flora

KLİNİK ÇALIŞMA/RESEARCH ARTICLE

FLORA 2010;15(2):59-67

Risk Factors for Mortality in Patients with Candidemia: A Prospective Case-Control Study

Kandidemi Gelişen Hastalarda Mortalite Risk Faktörleri: Prospektif Olgu-Kontrollü Çalışma

Evrim GÜLDEREN[1], Esragül AKINCI[1], Pınar ÖNGÜRÜ[1], Hürrem BODUR[1]

[1] Clinic of Infectious Diseases and Clinical Microbiology, Ankara Numune Training and Research Hospital, Ankara, Turkey

SUMMARY

Introduction: *Candidemia is a serious infection with a high mortality rate.*

Patients and Methods: *This prospective case-control study was conducted between January 2004 and December 2007. Hospitalized patients who had Candida spp. in their blood cultures were followed until death or discharge. Mortality was considered to be related to candidemia if the patient was receiving antifungal treatment for candidemia when death occurred or if they died before initiation of antifungal agent, if no other cause of death was detected. Variables of the patients with candidemia-related death and the patients who survived after a candidemia episode were compared statistically for the detection of candidemia-related mortality risk factors.*

Results: *A total of 124 patients were included in the study. The overall candidemia-related mortality was 66.1%. Univariate predictors associated with mortality were age ≥ 65 years, hospitalization in the intensive care unit (ICU), sepsis syndrome during the candidemia episode, Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score ≥ 10, presence of central venous catheter during candidemia, central venous catheter not removed after development of candidemia, total parenteral nutrition, Candida albicans etiology, and lack of antifungal therapy. In the multivariate analysis, age ≥ 65 years, hospitalization in ICU, sepsis syndrome during the candidemia episode, C. albicans etiology, and lack of antifungal therapy were independent factors adversely influencing outcome.*

Conclusion: *This study suggested that candidemia-related mortality can be reduced by starting empirical antifungal treatment in the high-risk ICU patients with refractory fever, especially for those under broad-spectrum antibiotics, and by removing the central venous catheter as a part of the treatment.*

Key Words: *Candida, Mortality, Risk factors*

ÖZET

Kandidemi Gelişen Hastalarda Mortalite Risk Faktörleri: Prospektif Olgu-Kontrollü Çalışma

Evrim GÜLDEREN[1], Esragül AKINCI[1], Pınar ÖNGÜRÜ[1], Hürrem BODUR[1]

[1] SB Ankara Numune Eğitim ve Araştırma Hastanesi, 2. İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği, Ankara, Türkiye

Giriş: *Kandidemi, mortalitesi yüksek ciddi bir infeksiyondur.*

Hastalar ve Metod: *Bu prospektif olgu-kontrollü çalışma Ocak 2004-Aralık 2007 tarihleri arasında yapıldı. Hastanede yatan ve kan kültüründe Candida spp. üreyen hastalar taburcu ya da eksitus olana kadar takip edildi. Kandidemi nedeniyle antifungal tedavi alırken*

Geliş Tarihi/Received: 04/01/2010 - Kabul Ediliş Tarihi/Accepted: 01/04/2010

ya da tedavi başlanamadan önce ölen ve ölümü açıklayacak başka bir neden bulunamayan hastalarda mortalitenin kandidemi ile ilişkili olduğu düşünüldü. Kandidemi atağı sonrası yaşayan hastalar ile kandidemi ilişkili ölüm düşünülen hastalara ait veriler istatistiksel yöntemlerle karşılaştırılarak kandidemi ile ilişkili mortalite risk faktörleri belirlendi.

Bulgular: *Toplam 124 hasta çalışmaya dahil edildi. Kandidemi ile ilişkili mortalite oranı %66.1 olarak bulundu. Tek değişkenli analizde, yaş ≥ 65, yoğun bakım ünitesi (YBÜ)'nde yatma, kandidemi epizodu sırasında sepsis varlığı, "Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II skoru ≥ 10, kandidemi sırasında santral venöz kateter varlığı, kandidemi geliştikten sonra santral venöz kateterin çekilmemesi, total parenteral nütrisyon, etkenin Candida albicans olması ve antifungal tedaviye başlanamaması mortalite risk faktörleri olarak bulundu. Çok değişkenli analizde, yaş ≥ 65, YBÜ'de yatma, kandidemi atağı sırasında sepsis varlığı, etkenin C. albicans olması ve antifungal tedaviye başlanamaması mortaliteyi etkileyen bağımsız risk faktörleri olarak tespit edildi.*

Sonuç: *Bu çalışma, YBÜ'de yatan yüksek riskli hastalarda, geniş spektrumlu antibiyotik tedavisine rağmen düşmeyen ateş varlığında ampirik antifungal tedavi başlanmasının ve varsa santral venöz kateterin çekilmesiyle kandidemi ile ilişkili mortalite oranının düşürülebileceğini göstermektedir.*

Anahtar Kelimeler: *Candida, Mortalite, Risk faktörleri*

INTRODUCTION

The incidence of candidemia has increased in recent decades[1-6]. *Candida* species are the fourth leading cause of nosocomial bloodstream infections in United States hospitals[1,3,7]. The increased incidence of candidemia has been attributed to increased use of indwelling central venous catheters, parenteral hyperalimentation, the growing number of bone marrow and solid organ transplantations, prolonged stays in intensive care units (ICUs), more aggressive antineoplastic regimens, more prolonged neutropenia, and the increased use of broad-spectrum antibiotics[8,9]. Although *Candida albicans* remains the most common cause of fungal bloodstream infections, a trend towards an increased prevalence of non-*albicans Candida* species has been detected[10,11]. This change was explained by widespread use of parenteral nutrition solutions and the increased use of fluconazole prophylaxis to prevent fungal infections[12-16].

Bloodstream infections caused by *Candida* spp. have become an important cause of morbidity and mortality in hospitalized patients. The mortality rate is high, ranging between 40% and 70%[17-19]. There is limited data in the literature about the risk factors for mortality in the patients who developed candidemia, and most of the studies were done retrospectively. We conducted this prospective case-control study to determine the risk factors for candidemia-related mortality and to suggest the strategies for decreasing the mortality rate.

PATIENTS and METHODS

Hospital Setting and Study Population

A prospective case-control study was carried out at our hospital between January 2004 and December 2007. Hospitalized patients who had *Candida* spp. in their blood cultures were followed until death or discharge, and candidemia-related mortality risk factors were detected.

Collection of Data

Laboratory records were examined daily and patients with positive blood cultures for *Candida* spp. were detected. These patients were visited daily until discharge or death and their medical data were recorded on standardized individual forms. The form included age, gender, primary diagnosis, date of the admission to hospital, time between hospital admission and positive blood culture for *Candida* spp., comorbidity (renal failure, hepatic failure, malignancy, diabetes mellitus, cardiac failure, chronic lung disease, transplantation), major surgical procedures, "Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II" score at admission, immunosuppressive treatment (steroids, chemotherapy) within the last month, indwelling central venous catheter during candidemia, replacement or removal of central venous catheter after development of candidemia, urinary catheter, hemodialysis, total parenteral nutrition (TPN), physical examination findings and laboratory test results after onset of candidemia, broad-spectrum antibiotics given to the patient within the last 30 days, nosocomial infections during hospitalization,

culture results of blood, urine and central venous catheter, identified *Candida* species and their antifungal susceptibilities, antifungal agents given to the patient, duration of antifungal therapy, and patient outcome.

Definitions

Candidemia was diagnosed when the patient had at least one positive blood culture for *Candida* spp. Source of candidemia was defined as urinary tract if urine culture revealed the same *Candida* species as that found in blood. Candidemia was considered to be central venous catheter-related if semiquantitative rol-plate culture of the catheter tip yielded at least > 15 colony-forming unit (cfu) of the same *Candida* species that was isolated from the bloodstream. Patients in whom no corresponding isolate was found in another type of specimen were defined to have candidemia of unknown source.

Sepsis was diagnosed with the presence of at least two of these criteria: Fever or hypothermia (body temperature > 38°C or < 36°C), tachycardia (heart rate > 90/min), tachypnea (respiratory rate > 20/min), and leukocytosis or leukopenia (leukocyte count > 12.000/mm^3 or < 4000/mm^3). When any other infection was detected within 48 hour before or after the isolation of *Candida* spp. from the blood culture, it was recorded as a concominant infection.

Mortality was considered to be related to candidemia if the patient was receiving antifungal treatment for candidemia when death occurred or if they died before initiation of antifungal agents, if no other cause of death was detected[8,20]. Only patients with candidemia-related mortality were included in the analysis of factors influencing mortality. Patients who died due to other reasons were excluded from the study. The patients with candidemia-related death (fatal cases) and the patients who survived after an episode of candidemia (survivors) were compared statistically.

Microbiological Investigations

Blood cultures were processed by BacT/Alert (BioMerieux, France) automated blood culture system. Yeasts were identified by germ tube test and API ID 32C system (BioMerieux, France). Susceptibility tests of the isolates against antifungal agents (amphotericin B, fluconazole, flucytosine, itraconazole) were performed by microdilution method recommended by the Clinical and Laboratory Standards Institute (CLSI) (M27-A2) and minimum inhibitory concentrations (MICs) were determined[21]. *Candida glabrata* ATCC 64677 was used for quality control.

Statistical Analysis

Statistical analyses were performed using the SPSS 13 (SPSS Inc., Chicago, Illinois). Univariate analyses were performed to detect risk factors for candidemia-related death. For categorical measures, Fisher's exact test or Pearson's chi-square test was used. For continuous measures, unpaired Student's t test was used. The Kolmogorov-Smirnov test was used to check the normality of distribution. Results of $p< 0.05$ were considered statistically significant. Variables with p values < 0.05 in the univariate analysis were included in the multivariate analysis. Backwards logistic regression analysis was used for multivariate analysis of independent risk factors associated with mortality in candidemic patients.

RESULTS

A total of 124 patients determined to have candidemia between January 2004 and December 2007 were included in the study. Of the 124 patients, 82 (66.1%) died related to candidemia and 42 (33.9%) survived. The mean duration between hospital stay and isolation of *Candida* spp. from blood culture was 33.8 days (4-120 days). The mean age was 53.3 ± 18.1 years (15-96 years), and 63 (51%) cases were female. Of the 124 patients, 88 (71%) were hospitalized in the ICU and 36 (29%) were hospitalized in the medical and surgical wards. Fifteen patients were hospitalized in the hemato-oncology ward. The most frequent sign on physical examination was fever. Clinical symptoms of sepsis syndrome were more common in fatal cases (Table 1).

With regard to the source of the candidemia, 30 (24.2%) patients had urinary-born candidemia and 22 (17.7%) had catheter-related candidemia. One (0.8%) patient had *Candida meningitidis* after cranial operation. Both cerebrospinal fluid (CSF) and blood cultures of these patients revealed the same *Candida* species. The source of candidemia could not be detected in 71 (57.3%) of the patients.

C. albicans was the predominant species and was isolated from the blood cultures of 49 (39.5%) patients. It was followed by *Candida parapsilosis* in 34

Table 1. Clinical and laboratory findings of the patients with candidemia

Findings	Survivors (n= 42) n	%	Fatal cases (n= 82) n	%	p
Fever (> 38°C)	32	76.2	53	64.6	0.190
Tachycardia (heart rate > 90/min)	10	23.8	49	59.8	< **0.001**
Hypotension (systolic blood pressure < 90 mmHg)	3	7.1	35	42.7	< **0.001**
Tachypnea (respiratory rate > 20/min)	3	7.1	25	30.5	**0.003**
Mental deterioration	12	28.6	49	59.8	**0.001**
Leukocytosis (leukocytes > 12.000/mm^3)	15	35.7	37	45.1	0.315
Neutropenia (neutrophils < 1000/mm^3)	6	14.3	7	8.5	0.361
Thrombocytopenia (platelets < 100.000/mm^3)	10	23.8	19	23.2	0.937
Anemia (Hb < 12 g/dL)	39	92.9	74	90.2	0.748
Serum creatinine level (median, mg/dL)	0.73		0.73		0.855
Serum ALT level (median, U/L)	26		28		0.642
APACHE II score (mean)	10.89 ± 3.78		14.58 ± 4.51		**0.002**

ALT: Alanine aminotransferase, APACHE: Acute Physiologic Assessment and Chronic Health Evaluation.

(27.4%), *C. glabrata* in 10 (8.1%) and *Candida tropicalis* in 10 (8.1%) patients. Other *Candida* species were isolated in 21 cases (16.9%). Of the 22 patients with central venous catheter-related candidemia, 9 (40.9%) had *C. albicans*, 8 (36.4%) had *C. parapsilosis*, 2 (9.1%) had *C. glabrata*, 1 (4.5%) had *Candida sake*, 1 (4.5%) had *Candida curvata*, and 1 (4.5%) had unidentified *Candida* species in the catheter tip and blood cultures. During the study period, no outbreak due to *Candida* species, including *C. parapsilosis*, was detected.

Concomitant infections were diagnosed in 13 (15.9%) fatal cases and 2 (4.8%) survivors. Two survivors and 11 fatal cases had concomitant bacteremia and two fatal cases had bacterial pulmonary infection.

Amphotericin B was the most effective antifungal agent in vitro. While 15 isolates (12.1%) were resistant to fluconazole (MIC ≥ 64 µg/mL), and itraconazole (MIC ≥ 1 µg/mL), all of the isolates were susceptible to amphotericin B. Seven of the fluconazole-resistant isolates were *C. albicans*. Flucytosine resistance was detected in only one isolate (MIC ≥ 32 µg/mL).

Antifungal treatment was given to 96 (77.4%) patients. Seventy (56.5%) cases received fluconazole, 19 (15.3%) amphotericin B, and 7 (5.6%) caspofungin therapy according to the antifungal susceptibility test results. None of the patients was given combination therapy. In seven patients, antifungal treatment was started empirically before positive blood cultures were obtained. All of these patients were hospitalized in the hemato-oncology units. In the other patients, antifungal treatment was started on the same day or 1-2 days after positive blood cultures were obtained. None of the patients was receiving fluconazole prophylaxis. The mean duration of antifungal therapy was 10 ± 8.06 days. Twenty-eight (22.6%) patients never received antifungal therapy. Of these patients, 26 died before positive blood culture results were available and two survivors had intestinal pathology and possibly transient candidemia.

The overall candidemia-related mortality was 66.1% (82 of 124 patients) in this study. The highest mortality occurred in patients infected with *C. albicans*. Of the patients who died of candidemia, 40 (48.8%) had *C. albicans,* and 42 (51.2%) had non-*albicans Candida* species. Univariate predictors associated with mortality were age ≥ 65 years, hospitalization in ICU, sepsis syndrome during the candidemia episode, APACHE II score ≥ 10, presence of central venous catheter during candidemia, central venous catheter not removed after development of candidemia, TPN, *C. albicans* etiology, and lack of antifungal therapy (Table 2). In the multivari-

Table 2. Candidemia-related mortality risk factors: univariate analysis results

Risk factors	Survivors (n= 42) n	%	Fatal cases (n= 82) n	%	p
Age (≥ 65 years)	4	10	30	37	< **0.001**
Gender (female)	19	45	44	54	0.375
ICU stay	19	45	69	84	< **0.001**
Duration from admission to candidemia (median, days)	32.5 (16-49)		35.6 (4-120)		0.586
Primary diagnosis					
Pulmonary disease	4	9.5	3	3.7	0.226
Gastrointestinal disease	7	16.7	22	26.8	0.206
Malignancy	18	42.9	23	28.0	0.097
Neurologic disease	2	4.8	12	14.6	0.137
Multiple trauma	4	9.5	14	17.1	0.259
Cardiovascular disease	1	2.4	5	6.1	0.663
Infectious disease	8	19.0	11	13.4	0.410
Underlying disease					
Diabetes mellitus	11	26.2	22	26.8	0.939
Renal failure	2	4.8	2	2.4	0.604
Congestive heart failure	2	4.8	5	6.1	1.000
Liver failure	1	1.2	0	0	1.000
Chronic lung disease	2	4.8	9	11	0.330
Immunosuppressive therapy within the last month	11	26.2	11	3.4	0.078
Splenectomy	1	7.1	-		
Hemodialysis	4	9.5	5	6.1	0.486
Previous surgery	20	47.6	44	53.7	0.524
Broad-spectrum antibiotic therapy within the last 30 days					
Quinolones	4	9.5	10	12.2	0.771
Glycopeptides	27	64.3	59	72.0	0.381
Carbapenems	32	76.2	65	79.3	0.694
Cephalosporins	21	50.0	35	42.7	0.438
Penicillins	14	33.3	21	25.6	0.366
Aminoglycosides	15	35.7	36	43.9	0.381
Sepsis during the episode of candidemia	26	61.9	68	82.9	**0.010**
Anemia	39	92.9	74	90.2	0.748
Neutropenia	6	14.3	7	8.5	0.361
Serum creatinine level (median, g/dL)	0.73 (0.67-0.80)		0.73 (0.2-5.5)		0.855
Serum ALT level (median, U/L)	26 (16-36)		28 (2-3086)		0.642
APACHE II score ≥ 10 at admission	9	21.4	56	68.3	< **0.001**
Candiduria	17	40.5	30	36.6	0.673
Central venous catheterization during candidemia	28	66.7	76	92.7	< **0.001**
Central venous catheter removal after development of candidemia	15	53.6	32	42.1	**0.001**
Total parenteral nutrition	25	59.5	74	90.2	< **0.001**
***Candida albicans* etiology**	9	21.4	40	48.8	**0.003**
Fluconazole resistance	8	19	7	8.5	0.089
Lack of antifungal treatment	2	4.8	26	31.7	**0.001**
Concomitant infection	2	4.8	13	15.9	0.073

ICU: Intensive care unit, ALT: Alanine aminotransferase, APACHE: Acute Physiologic Assessment and Chronic Health Evaluation.

Table 3. Candidemia-related mortality risk factors: multivariate analysis results

Risk factors	Odds ratio	95% confidence intervals (CI)	p
Age (≥ 65 years)	6.110	1.604-23.270	**0.008**
ICU stay	6.414	2.259-18.213	< **0.001**
Sepsis during the episode of candidemia	4.151	1.349-12.775	**0.013**
Candida albicans etiology	4.818	1.685-13.780	**0.003**
Lack of antifungal therapy	7.777	1.489-40.615	**0.015**

ICU: Intensive care unit.

ate analysis, age ≥ 65 years, hospitalization in ICU, sepsis syndrome during the episode of candidemia, *C. albicans* etiology, and lack of antifungal therapy were independent factors adversely affecting outcome (Table 3).

DISCUSSION

Candidemia has become an important cause of morbidity and mortality in hospitalized patients. Until the late 1980s, *C. albicans* caused the vast majority of cases of disseminated candidiasis. However, in recent series, *C. albicans* caused about 50% of cases of disseminated candidiasis and was followed by *C. glabrata, C. parapsilosis* and *C. tropicalis*[22]. Although *C. albicans* remains the most prevalent yeast isolated from blood cultures, non-*albicans* species of *Candida* are increasingly associated with candidemia[4,10,11,18,23-25]. In this prospective case-control study, the rate of non-albicans *Candida* species isolated from blood cultures was found as 60.5%. This epidemiological change in candidemia is explained by the widespread use of parenteral nutrition solutions and the increasing use of fluconazole prophylaxis to prevent fungal infections[9,12-16,23,26]. Although none of the patients in this study was receiving fluconazole prophylaxis, most of the patients had indwelling central venous catheters and received TPN solutions during candidemia.

In the presented study, *C. parapsilosis* was the second most commonly recovered isolate, similar to the studies from Spain and other European countries[8,9,26-29]. The increased prevalence of *C. parapsilosis* isolates is related to the increased use of central venous catheters and parenteral nutrition solutions[30,31]. Some studies reported *C. parapsilosis* as the most common cause of catheter-associated candidemia[8,27]. This was explained as particular affinity of this species for synthetic materials and its characteristic as a frequent colonizer of the skin[32]. In this study, after *C. albicans*, *C. parapsilosis* was the second most common etiological agent in patients with central venous catheter-related candidemia. The same result was found in a previous publication[33].

Mortality associated with candidemia remains high. In the literature, overall mortality rates related to candidemia were reported between 42 and 71%, similar to our result (66%)[8,17-19,26-28,34]. However, the attributed mortality rate of candidemia was detected at a lower rate, and reported between 25 and 49%[2,8,34,35].

In this study, candidemia-related mortality was defined according to the literature. Mortality was considered to be related to candidemia if the patient was receiving antifungal treatment for candidemia when death occurred or if they died before initiation of antifungal agents, if no other cause of death was detected[8,20]. Postmortem autopsy could not be done to confirm the cause of death. In the other studies investigating the risk factors for mortality related to candidemia, autopsy was not performed; mortality related to candidemia was defined according to the time from positive blood culture to death or when no other cause of death was identified, similar with our study[8,18,20,26,27,36].

There are limited studies about the risk factors for mortality in the patients with candidemia and most of them were done retrospectively. In these studies, consistent with our findings, hospitalization in ICU, age > 65 years, lack of antifungal therapy, presence of central venous catheter, central venous catheter not changed during infection, neutropenia, corticos-

teroid therapy, high APACHE II score, development of sepsis syndrome during the episode of candidemia, *C. albicans* etiology, immunosuppression, renal failure, and chronic obstructive lung disease were found as independent factors adversely influencing the outcome of the candidemia[8,17-20,26-28]. Older age, hospitalization in ICU, high APACHE II score, and presence of sepsis syndrome reflect immune compromise, severe underlying diseases, multiple invasive procedures, and poor clinical progress of the patient. Thus, a higher mortality rate is expected in these conditions.

This study demonstrated that bloodstream infections with *C. albicans* were significantly more severe and fatal than the infections with other *Candida* species. However, according to several reports, some non-*albicans Candida* bloodstream infections (*C. krusei, C. glabrata* and *C. tropicalis*) carry the highest mortality rates[2,4,8,9,18,28,36]. In one of these studies, infections due to *C. krusei* and *C. glabrata* carried the highest (40%) and *C. parapsilosis* carried the lowest attributable mortality rates (20%). Attributable mortality for *C. albicans* was 33.9%[8]. In another study, the highest mortality occurred in patients with *C. glabrata* fungemia (73%) and the lowest mortality occurred in patients with *C. parapsilosis* fungemia (20%)[18]. However, a study reported *C. albicans* as the most common etiological agent in the fatal cases, as in our study. In that study, 22 of 31 patients (71%) died. Of the patients who died of candidemia, 17 (77%) had *C. albicans*, 4 (18%) had *C. tropicalis* and 1 (4%) had *C. glabrata*[19].

In this study, lack of antifungal treatment affected the outcome adversely, and significantly higher mortality rates among untreated patients were detected, similar to previously reported articles[8,18,27,37]. Attributable mortality rates were reported as 28.1% in patients who had received antifungal therapy and as 47.1% in those who had not[8]. It was reported that 52.7% of untreated patients died within the first 48 hours before the result of the first positive blood culture became available[26]. The mortality rate was found nearly two-fold higher in patients who received no antifungal treatment (63% versus 34%)[18]. In our ICUs, the most common approach was the initiation of antifungal agents after positive blood culture results had confirmed the presence of *Candida* species. This practice was recently changed to empirical treatment with antifungal agents for the critically ill patients in ICUs who demonstrated symptoms of infection despite broad-spectrum antibiotics.

Early initiation of appropriate antifungal treatment is essential for reducing the morbidity and mortality of invasive fungal infections[38]. However, in a recent study, although non-receipt of systemic antifungal treatment was independently associated with mortality, duration of the delay in the initiation of antifungal treatment was not associated with greater mortality[37]. We need more studies to confirm this result.

The role of the central venous catheter placement in the development of candidemia and the influence of their removal on the prognosis of fungemia is well known. The removal of central venous catheters from patients with candidemia is standard care. Whenever possible, removal of an indwelling central venous catheter is recommended[39]. However, this is not always possible in routine practice. Usually, the patients with poor prognosis are not considered good candidates for catheter removal or its cost and potential complications cause retention of a central line. In this study, most of the central venous catheters were not withdrawn as a part of treatment after the development of candidemia and non-removal of catheters influenced the outcome of the patients adversely. Some other studies also reported that non-removal of the central venous catheters was strongly associated with the persistence of candidemia and increased risk of death[19,26,27,36,40,41]. Our data, therefore, support the removal of central venous catheters in addition to the antifungal treatment when candidemia is detected. The low rate of catheter removal also affected the detection of the source of candidemia. In this study, source of candidemia could not be detected in approximately two-thirds of the patients.

This is a prospective, case-control study including a large number of patients, and these can be considered the strengths of the study. However, autopsy could not be performed to confirm the cause of the death and this is a limitation of the study.

In conclusion, the mortality of candidemia remains high despite antifungal therapy. Fever is the most frequent symptom in the patients with candidemia.

According to the results of this study, it can be suggested that candidemia should be considered when refractory fever is observed in a high-risk ICU patient, especially in patients under broad-spectrum antibiotic therapy. Starting empirical antifungal treatment in these patients should be considered before obtaining the results of the blood cultures. It should also be kept in mind that adequate antifungal treatment with catheter removal is associated with improved outcome.

REFERENCES

1. *Edmond MB, Wallace SE, McClish DK, Pfaller MA, Jones RN, Wenzel RP. Nosocomial bloodstream infections in United States hospitals: A three-year analysis. Clin Infect Dis 1999; 29:239-44.*
2. *Gudlaugsson O, Gillespie S, Lee K, Vande Berg J, Hu J, Messer S, et al. Attributable mortality of nosocomial candidemia, revisited. Clin Infect Dis 2003;37:1172-7.*
3. *National Nosocomial Infections Surveillance (NNIS) System report, data summary from January 1990-May 1999, issued June 1999. Am J Infect Control 1999;27:520-32.*
4. *Viscoli C, Girmenia C, Marinus A, Collette L, Martino P, Vandercam B, et al. Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC). Clin Infect Dis 1999;28:1071-9.*
5. *Voss A, Kluytmans JA, Koeleman JG, Spanjaard L, Vandenbroucke-Grauls CM, Verbrugh HA, et al. Occurrence of yeast bloodstream infections between 1987 and 1995 in five Dutch university hospitals. Eur J Clin Microbiol Infect Dis 1996;15:909-12.*
6. *Blumberg HM, Jarvis WR, Soucie JM, Edwards JE, Patterson JE, Pfaller MA, et al; National Epidemiology of Mycoses Survey (NEMIS) Study Group. Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study. The National Epidemiology of Mycosis Survey. Clin Infect Dis 2001;33:177-86.*
7. *Jarvis WR. Epidemiology of nosocomial fungal infections with emphasis on Candida species. Clin Infect Dis 1995; 20:1526-30.*
8. *Viudes A, Peman J, Canton E, Ubeda P, Lopez-Ribot JL, Gobernado M. Candidemia at a tertiary-care hospital: Epidemiology, treatment, clinical outcome and risk factors for death. Eur J Clin Microbiol Infect Dis 2002;21:767-74.*
9. *Bedini A, Venturelli C, Mussini C, Guaraldi G, Codeluppi M, Borghi V, et al. Epidemiology of candidaemia and antifungal susceptibility patterns in an Italian tertiary-care hospital. Clin Microbiol Infect 2006;12:75-80.*
10. *Trick WE, Fridkin SK, Edwards JR, Hajjeh RA, Gaynes RP and the National Nosocomial Infections Surveillance System Hospitals. Secular trend of hospital-acquired candidemia among intensive care unit patients in the United States during 1989-1999. Clin Infect Dis 2002;35:627-30.*
11. *Pfaller MA, Diekema DJ. Role of sentinel surveillance of candidemia: trends in species distribution and antifungal susceptibility. J Clin Microbiol 2002;40:3551-7.*
12. *Girmenia C, Martino P, De Bernardis F, Gentile G, Boccanera M, Monaco M, et al. Rising incidence of Candida parapsilosis fungemia in patients with hematologic malignancies: clinical aspects, predisposing factors, and differential pathogenicity of the causative strains. Clin Infect Dis 1996;23:506-14.*
13. *Kuhn DM, Mikherjee PK, Clark TA, Pujol C, Chandra J, Hajjeh RA, et al. Candida parapsilosis characterization in an outbreak setting. Emerg Infect Dis 2004;10:1074-81.*
14. *Safdar A, Perlin DS, Armstrong D. Hematogenous infections due to Candida parapsilosis: Changing trends in fungemic patients at a comprehensive cancer centre during the last four decades. Diagn Microbiol Infect 2002;44:11-6.*
15. *Jarque I, Saavedra S, Martin G, Peman J, Perez Belles C, Sanz MA. Delay of onset of candidemia and emergence of Candida krusei fungemia in hematologic patients receiving prophylactic fluconazole. Haematologica 2000;85:441-3.*
16. *Wingard JR, Merz WG, Rinaldi MG, Johnson TR, Karp JE, Saral R. Increase in Candida krusei infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. N Engl J Med 1991;325: 1274-7.*
17. *Cheng MF, Yang YL, Yao TJ, Lin CY, Liu JS, Tang RB, et al. Risk factors for fatal candidemia caused by Candida albicans and non-albicans Candida species. BMC Infect Dis 2005;5:22.*
18. *Ben-Abraham R, Keller N, Teodorovitch N, Barzilai A, Harel R, Barzilay Z, et al. Predictors of adverse outcome from candidal infection in a tertiary care hospital. J Infect 2004;49:317-23.*
19. *Akbar DH, Tahawi AT. Candidemia at a University Hospital: epidemiology, risk factors and predictors of mortality. Ann Saudi Med 2001;21:178-82.*
20. *Cheng YR, Lin LC, Young TG, Liu CE, Chen CH, Tsay RW. Risk factors for candidemia-related mortality at a medical center in central Taiwan. J Microbiol Immunol Infect 2006; 39:155-61.*
21. *Clinical and Laboratory Standards Institute. Reference method for broth dilution antifungal susceptibility testing of yeasts. Approved standard M27-A2. Wayne, PA: Clinical and Laboratory Standards Institute, 2002.*
22. *Spellberg BJ, Filler SG, Edwards JE. Current treatment strategies for disseminated candidiasis. Clin Infect Dis 2006;42: 244-51.*

23. *Abi-Said D, Anaissie E, Uzun O, Raad I, Pinzcowski H, Vartivarian S. The epidemiology of hematogenous Candidiasis caused by different Candida species. Clin Infect Dis 1997; 24:1122-8.*
24. *Nguyen MH, Peacock JE Jr, Morris AJ, Tanner DC, Nguyen ML, Snydman DR, et al. The changing face of candidemia: emergence of non-Candida albicans species and antifungal resistance. Am J Med 1996;100:617-23.*
25. *Fridkin SK, Jarvis WR. Epidemiology of nosocomial fungal infections. Clin Microbiol Rev 1996;9:499-511.*
26. *Almirante B, Rodríguez D, Park BJ, Cuenca-Estrella M, Planes AM, Almela M, et al; Barcelona Candidemia Project Study Group. Epidemiology and predictors of mortality in cases of Candida bloodstream infection: results from population-based surveillance, Barcelona, Spain, from 2002 to 2003. J Clin Microbiol 2005;43:1829-35.*
27. *Luzzati R, Amalfitano G, Lazzarini L, Soldani F, Bellino S, Solbiati M, et al. Nosocomial candidemia in non-neutropenic patients at an Italian tertiary care hospital. Eur J Clin Microbiol Infect Dis 2000;19:602-7.*
28. *Alonso-Valle H, Acha O, Garcia-Palomo JD, Farinas-Alvarez C, Fernandez-Mazarrasa C, Farinas MC. Candidemia in a tertiary care hospital: Epidemiology and factors influencing mortality. Eur J Clin Microbiol Infect Dis 2003;22:254-7.*
29. *Pfaller MA, Jones RN, Doern GV, Fluit AC, Verhoef J, Sader HS, et al. International surveillance of blood stream infections due to Candida species in the European SENTRY Program: species distribution and antifungal susceptibility including the investigational triazole and echinocandin agents. SENTRY Participant Group (Europe). Diagn Microbiol Infect Dis 1999;35:19-25.*
30. *Weems JJ, Chamberland ME, Ward J, Willy M, Padhye AA, Solomon SL. Candida parapsilosis fungemia associated with parenteral nutrition and contaminated blood pressure transducers. J Clin Microbiol 1987;25:1029-32.*
31. *Levin AS, Costa SF, Mussi NS, Basso M, Sinto SI, Machado C, et al. Candida parapsilosis fungemia associated with implantable and semi-implantable central venous catheters and the hands of healthcare workers. Diagn Microbiol Infect Dis 1998;30:243-9.*
32. *Weems JJ Jr. Candida parapsilosis: Epidemiology, pathogenicity, clinical manifestations and antimicrobial susceptibility. Clin Infect Dis 1992;14:756-66.*
33. *Lecciones JA, Lee JW, Navarro EE, Witebsky FG, Marshall D, Steinberg SM, et al. Vascular catheter-associated fungemia in patients with cancer: analysis of 155 episodes. Clin Infect Dis 1992;14:875-83.*
34. *Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Hospital-acquired candidemia: The attributable mortality and excess length of stay. Arch Intern Med 1988;148:2642-5.*
35. *Wenzel RP, Edmond MB. The impact of hospital-acquired bloodstream infections. Emerg Infect Dis 2001;7:174-7.*
36. *Choi HK, Jeong SJ, Lee HS, Chin BS, Choi SH, Han SH, et al. Blood stream infections by Candida glabrata and Candida krusei: a single-center experience. Korean J Intern Med 2009;24:263-9.*
37. *Marriott DJ, Playford EG, Chen S, Slavin M, Nguyen Q, Ellis D, et al; Australian Candidaemia Study. Determinants of mortality in non-neutropenic ICU patients with candidaemia. Crit Care 2009;13:R115.*
38. *Méan M, Marchetti O, Calandra T. Bench-to-bedside review: Candida infections in the intensive care unit. Crit Care 2008;12:1-9.*
39. *Pappas PG, Rex JH, Sobel JD, Filler SG, Dismukes WE, Walsh TJ, et al; Infectious Diseases Society of America. Guidelines for treatment of candidiasis. Clin Infect Dis 2004;38:161-89.*
40. *Eggiman P, Garbino J, Pittet D. Management of Candida species infections in critically ill patients. Lancet Infect Dis 2003;3:772-85.*
41. *Kibbler CC, Seaton S, Barnes RA, et al. Management and outcome of bloodstream infections due to Candida species in England and Wales. J Hosp Infect 2003;54:18-24.*

Yazışma Adresi/Address for Correspondence

Doç. Dr. Esragül AKINCI

SB Ankara Numune Eğitim ve
Araştırma Hastanesi
2. İnfeksiyon Hastalıkları ve
Klinik Mikrobiyoloji Kliniği
06100 Samanpazarı, Ankara-Türkiye

E-posta: esragulakinci@yahoo.com