatment, clinical response and mortality were evaluated retrospectively. *Candida* species and antifungal susceptibilies were identified using the automated system VITEK®2 (bioMérieux, Marcy l'Etoile, France).

Results: A total of 44 patients with candidemia participated; the median age was 57, and 27 (61.3%) were male. The median length of stay was 33.5 days. Forty-two (95.4%) of the cases were accompanied by multiple comorbidities, and the most common aetiology was malignancy (59%). Most (97.7%) of the patients had received broad-spectrum antibiotic treatment in the last month. Central venous catheters (CVCs) were used in 35 (79.5%) of the cases and 50% of them were treated with TPN. *Candida albicans* (54.6%) was the most common species, followed by *Candida tropicalis* (18.2%). Non-albicans species were observed to increase over time. Thirty-day mortality was 36.3%.

ÖZET

Amaç: Kandidemiler sağlık bakımı ile ilişkili infeksiyonlar arasında mortalitesi yüksek olan bir grubu oluşturmaktadır. *Albicans* dışı türlerin sebep olduğu kandidemilerin insidansındaki artış, tür düzeyinde tanımlamanın ve bu sayede etkin antifungal tedaviyi uygulamanın önemini ortaya koymuştur. Çalışmamızda; hastanemizdeki kandidemi olgularının epidemiyolojik özellikleri, risk faktörleri ve mortaliteleri açısından değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Ocak 2013-Ekim 2019 tarihleri arasında yatışı sırasında alınan en az bir şişe kan kültüründe *Candida* türlerinin izole edildiği 44 hasta çalışmaya dahil edildi. Hastaların demografik bilgileri, komorbiditeleri, yatış süresi-yattığı ünite, son bir ayda yapılan cerrahi girişimler, nötropeni, total parenteral beslenme (TPN), steroid uygulaması ve invazif araç kullanımı, son bir ayda ve ayrıca kandidemi sırasında kullandığı antimikrobiyal tedaviler, kandideminin kaynağı, akut faz göstergeleri, *Candida* türü ve antifungal direnci, antifungal tedavi türü ve süresi, tedaviye klinik yanıt ve gelişen mortaliteler retrospektif olarak değerlendirildi. *Candida* türleri ve antifungal duyarlılıkları VITEK®2 (bioMérieux, Marcy l'Etoile, Fransa) otomatize sistemi ile tanımlandı.

Bulgular: Toplam 44 kandidemili hastanın; ortanca yaşı 57 (0-87), 27 (%61,3)'si erkek, 17 (%38,6)'si kadındı. Ortanca yatış süresi 33,5 gündü. Olguların 42 (%95,4)'sine çeşitli komorbiditeler eşlik etmekte olup, en sık etiyoloji malignite (%59) olarak saptandı. Hastaların 43 (%97,7)'ü son bir ayda geniş spektrumlu antibiyotik tedavisi almıştı. Olguların 35 (%79,5)'inde SVK vardı ve yarısına TPN tedavisi uygulanıyordu. Tür dağılımında en sık *Candida albicans* (%54,6) görülürken, ikinci sırayı *Candida tropicalis* (%18,2) izliyordu ve zamanla *albicans* dışı türlerin arttığı gözlendi. Otuz günlük mortalite %36,3 olarak saptandı.

Conclusion: Non-*albicans* candidemia was found to have increased over the years in our study. The main risk factors for candidemia were determined as the presence of comorbidities, especially malignancy, prior broad-spectrum antibiotherapy use, TPN treatment and the presence of CVC. The mortality rate in this study was also consistent with the literature.

Keywords: Candidemia, epidemiology, risk factors

Sonuç: Çalışmamızda tek merkezin kandidemi sonuçları irdelenmiş; yıllar içinde *albicans* dışı kandidemilerin artış gösterdiği saptanmıştır. Kandidemi için başlıca risk faktörlerinin malignite başta olmak üzere komorbiditelerin varlığı, öncesinde geniş spektrumlu antibiyoterapi uygulanması, TPN tedavisi ve SVK varlığı olarak belirlenmiştir. Mortalite oranı da literatürle uyumludur.

Anahtar Kelimeler: Kandidemi, epidemiyoloji, risk faktörleri

INTRODUCTION

Candidemia, which constitutes an important part of invasive *Candida* infections, is an important cause of mortality in hospitalized patients and is the fourth most common cause of bloodstream infections in hospitals. Nowadays, increasingly complex surgical interventions, patients at high risk of infection, and changing demographic characteristics of patients have increased the frequency of candidemia (1). Two important groups of patients are at risk for candidemia: immunosuppressed patients and intensive care unit patients. Neutropenia, chemotherapy, broad-spectrum antibiotherapy, invasive device use, total parenteral nutrition (TPN) treatment, comorbidities (chronic kidney failure, advanced age, etc.) and surgery are considered predisposing risk factors for candidemia in these patients (2).

Candidemia can originate endogenously from the gastrointestinal tract, skin and mucous membranes. In the literature, it has been determined that the most important risk factor for dissemination of infection into the bloodstream is *Candida* colonization in the mucous membranes. In fact, in 80% of patients who develop a bloodstream infection due to *Candida albicans* and *Candida glabrata*, mucous membrane colonization develops before the development of candidemia (3, 4). In addition, intravenous catheter use, contaminated TPN and hands of healthcare workers have also been associated with exogenous candidemia (4).

Candidemia can cause acute sepsis, which is usually indistinguishable from bacterial bloodstream infections. It can also cause insidious clinical presentation accompanied by fever. Common clinical presentation is fever and clinical deterioration that do not respond to antibiotic treatments in patients with risk factors for candidemia (5). It is still difficult to diagnose candidemia in our current clinical practice because clinical symptoms are not specific, blood culture tests are missing in 50% patients, biomarkers indicating *Candida* infections (β-D-glucan, T2 magnetic resonance, etc.) are not widely used and there is still insufficient data in polymerase chain reaction-based tests (5, 6). Although the distribution of isolates in candidemia may vary according to the geographic region and patient groups, the dominant isolate is mostly *C. albicans*. Studies conducted in recent years show that infections related to non-*albicans* species (NAC) are also increasing (7).

The main objective of this study is to evaluate epidemiological features, risk factors, distribution of *Candida* species, antifungal resistance, response to antifungal therapy and mortality of candidemia cases followed in our centre.

MATERIAL AND METHOD

Forty-four patients with isolated candidemia, ranging in age from 0 to 87 years and who were hospitalized between January 2013 and October 2019, were enrolled in the study. Candidemia was defined as the isolation of the *Candida* strain in at least one vial of blood culture with clinical illness. The diagnosis of catheter-related bloodstream infection was defined according to the American Centers for Disease Control and Prevention criteria (8). Identical *Candida* species of one patient on different days was considered as a single infection. Clinical response to antifungal treatment was determined as fever regression with a decrease in inflammatory markers (C-reactive protein [CRP], procalcitonin [PCT] and leukocyte count). Patients' demographic information, existing comorbidities, duration of hospitalization, hospitalization ward, surgical interventions in the last month, neutropenia, TPN, systemic steroid administration and invasive device use (central venous catheter [CVC], mechanical ventilation, urinary catheter), antibiotic and antifungal therapies within the last month, antibiotherapies applied during candidemia and the source of candidemia were recorded. In addition, acute phase indicators (leukocyte count, CRP and PCT), *Candida* species and antifungal susceptibilities, antifungal therapy and duration, clinical response to therapy and mortality were evaluated retrospectively from the hospital and clinical microbiology laboratory records.

A BACTEC 9240 (Becton Dickinson, Sparks, MD, USA) automated blood culture system was used for blood cultures. Cultures were incubated for 7 days. Gram stain and subculture on plate media (5% sheep blood agar, MacConkey agar, chocolate agar, Sabouraud dextrose agar) were applied to positive blood cultures. Plates were incubated at 37°C for 48–72 hours. A VITEK 2 Compact® (bioMérieux, Marcy l'Etoile, France) automated system was used for identification and antifungal susceptibility tests of all *Candida* species. All data analysis was conducted *using* the Statistical Package for Social Sciences (*SPSS*, Chicago, IL, USA), version 11.0.

RESULTS

The median age of 44 patients was 57 (0–87 years); 27 (61.3%) were male and 10 were in the paediatric age group (<16 years). The median length of stay was 33.5 (2–125) days. Average number of leukocytes was 12052±9840.3/mm^3 and CRP was 137.1±105 mg/L; PCT was determined as 11.6±22.2 ng/ml. During candidemia, 54.5% cases were receiving in-patient services and the remaining 45.5% were in intensive care units (34.1% medical intensive care, 6.8% paediatric intensive care and 4.5% surgical intensive care). Candidemia was diagnosed after a mean duration of 23.5±24.7 (2–107) days after hospital admission. Multiple comorbidities accompanied 42 (95.4%) of the cases. These comorbidities, in order of frequency, were malignancy (26 patients; 24 patients solid organ tumour, two patients haematological malignancy), cerebrovascular events (six patients), kidney failure (five patients), cardiovascular diseases (four patients), diabetes (three patients), hypertension (two patients), low birth weight (one patient), short bowel syndrome (one patient), Down syndrome (one patient) and severe burn (one patient). Forty-three patients (97.7%) had received broad-spectrum antibiotic therapy in the past month, and 41 (93.1%) patients were receiving broad-spectrum antibiotic therapy during candidemia. Thirty-five (79.5%) of the cases had a CVC and TPN therapy was applied in 50% of those who developed candidemia. Systemic steroid use in supraphysiological doses was applied for anti-oedema effect in six patients with the diagnosis of intracranial malignancies. The demographics, laboratory findings and risk factors of the patients are summarized in Table 1.

C. albicans (54.6%) was the predominant species followed by *Candida tropicalis* (18.2%; Figure 1a). It has been observed that non-*albicans* species have increased over the years (Figure 1b). The source of candidemia was determined as CVC in 13 (29.5%) patients (Table 2). Fluconazole resistance was not detected in any of the identified *C. albicans* strains. In NAC, fluconazole resistance was 20% (5/20). Only seven of the patients with candidemia were examined with dilated fundoscopy and none of them had ocular disease. However, in the follow-up of a patient with biliary tract candidemia (due to complaints of vision loss), fundoscopic examination revealed ocular involvement. Endocarditis was not detected in any of the 13 (29.5%) patients who underwent echocardiography. In this study, fluconazole was the most (50%) empirical antifungal therapy used for candidemia followed by echinocandins (36.4%). Patients were given antifungals for a mean duration of 16.7±10.1 (range 0–42) days. Clinical response was obtained to antifungal treatment given in 33 (75%) cases of candidemia. Crude 30-day mortality was 36.3% (16/44 patients). There was no difference in mortality between *C. albicans* and NAC patients.

Table 1: Risk factors for candidemia

Risk factors	Patients n=44 (%)
Comorbidity/malignancy	42 (95.4%)/26 (59%)
Age (≥65/≤1)	13 (29.5%)/2 (4.5%)
Central venous catheter Mechanical ventilation Urinary catheter use	35 (79.5%) 16 (36.3%) 25 (56.8%)
Total parenteral nutrition administration	22 (50%)
Surgical intervention last month / intra-abdominal surgery	15 (34.1%)/11 (25%)
Neutropenia	5 (11.4%)
Systemic steroid use	6 (13.6%)
Chronic renal failure	5 (11.4%)
Intensive care unit patients	20 (45.5%)
Broad-spectrum antibiotic use last month	43 (97.7%)
Severe burn	1 (2.2%)
Low birth weight	1 (2.2%)
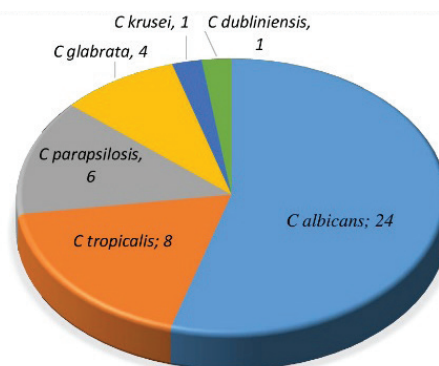
Figure 1a: Species distribution of *Candida* isolates.
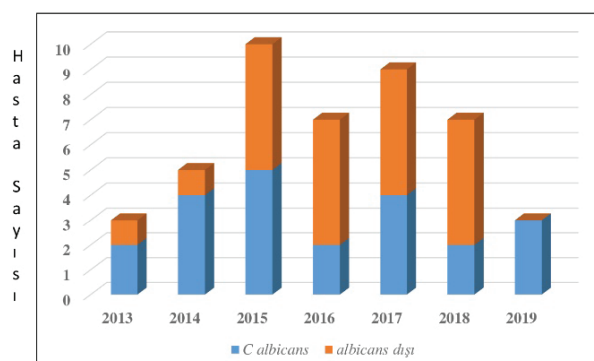
Figure 1b: Distribution of *Candida* species by years.

Table 2: Source of candidemia

Source of candidemia	Patients n=44 (%)
Unknown	15 (34%)
Central venous catheter	13 (29.5%)
Urinary tract	11 (25%)
Gastrointestinal system	5 (11.3%)

DISCUSSION

Candidemia is the most common clinical form of invasive *Candida* infection, and its incidence may differ between countries. Candidemia has been associated with features such as age group and characteristics of patients evaluated, healthcare-associated factors, blood culture techniques, unnecessary antibiotic use and antimicrobial resistance (9).

In candidemia, the rate of pathogen isolation in the blood culture is about 50%. This limitation causes difficulties in determining the epidemiology and incidence of *Candida* species (10). The incidence of candidemia was 0.47–7.07 per 1000 admissions in European hospitals and was much higher in the intensive care units of these hospitals (9,11-13). The incidence of candidemia was determined as 0.3–1.76 per 1000 admissions in studies conducted in our country (14-17). In our study, the average incidence of candidemia for 6 years and 10 months was found as 0.41 per 1000 admissions.

The incidence of candidemia is high in extremes of age. It has been determined that the most important reason for the high incidence in infants under one year of age is low birth weight (18). In older age, the incidence of candidemia is much higher due to comorbidities (19). In our study, approximately one-third (29.5%) of patients with candidemia were elderly patients. In fact, studies have shown that *Candida* infections develop due to impaired defence mechanisms of the host rather than the pathogenicity of the microorganism; existing comorbidities is the most important factor disrupting the host's defence mechanism (20).

As in our study, the most common comorbidity in patients with candidemia is malignancy, especially in those with haematological malignancy. Chemotherapy, concomitant neutropenia, the presence of mucositis in the digestive system and corticosteroid therapies used can also be considered important risk factors contributing to the development of invasive *Candida* infections. On the other hand, candidemia that developed in patients with solid organ tumours has been associated with surgical complications, intensive care hospitalization, mechanical ventilation, TPN treatment and CVC use (21). In our study, 92.3% (24/26 patient) of cases with malignancy were accompanied by a solid organ tumour.

Other risk factors determined for candidemia in the literature include corticosteroid administration, CVC use, abdominal surgery, severe burns, renal failure requiring dialysis, broad-spectrum antibiotic use and low birth weight in newborns (22). In our study, prior broad-spectrum antibiotic therapy (97.7%), CVC use (79.5%) and TPN therapy (50%) were found to be compatible with the literature (Table 1). According to the literature, 33%–55% of candidemia develops in intensive care units (23). The data we obtained from the past 7 years showed that 45.5% of candidemia developed in intensive care units.

Distribution of candidemia species may vary between geographic regions and institutions. Globally, while candidemia related to *C. albicans* is decreasing, the incidence of *C. glabrata* and *Candida krusei* remains unchanged, and the incidence due to *Candida parapsilosis* and *C. tropicalis* is increasing (10). In studies conducted in our country, while the rates related to *C. albicans* varied between 48.1% and 75%, it was determined that non-*albicans* species have increased over time, similar to the literature (14, 16, 24). Similarly, in our study, while the most common cause of candidemia was *C. albicans* (54.6%), NAC species were determined to have increased over the years (Figure 1b).

Candidemia developing with NAC depends on the underlying features of the patient. *C. parapsilosis* is mostly associated with exogenous infection, such as CVC colonization and parenteral nutrition, and the incidence is significantly higher in Mediterranean countries (21, 25). *C. glabrata* and *C. krusei* are associated with recent major abdominal surgery, solid organ tumours, advanced age, neutropenic newborns, transplant recipients and steroid-treated patients. The *C. glabrata* rate is higher in the United States (21.1%) compared to other countries in the world (7.6%–12.6%) (21). *C. tropicalis* is usually isolated in patients with solid tumours and haematological cancer, and it is the second most common species in Asia and Latin America (21). The widespread use of azoles in the last two decades has been associated with a decrease in infections related to *C. tropicalis* and *C. albicans* (26). The second most common isolate in our study was *C. tropicalis*, following *C. albicans*. Similar to the literature, the underlying disease was solid organ malignancy in the vast majority of these patients (7/8 patients). Yapar et al. reported that the most common isolate among non-*albicans* candidemia was *C. tropicalis,* similar to our study. This frequent isolation was explained by a lower ratio of patients receiving fluconazole prophylaxis applied in the study centre (15). A small number of patients (2/44 patients) were found to have fluconazole prophylaxis in our study as well. *C. parapsilosis* was identified in our study as the third highest frequency. *C. glabrata*, which does not differ between centres and is generally found between 9% and 12%, was found to be 9.1%, in accordance with the literature in our centre.

Crude mortality has been reported to be 30%–60% in candidemia (27, 38). Treatment early and with an appropriate antifungal agent significantly reduces mortality. Therefore, knowing the causative agent in candidemia enables the empirical treatment selection to be directed correctly (10). Current guidelines recommend echinocandins as the first-line treatment for candidemia and recommend fluconazole treatment only in non-critical patients (29). In fact, it has been shown in a study that echinocandin therapy does not improve the outcome of non-critical care unit patients with septic shock due to candidemia (30). In the selection of empirical treatment, the patient's clinical presentation, prior use of azole, presence of neutropenia and surveillance data of the relevant centre should be taken into consideration. Considering these factors, fluconazole was the preferred treatment in 50% of patients in our study, followed by echinocandins, and our crude 30-day mortality rate was also found to be consistent with the literature.

In conclusion, candidemia should be considered in patients with risk factors such as malignancy, broad-spectrum antibiotherapy, CVC and TPN use, in intensive care units and advanced age. The recent increase in non-*albicans* candidemia cases should not be ignored. In our centre, similar to the literature, NAC has increased over the years. Our study presents the epidemiological and clinical features of retrospective candidemia cases of a single centre. The most important limiting factor is the low number of cases. Importantly, the crude mortality of candidemia is high despite advances in diagnosis, and each centre should guide the treatment knowing its own *Candida* epidemiology and antifungal resistance.

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