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Evaluation of Risk Factors for Candida Colonization and Infection in Non-Neutropenic Intensive Care Patients

Nötropenik Olmayan Yoğun Bakım Hastalarında Kandida Kolonizasyonu ve Enfeksiyonu İçin Risk Faktörlerinin Değerlendirilmesi

Müge AYHAN[a],
Mehmet Serhat BİRENGEL[b],
Gülden YILMAZ[c],
Belgin COŞKUN[d],
Elif Mukime SARICAOĞLU[e]

[a]Clinic of Infectious Diseases and Clinical Microbiology, Ankara Atatürk Training and Research Hospital,
[b]Department of Infectious Diseases and Clinical Microbiology, Ankara University Faculty of Medicine,
[c]Clinic of Infectious Diseases and Clinical Microbiology, Ankara Gülhane Training and Research Hospital,
[d]Clinic of Infectious Diseases and Clinical Microbiology, Ankara Yenimahalle Training and Research Hospital,
Ankara, TURKEY
[e]Clinic of Infectious Diseases and Clinical Microbiology, Bartın State Hospital,
Bartın, TURKEY

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Correspondence:
Müge AYHAN
Ankara Atatürk Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Ankara, TURKEY/TÜRKİYE
dr.mugeayhan@hotmail.com

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ABSTRACT Objective: In patients who are followed in intensive care unit (ICU), colonization and/or invasive infections with Candida species occur in the presence of various risk factors. Difficulties in diagnosis cause delays in antifungal therapy and this is related with increased mortality. **Material and Methods:** In this retrospective case control study, patients were classified as colonized, infected and control group and independent risk factors for Candida colonization and invasive Candida infections were evaluated. Patients followed in Anesthesiology-Reanimation and Medical ICUs of Ankara University Ibn-i Sina Hospital between June 2013 and June 2015 were retrospectively screened. A total of 225 patients, who stayed more than 48 hours in ICU, who were non-neutropenic and above 18 years were included. All demographics and risk factors were recorded. **Results:** Central venous catheter and sepsis/septic shock were found to be the independent risk factors for Candida colonization; presence of central venous catheter, total parenteral nutrition (TPN) use and sepsis/septic shock were found to be the independent risk factors for Candida infection. **Conclusion:** In high risk patients, early and appropriate antifungal therapy decreases mortality. Therefore, for doctors, who works with intensive care, identifying high risk patients for invasive Candida infections is important. Presence of central venous catheter, sepsis/septic shock and TPN use should be considered in intensive care patients.

Keywords: Critical care; candidiasis; risk factors; antifungal agents

ÖZET Amaç: Yoğun bakım ünitesi (YBÜ)'nde takip edilen hastalarda çeşitli risk faktörlerinin varlığında Kandida türleri ile kolonizasyon ve enfeksiyon gelişebilmektedir. Tanıdaki gecikme antifungal tedavinin de gecikmesine yol açmakta ve bu durum mortalitede artışla sonuçlanmaktadır. **Gereç ve Yöntemler:** Çalışma retrospektif vaka kontrol çalışması şeklinde yapılmış olup hastalar kolonize, enfekte ve kontrol grubu olarak ayrılmış Kandida kolonizasyonu ve invaziv Kandida enfeksiyon gelişimi için bağımsız risk faktörleri değerlendirilmiştir. Ankara Üniversitesi İbn-i Sina Hastanesi Anesteziyoloji-Reanimasyon ve Dahiliye YBÜ'de 2013-2015 yılları arasında takip edilen hastalar retrospektif olarak taranmıştır. YBÜ'de en az 48 saat yatışı olan, nötropenik olmayan 18 yaş üzeri toplam 225 hasta çalışmaya alınmıştır. Hastalara ait demografik bilgiler ve risk faktörleri kaydedilmiştir. **Bulgular:** Santral venöz kateter kullanımı ve sepsis/septik şok Kandida kolonizasyonu için, santral venöz kateter kullanımı, total parenteral nutrisyon (TPN) kullanımı ve sepsis/septik şok ise invaziv Kandida enfeksiyonu için bağımsız risk faktörleri olarak bulundu. **Sonuç:** Yüksek riskli hastalarda, erken ve uygun antifungal tedavi mortaliteyi azaltmaktadır. Bu nedenle yoğun bakım hastaları ile çalışan hekimler için invaziv Kandida enfeksiyonları için yüksek riskli hastaları belirlemek önemlidir. Santral venöz kateter varlığı, sepsis/septik şok ve TPN kullanımı yoğun bakım hastalarında göz önünde bulundurulmalıdır.

Anahtar Kelimeler: Yoğun bakım; kandidiyazis; risk faktörleri; antifungal ajanlar

With widely usage of antibiotics in 1940's, incidence of Candida infections increased.[1] In United States, Candida species are fourth among isolated agents from bloodstream infections.[2] In a worldwide study, which was conducted in 43 countries,39 of which reported available data on candidemia, the highest prevalance of candidemia was reported in Pakistan (38.795 cases, 21 cases per 100.000) followed by

Brazil (28.991 cases, 14.9 cases per 100.000) and Russia (11.840 cases, 8.29 cases per 100.000). The incidence of candidemia was higher in middle income countries.[3]

In a recent study, the total incidence of candidemia in Turkey is reported as 3847 cases per year, 1701 of them occured in intensive care setting and 1930 occured in cancer and immunsuppressed patients.[4] Between 2000 and 2005, rate of hospital admissions due to Candida infections 52% increased. Not only bloodstream infections, but also other infections including arthritis, osteomyelitis, endophthalmitis, myocarditis, pericarditis, pacemaker related endocarditis, ventricule asist device-related infections, meningitis, peritonitis, myositis, pancreatitis increased.

Increase in the number of immunocompromised patients and transplantations, advances in life support systems, widely usage of prosthetic materials resulted in an increase in Candida infections.[5] Candida infections can lead to serious clinical manifestations not only in immunocompromised patients but also in intensive care patients with underlying diseases.[6]

While Candida colonization develops in most of the ICU patients, only a few of them develop systemic Candida infections.[7]

This was performed to compare colonized and infected patients with control group for known risk factors for systemic Candida infection.

MATERIALS AND METHODS

This study was a retrospective, observational study and approved by the ethics commitee of the study hospital. All patients (n=852) followed in Anesthesiology-Reanimation and Medical ICUs of Ankara University Ibn-i Sina Hospital between June 2013 and June 2015, were retrospectively screened for inclusion criteria. Five hundred and thirty patients met inclusion criteria. Infected and colonized groups were determined due to culture results and clinical signs and symptoms. Groups were matched for age and gender for preventing selecting bias and a total of 225 patients (75 patients for each group), older than 18 years of age who were hospitalized at least 48 hours in medical and surgical intensive care units (ICUs) of Ankara University İbni Sina Hospital, who were non-neutropenic and colonized or infected with Candida species and also control group were included. Ethics committee approval was obtained from Ankara University Ethics Committe (number: 13-519-15, date of 31.08.2015). Informed consent was not obtained due to the retrospective design of the study. The study has been performed in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki and its later amendments.

DATA COLLECTION

Data including culture results, age, cause of hospitalization, medical history, previous hospitalization, surgical history, presence of central venous catheter, steroid use, malignancies, presence of sepsis, previous antibiotic use, isolated Candida species, duration of hospital stay and the outcome were recorded on a patient follow-up form.

PATIENT GROUPS

Presence of Candida species in tracheal aspirate and urine without clinical symptoms, throat, sputum and other screening cultures and urinary catheter (if it isn't isolated after urinary catheter change) were considered as "Candida colonization".

Urine culture growth above 10^5 cfu/ml of *Candida* spp. with existing pyuria and fever, repeated isolation of *Candida* spp. after urinary catheter change are considered as "urinary tract infection due to *Candida* spp".

Candida growth in sputum and endotracheal aspirates with the presence of pneumonic infiltration on radiography and increase in secretion under wide spectrum antibiotic therapy was considered as "fungus pneumonia due to *Candida* spp".

Candida growth in cultures which obtained perioperatively under sterile conditions from infected sites in abdomen or abscesses were considered as intraabdominal Candida infection.

Positive hemocultures for Candida species, which were taken under appropriate conditions

from peripheral blood and central catheters, were considered as "candidemia".

STATISTICAL ANALYSIS

Descriptive statistics were shown as median (minimum-maximum) for normally distributed variables and percent (%) for nominal variables. Differences for median value between groups were tested using Kruskal Wallis test. Nominal variables were analyzed with Pearson Chi Square test or Fisher's Exact Chi Square test. Risk factors P value <0.2 in univariate analysis, were reanalyzed with multi-variate logistic regression model between each group. A p value of <0.05 was considered statistically significant. All analysis were performed using SPSS for Windows v11.5.

RESULTS

A total of 225 patients were enrolled, 107 (47.55%) were women and 118 (52.44%) were men. Mean age was 67.3 years in colonized group, 63.7 in infected group and 57.2 in control group. Patient demographics, underlying diseases and risk factors for Candida infection are shown in Table 1. In majority of patients (82.2% 185/225) cause of hospitalization was medical. Most patients (66.6% 150/225) had mechanical ventilation. The most common underlying disease was diabetes (24.4% 55/225), followed by renal failure (24% 54/225). The vast majority of the patients (93.3% 210/225) had previous antibiotic use. In 60% of infected patients, previous Candida colonization was found.

Candida infection sites were candidemia (36/75), intraabdominal infection (13/75), urinary (10/75), catheter related blood stream infection (9/75) and pneumoniae (6/75).

In univariate analysis of risk factors between groups, presence of central catheter *(p<0.001)*, TPN use *(p=0.018)*, sepsis/septic shock *(p<0.001)* and previous antibiotic use (*p<0.001*) was significantly high in infected group than colonized and control groups (Table 2).

P values of diabetes, renal failure, malignancy, surgical procedure, presence of central venous catheter, TPN use, sepsis/septic shock and previous antibiotic use were <0.2 and these were reanalyzed with multivariate logistic regression model. Presence of central venous catheter and sepsis/septic shock was significantly higher in colonized group than control group in multivariate analysis (Table 3).

Presence of central venous catheter, TPN use and sepsis/septic shock was higher in infected group than control group in multivariate analysis (Table 4).

TABLE 1: Demographic statistics, underlying diseases and risk factors for Candida infection between groups.

	Colonized (75) N (%)	Infected (75) N (%)	Control (75) N (%)	Total (225) N (%)
Cause of admission				
Medical	61 (82)	64 (85.3)	60 (80)	185 (82.2)
Surgical	8 (10.8)	9 (12)	9 (12)	26 (11.5)
Trauma	5 (6.8)	2 (2.7)	6 (8)	13 (5.7)
Mechanical ventilation	55 (73.3)	65 (86.7)	40 (53.3)	150 (66.6)
COPD	23 (30.7)	20 (26.7)	5 (6.7)	48 (21.3)
Hepatic failure	6 (8.1)	2 (1.4)	1 (1.4)	9 (4)
Heart failure	13 (17.3)	10 (13.3)	13 (17.3)	36 (16)
Renal failure	22 (29)	21 (28)	11 (14.7)	54 (24)
Diabetes	20 (26.7)	23 (30.7)	12 (16)	55 (24.4)
Corticosteroid use	7 (9.3)	4 (5.3)	3 (4)	14 (6.2)
Malignancy	9 (12)	19 (25.3)	12 (16)	40 (17.7)
Previous antibiotics	72 (96)	75 (100)	63 (84)	210 (93.3)
Transplantation	3 (4)	1 (1.3)	1 (1.3)	5 (2.2)

COPD: Chronic obstructive pulmonary disease.

TABLE 2: Univariate analysis of risk factors between patient groups.

Risk factor/Patient group	Colonized (75) N (%)	Infected (75) N (%)	Control (75) N (%)	Total (225) N (%)	p value
Diabetes	20 (26.7)	23 (30.7)	12 (16)	55 (24.4)	0.097
Renal failure	22 (29.3)	21 (28)	11 (14.6)	54 (24)	0.067
Corticosteroid use	7 (9.3)	4 (5.3)	3 (4)	14 (6.2)	0.477
Malignancy	9 (12)	19 (25.3)	12 (16)	40 (17.7)	0.091
Surgical procedure	31 (41.3)	44 (58.6)	36 (48)	111 (49.3)	0.101
Central venous catheter	57 (74)	64 (85)	40 (53.3)	161 (71.5)	<0.001
TPN use	18 (24.3)	29 (38.7)	14 (18.7)	61 (27.1)	0.018
Sepsis/septic shock	35 (48)	59 (78.6)	22 (29.3)	117 (52)	<0.001
Previous antibiotic use	72 (96)	75 (100)	63 (84)	210 (93.3)	<0.001

TPN: Total parenteral nutrition.

TABLE 3: Analysis of independent risk factors of colonization with multivariate logistic regression model between colonized and control groups.

Risk Factor	B	Odds ratio	95% CI	p value
Central venous catheter	.962	2.616	1.250-5.475	0.011
Sepsis/septic shock	.864	2.371	1.158-4.858	0.018

Distribution of Candida species is shown in Table 5. *C. albicans* was seen in 41.3% of colonized patients and 50.7% of infected patients.

Death occured in 62.7% of the infected patients and was significantly higher in infected group than the other groups (Table 6). Mean duration of hospital and ICU stay was significantly higher in infected group than two groups and higher in colonized group than the control group. (Table 7).

DISCUSSION

Candida species are the leading cause of nosocomial infections and the most frequent cause of fungal infections.[8] Candida infection incidence has increased in the last two decades.[9]

Widespread use of immunosuppressive therapies, the improvements in life support systems, the increase in the number of patients in intensive care unit and the length of their stay, developments in organ transplants, increase in use of invazive tools are the main cause of this increase.[2]

Invasive Candida infections are associated with sepsis, septic shock and multiorgan failure with high morbidity and mortality.[5] In studies, attributable mortality due to Candida infections varies between 5% and 71%.[9,10] Due to long hospitalization and stay in the ICU, these infections cause high costs.[9] Increase in mortality by 14.5% and mean hospital stay by 10.1 day in adult patients due to candidemia was shown by Zaoutis et al.[11]

With the initiation of early and appropriate antifungal therapy, the rate and mortality of invasive infection due to Candida infections decrease.[12] Because of the lack of a specific symptom, late growth of Candida species in blood cultures and the difficulty of growth in the presence of concomitant bacterial infections, early diagnosis may be difficult in invasive Candida infections.[13] Therefore, it was needed to determine risk factors to identify

TABLE 4: Analysis of independent risk factors of infection with multivariate logistic regression model between infected and control groups.

Risk Factor	B	Odds ratio	95% CI	p value
Central venous catheter	.971	2.640	1.063-6.561	0.037
TPN use	.938	2.554	1.042-6.260	0.040
Sepsis/septic shock	2.066	7.893	3.545-17.576	<0.001

TABLE 5: Candida species distribution in groups.

	Colonized (75) N (%)	Infected (75) N (%)
Candida albicans	31 (41.3)	38 (50.7)
Non-albicans Candida	44 (58.6)	37 (49.3)
Unidentified	38 (50.7)	12 (16)
C. tropicalis	2 (2.7)	4 (5.3)
C. glabrata	1 (1.3)	7 (9.3)
C. parapsilosis	1 (1.3)	12 (16)
C. krusei	-	1 (1.3)
C. dubliniensis	-	1 (1.3)
C. kefyr	1 (1.3)	-
C. lusitaniae	1 (1.3)	-

high-risk patients for early antifungal therapy and to predict invasive infection.[14]

Preemptive antifungal therapy can be considered in high-risk patients by identifying and evaluating risk factors including the Candida colonization for invasive Candida infection.[7] Risk prediction methods such as Candida colonization index (BMI) and Candida score were developed and used to identify high-risk patients.[15,16]

Our study was conducted retrospectively with the aim of comparing the risk factors between colonized, infected and control groups. In a review, risk factors for candidemia was described as parenteral nutrition, intravascular catheters, trauma, hypotension, corticosteroid treatment and previous antibiotic use.[17] In the National Epidemiology of Mycoses Survey (NEMIS) prospective multicenter study, independent risk factors for candidemia were identified as previous surgery, acute renal failure and total parenteral nutrition.[18] In some studies, APACHE II score, which is a severity score for the ICU patients, has been reported as a risk factor for candidal blood stream infections.[16,19] In a study including 1483 critical patients with and without candidemia were compared for risk factors and an increase in risk of candidemia for TPN by 3.2 folds, for central catheter use 1.8 folds and previous antibiotic use by 3.2 folds was found.[9] Due to the absence of APACHE II records for some patients, it was not evaluated in risk factors. So disease severity could not be compared between groups. In multivariate analysis, independent risk factors for Candida colonization were presence of central venous catheter (OR=2.616 95% CI (1.250-5.475 p:0.11) and sepsis/septic shock (OR=2.371 95% CI (1.158-4.958 p=0.018). Independent risk factors for Candida infection included presence of central venous catheter (OR=2.640 95% CI (1.063-6.561)), TPN use (OR=2.554 95% CI (1.042-6.260)) and sepsis/septic shock (OR=7.893 95% CI (3.545-17.576))and these results were consistent with the literature.

In a study which was conducted in a university hospital in Turkey, Candida species in candidemia cases were 55% *C. albicans* and 28.9% *C. parapsilosis.*[20] In a French study, Candida species isolated from blood cultures in research hospitals were 51.4% *C. albicans*, 16.5% *C. parapsilosis*, 9.2% *C. glabrata*, 4.6% *C. krusei*, 11.9% *C. tropicalis*, 1.8% *C. pseudotropicalis*. In same study, in

TABLE 6: Clinical outcome in patient groups.

	Colonized N (%)	Infected N(%)	Control N(%)	P value
Death in ICU	35 (47.4)	47 (62.7)	25 (33.3)	
Transfer to ward	30 (40)	21 (28)	33 (44)	0.007
Discharge from ICU	10 (13.5)	7 (9.3)	17 (22.7)	

TABLE 7: Duration of hospital and ICU stay in patient groups.

		Colonized	Infected	Control	P value
ICU stay	Mean day	40.2	63.7	16.6	<0.001
Hospital stay	Mean day	60.1	81.5	28.6	<0.001

government hospitals Candida species isolated from blood cultures were 59.3% *C. albicans*, 14.8% *C. parapsilosis*, 18.5% *C. glabrata*, 3.7% *C. krusei*.[21] In our study, in colonized group non-albicans Candida species (58.6%) were more frequent and this was different from the literature but in infected group nearly half of the species were *C.albicans* (50.7%) and half were non-albicans Candida species (49.3%), consistently with the literature. Difference in the colonized group was suggested to be the previous intensive care admissions and previous colonization data were missing.

Crude mortality rate of invasive invasive Candida infections are ranging between 40% to 75%. In a four year study of 108 nosocomial candidemia patients, candidemia-related mortality rate was found 61%.[22] In a review including seven randomized controlled trials, mortality rate was found 31%. In this study high age, high APACHE II score, immunsupressive treatment use and *C.tropicalis* infection were found to be associated with increased mortality rate, central catheter removal and echinocandin treatment were associated with decreased mortality rate.[23] As in literature, in our study crude mortality rate was high as 62.7% in infected group, and it was higher than colonized and control groups.

In our study, mean duration of intensive care stay was 40.2 days in colonized group, 63.7 in infected group and 16.6 in control group. In infected and colonized groups, it was significantly higher than the control group. These results can be interpreted as longer hospital stay's being associated with colonization and infection but candidemia patients were reported to have average 10.1 days longer hospitalization.[11] According to these results and our study results, Candida colonization and infection, prolong both hospital and intensive care unit stays.

The main limitation of the present study was small number of patients. Another limitation is that the disease severity could not be determined due to the lack of APACHE scores.

CONCLUSION

In patients with long-term hospitalization and with various risk factors, early and appropriate antifungal therapy may decrease mortality. Therefore, for physicians working with intensive care patients, it is important to determine the risk factors and high risk for invasive Candida infection. Presence of central venous catheter, sepsis/septic shock and TPN should be taken into account when evaluating risk factors in intensive care patients.

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During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Müge Ayhan, Gülden Yılmaz;* ***Design:*** *Müge Ayhan, Gülden Yılmaz;* ***Control/Supervision:*** *Müge Ayhan, Mehmet Serhat Birengel;* ***Data Collection and/or Processing:*** *Müge Ayhan, Belgin Coşkun, Elif Mukime Sarıcaoğlu;* ***Analysis and/or Interpretation:*** *Müge Ayhan, Mehmet Serhat Birengel, Gülden Yılmaz;* ***Literature Review:*** *Müge Ayhan, Belgin Coşkun, Elif Mukime Sarıcaoğlu;* ***Writing the Article:*** *Müge Ayhan;* ***Critical Review:*** *Müge Ayhan, Gülden Yılmaz;* ***References and Fundings:*** *Müge Ayhan;* ***Materials:*** *Müge Ayhan.*

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