ORIGINAL ARTICLE

Risk factors, incidence and outcome of candidemia in a Turkish intensive care unit: a five-year retrospective cohort study

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ABSTRACT

Background: Invasive fungal infections are important life threatening infections seen in immunocompromised and critically ill patients. *Candida* species are the most common fungal pathogens among these patients; and the most commonly recognized clinical entity of fungal infections is candidemia. The aim of this study was to investigate the incidence, risk factors and 30-day mortality associated with candidemia in the intensive care unit (ICU).

Methodology: A retrospective cohort study in a tertiary care hospital ICU was undertaken from January 2004 to December 2008. Demographic and clinical data were collected from medical and microbiology laboratory records retrospectively.

Results: In five years period, 66 candidemia cases were identified among 1076 cases. Overall incidence of candidemia was 12.3 per 1000 admissions and 23.1/10000 patient days. *Candida albicans* was the most common species (53.1%) isolated from blood specimens followed by *Candida parapsilosis* (21.1%). The frequencies of tracheotomy, femoral artery catheterisation, red blood cell transfusions, parenteral nutrition, abdominal surgery, and previous use of antibiotics were significantly high in candidemia group. In multivariate logistic regression model, parenteral nutrition and use of broad spectrum antibiotic combinations were found to be associated with candidemia. Crude mortality rate at 30th day was 43.9% and mortality rate of candidemia associated with *C. albicans* was significantly higher than with non-*albicans Candida* strains.

Conclusion: Candida albicans was the most common isolate in candidemia patients and was associated with high mortality rates. Use of invasive procedures and broad spectrum antibiotics poses significant risks in development of candidemia.

Key words: Candidemia; Intensive care units; Incidence; Risk factors; Mortality

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INTRODUCTION

In parallel with advances in organ transplantation and cancer treatment, survival rates of immunocompromised patients at risk of fungal infections have improved. Likewise, in recent years the use of invasive monitoring and aggressive therapeutic techniques increased in the intensive care units (ICUs) and this also contributed to an increase in the ratio of patients susceptible to fungal infections.[1-4] Invasive fungal infections are important life threatening infections seen in immunocompromised and critically ill patients. *Candida* species are the most common fungal pathogens isolated from those patients and the most commonly recognized clinical manifestation is candidemia.[3] *Candida* species are the fourth leading cause of nosocomial blood stream infections (BSIs) in USA and sixth in Turkey.[5,6] In a prospective survey conducted by European Confederation of Medical Mycology (ECMM) in seven European countries, incidence rates of candidemia were reported between 0.20 and 0.38 per 1000 hospital admissions. Of those patients, 40.2% was hospitalized in intensive care

units.[7] In our hospital, the incidence of candidemia was reported as 0.56/1000 hospital admissions in 2000-2003 period and 53.8% of the patients with candidemia were hospitalized in ICU.[8] *Candida* infections are also associated with high mortality rates, increased length of hospital stay and health care costs.[4,5,9-11]

Aims of this study were to find the incidence, etiologic pathogens, risk factors and the outcome of candidemia in our ICU.

METHODOLOGY

It was a five year retrospective cohort study undertaken from 1 January 2004 to 31 December 2008, in a 14 bedded general ICU of a tertiary care hospital. All patients hospitalized in the ICU were included in the study. Case of candidemia was defined as any patient hospitalized in the ICU for more than 48 hours and having at least one positive blood culture yielding *Candida* species and signs and symptoms of infection, sepsis or septic shock.

All patients hospitalized in the ICU for more than 48 hours who had negative blood and urine candida cultures were included in the control group.[3,7,12]

Data collection:

Cases were identified by finding patients with positive candida blood cultures through microbiology laboratory records. Medical records of all the eligible patients (cases and controls) were then reviewed and data about demographic characteristics, current diagnosis, severity of illness, pre-existing illnesses and use of invasive devices were recorded. Severity of illness at the time of admission was assessed by Acute Physiology and Chronic Health Evaluation - II (APACHE-II) score.

Risk factors occurring within 30 days prior to the onset of candidemia were noted. Surgical interventions, trauma, use of invasive devices [endotracheal intubation, tracheostomy, central venous catheters (CVC), urinary catheters and implants etc.], hemodialysis, red blood cell (RBC) transfusions, mechanical ventilation, total parenteral nutrition (TPN), antibiotic or antifungal therapy, and immunosuppressive conditions (solid organ or hematopoietic stem cell transplantation, treatment with corticosteroids, human immunodeficiency virus infection, cancer chemotherapy, solid or hematologic malignancies) were considered as risk factors for fungemia.

Crude mortality rate from candidemia was defined as the death rate within 30 days after the first isolation of *Candida* spp. form blood culture.

Cultivation of blood samples:

BACTEC 9240 (plus, aerobic/F, Becton Dickinson, Sparks, MD, USA) blood culture system was used for taking blood samples. For this purpose, 10 ml of blood taken from peripheral veins and placed lines was inoculated into the sample bottles and sent to microbiology laboratory. Bottles were then placed in a BACTEC blood culture device in laboratory and incubated for seven days. 0.1-ml aliquots were withdrawn from each positive bottle if growth signal was flagged by the system and they were subcultured on to blood agar (Becton Dickinson, BD Diagnostics, Heidelberg, Germany), chocolate agar (Becton Dickinson, BD Diagnostics, Heidelberg, Germany) and Eosin Methylene Blue agar (Becton Dickinson, BD Diagnostics, Heidelberg, Germany). Agar plates were incubated at 37ºC for 24-48 hours and the growth on the plates were evaluated. If yeast growth was obtained, agar plates were processed in mycology laboratory.

Identification of yeasts:

Yeast isolates were identified to the species level by germ tube formation and morphological characteristics on Corn Meal Agar™ (Oxoid, Hampshire, England) with Tween 80™ (Riedel-de Haen, Seelze, Germany) or by colony color on CHROMagar™ (CHROMagar, Paris, Fracnce) and API 20 C AUX system™ (BioMe´rieux, Marcyl'Etoile, France) [13,14

Statistical analysis:

The chi-square test or Fisher's exact test was used for evaluating categorical variables and the t-test for continuous variables. Fisher's Exact test is employed when sample sizes are small, in practice. Therefore we used this test for small sample sizes. A p-value of <0.05 was considered statistically significant. Variables that found as significant in these tests were considered as candidates for the multivariate analysis. To investigate risk factors independently associated with candidemia, we performed multivariate, backwards stepwise, logistic regression analysis. All statistical analyses were performed with Statistical Package for the Social Sciences (SPSS™, Version 15.0, Chicago, Il, USA) and CDC software EPI INFO™ (version 6.0, Atlanta,GA,USA).

RESULTS

Incidences

During five year study period, 5353 patients admitted to the ICU were included in the study and 1076 of them were hospitalized more than two days. Of these 1076 patients, 66 developed candidemia. The median interval from ICU admission to the onset of candidemia was 15 (3-188) days.

Total incidence rate of candidemia was 12.3 per 1000 admissions and 23.1/10 000 patient days. A significant increase in candidemia incidence was noted between year

Table 1: Patient characteristics and underlying diseases

	Cases n (%)	Controls n (%)	p
Age	54.4 ± 23.9	53.2 ± 23.0	0.698
Gender (Male)	35 (53)	637 (63)	0.103
Diabetes mellitus	9 (13.6)	165 (16.3)	0.564
Chronic renal failure	5 (7.5)	52 (5.1)	0.394
COPD*	6 (9)	118 (11.7)	0.523
Trauma	8 (12.1)	213 (21.1)	0.08
Corticosteroid therapy	5 (7.5)	50 (4.9)	0.378
Cancer chemotherapy	7 (10.6)	51 (5)	0.053
Liver transplantation	7 (10.6)	87 (8.6)	0.579
Malignancy	20 (30.3)	210 (20.8)	0.06
APACHE II (mean)	22.9 ± 6.8	20.4 ± 7.6	**0.04**

*COPD: Chronic obstructive pulmonary disease

Table 2: Number of *Candida* species isolated from blood in years

Candida species	Years					Total
	2004	2005	2006	2007	2008	
Candida albicans	6	8	7	10	4	35
Candida parapsilosis	1	3	6	1	3	14
Candida tropicalis	1	2	1	1	0	5
Candida glabrata	0	0	2	1	1	4
Candida utilis	0	1	1	2	0	4
Candida lusitaniae	0	2	0	0	0	2
Candida krusei	0	1	0	0	0	1
Candida kefyr	0	0	1	0	0	1
Total	8	17	18	15	8	66

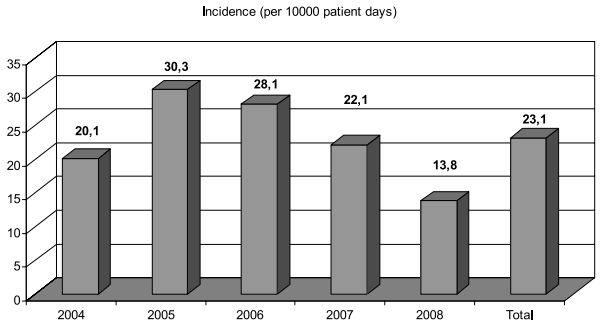

Figure 1: Annual incidence rates of candidemia

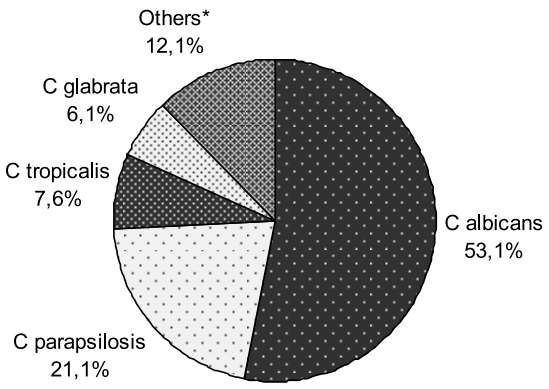

Figure 2: Species distribution of isolates

*Others: *C. utilis, C. lusitaniae, C. krusei, C. kefyr*

Table 3: Invasive procedures and therapy of patients

	Cases n (%)	Controls n (%)	p
Presence of urinary catheter	65 (98.4)	995 (92.4)	0.984
Presence of CVC	66 (100)	956 (88.8)	0.054
Mechanical ventilation	64 (96.9)	936 (86.9)	0.187
Hemodialysis	10 (15.1)	108 (10.0)	0.261
Tracheotomy	24 (36.3)	192 (17.8)	**<0.01**
Erythrocyte transfusion	51 (77.2)	556 (51.6)	**<0.01**
Prior surgical procedures (total)	45 (68.2)	618 (57.4)	0.25
• Abdominal surgery	34 (51.5)	376 (34.9)	**0.02**
• Neurosurgery	5 (7.5)	84 (7.8)	0.832
Nasogastric tube	64 (96.9)	950 (88.2)	0.326
TPN	42 (63.6)	413 (38.3)	**<0.01**
Catheterization of femoral artery	15 (22.7)	123 (11.4)	**0.01**
Previous use of antibiotics	64 (96.9)	843 (78.3)	**<0.01**
• Antibiotic combinations (>2 antibiotics)	39 (59.1)	246 (22.8)	**<0.01**
• Third generation cephalosporins	14 (21.2)	181 (16.8)	0.501
• Quinolones	17 (25.7)	199 (18.4)	0.234
• Glycopeptides	42 (63.6)	232 (21.5)	**<0.01**
• Carbapenems	29 ((43.9)	163 (15.1)	**<0.01**
• Metronidazole	8 (12.1)	123 (11.4)	0.989
• Beta lactam beta lactamase inhibitors	33 (50)	323 (30.0)	**<0.01**
• Aminoglycosides	25 (37.9)	181 (16.8)	**<0.01**
Antifungal agents	6 (9)	68 (6.3)	0.463

2004 and 2005 (p=0.03). After which, there was a gradual decline in candidemia (Figure 1).

Demographic and clinical characteristics

Of the 66 candidemia cases, 53% (n=35) were males and 47% (n=31) were females. Mean age was 54.4 (SD±23.9) years in candidemia group and 53.2 (SD±23.0) years in control group. Of the candidemia cases, 43.9% (n=29) were surgical and 56.1% (n=37) were medical patients. There was no statistically significant difference in terms of demographic features or underlying illnesses between cases and controls (Table 1). Some underlying illnesses and conditions were rare in our study group and they were not included in the statistical analyses such as neutropenia, splenectomy, and burns. None of the patients were positive for HIV and recipient of hematopoietic stem cell transplantation. We have been able to reach APACHE II scores of 616 patients (41 of cases and 575 of controls). In this group, mean APACHE II scores of patients with candidemia was significantly higher than the others (p=0.04).

Fungal isolates

Candida albicans was the most common isolate 53% (n=35) followed by *Candida parapsilosis 21.1%* (n=14). Non-*albicans Candida* spp were responsible for 46.9% (n=31) of candidemia episodes. Species distribution of isolates are given in Figure 2 and Table 2.

Risk Factors

At first, we performed chi-square test for evaluation of invasive procedures and therapeutic approaches as possible risk factors. The frequencies of tracheotomy, femoral artery catheterization, RBC transfusion, TPN, abdominal surgery, and previous use of antibiotics were significantly high in candidemia group (Table 3). In multivariate logistic regression model, TPN (p= 0.02, OR= 1.86, 95% CI= 1.07-3.23) and previous use of broad spectrum antibiotic combinations (more than two antibiotics) (p<0.001, OR=3.2, 95% CI=1.86-5.53) were associated with an increased risk of candidemia.

Outcome

Mean length of stay of patients was 30.9±33. days in candidemia group and 12.9±13 days in control group (p<0.001). Crude mortality rate on day 30 was 43.9% (29 out of 66) in the candidemia group whereas it was 32.2% (326 of 1010) in the control group. There was no significant difference between the mortality rates of candidemia and control groups (p=0.05). Twenty out of 35 patients (57.1%) and 9 out of 31 (29%) died in *C. albicans* group and non-*albicans Candida* group, respectively. Mortality rate of candidemia associated with *C. albicans* was significantly higher than with non-*albicans Candida* strains (p=0.02, OR=3.26, 95%CI=1.05-10.4).

DISCUSSION

In our study, the incidence of candidemia was 23.1 per 10,000 patient-days and 12.3 per 1000 admissions. In a previous study conducted in our hospital between 2000 and 2003, the overall incidence was 0.56 per 1000 hospital admissions.[8] But that data represents whole hospital and therefore is not comparable with the data of the study presented here. In the European Confederation of Medical Mycology (ECMM) survey, 2089 cases of candidemia were documented by 106 hospitals from seven countries. In that study incidence rates of candidemia were reported ranging from 3.0 to 4.4 per 10 000 patient-days[7] In Europe, the highest candidemia incidence was reported from Denmark with 11.0 cases /10 000 patient-days.[15] Incidence of candidemia varies between institutes depending upon diagnostic approach, studied population and exposure to the risk factors. Moreover it can even vary between different patient areas of the same institute [[15] It is well known that the incidence of candidemia is significantly

higher in the ICUs than in the other hospital wards. For instance, a study by Luzzati et al., incidence of candidemia was 0.99 per 10 000 patient-days in ward patients whereas it was 15.8/10000 patient-days in ICU patients.[16] They calculated that candidemia was 105 times more frequent in ICU than medical wards. In another study, Bougnoux et al.[17] observed 6.7 candidemia cases per 1000 admissions in French ICU patients. The highest rate in the literature was 3.8 cases per 1000 patient-days reported from an ICU in Greece.[18] We have observed higher rates of candidemia in our study than reported in literature. The incidence of candidemia increased during 2004 and 2005 after which there was a significant decline in the number of cases. One explanation of this unusually high incidence is carrying out of renovation work in our ICU during specified period; which could be responsible for break in infection control practices. A gradual decline in candidemia incidence from 30.3 in 2005 to 13.8 per 10,000 patient days in 2008 also strengthen this explanation.

The median interval from ICU admission to onset of candidemia was 15 (3-188) days in our study which is comparable to formerly published reports.[10] The mean interval between ICU admission and candidemia was 19.0±2.9 days in a French study.[17] Anunnatsiri et al[19] found that median duration of hospitalization prior to candidemia was 16.5 days. In our study, average length of hospital stay was 18 days longer in candidemia patients than control consistent with the literature.[20]

In our study, *C. albicans* remained the predominant species and there was no increase in number of *C. glabrata* and *C. krusei* known as azole resistant non-*albicans Candida* species. Most common non-*albicans Candida* species was *C. parapsilosis* followed by *C. tropicalis* and *C. glabrata*. The reported distribution of different Candida species vary in literature.

For instance, in a multicentre, prospective study in Fench ICUs (AmarCand Study), Leroy O. et al[21] reported *C. albicans* as the most common isolate (57%) followed by *C. glabrata* (16.7%), *C. parapsilosis* (7.5%), *C. krusei* (5.2%) and *C. tropicalis* (4.9%) in 271 episodes of invasive candidiasis. On the other hand, Xess I et al[22] reported that *C. tropicalis* was predominant pathogen (35.3%) in the five years study period in North India. In another study conducted in Thailand, *C. parapsilosis* was the most common isolate followed by *C. albicans* and *C. tropicalis*[19] The investigators from Italy reported very similar results to our study showing *C. albicans* as a predominant isolate followed by *C. parapsilosis*, *C. glabrata*, and *C. tropicalis* in two different surveys conducted in tertiary care hospitals.[16,23]

Candida parapsilosis is known to adhere to bio prosthetic surfaces such as catheters forming a biofilm layer of glycosylated serum and can cause epidemics especially in pediatric ICUs.[3,5] The frequency of this pathogen can be explained by inadequate catheter care, increase in use of parenteral nutrition or poor infection control practices mentioned above. The retrospective nature of our study limits the investigation of these factors.

Candida glabrata is one of the fluconazole resistant non-*albicans Candida* species was not common in our study group. This pathogen has become an important and common species in the United States.[24] In contrast, it is much less common cause of BSIs in most other countries. In some studies from Latin America, Asia-Pacific, Europe and Turkey frequency of candidemia due to *C. glabrata* was reported between 4% and 10%.[5,8,25,26] In Artemis Disk Global Antifungal Surveillance Program, a total of 201 653 isolates were collected from 133 centers between January 2001 and December 2007. The frequency of *C. glabrata* isolation was lower in Turkey (3.1%) than other countries,[27] The reasons for the frequency variation of *C. glabrata* are not clear but may include prior azole exposure, age, geographic location, blood culture systems used for diagnosis or other unknown features.[5]

Risk factors for candidemia can be divided in to two groups: Host related factors and underlying health conditions; health-care associated factors such as catheters, surgical interventions and medications. In our study, there was no statistically significant difference in terms of underlying illnesses between the cases and controls except for higher APACHE II scores in candidemia group than in controls. ACHE II scores of cases were significantly higher than control patients. However we could not reach APACHE II scores of all patients from medical records reviewed retrospectively which is one of the limitations of our study.

Predisposing factors for candida BSIs described in literature are: previous exposure to antibiotics or antifungals, central venous or urinary catheters, total parenteral nutrition, steroids, prolonged hospitalization, abdominal surgery, immunosuppressive therapy, and renal failure.[5,16,23,28] We found similar risk factors in our study group. However, central venous catheterization and mechanical ventilation were not found to be significant in our study. In multivariate analysis, TPN and previous use of broad spectrum antibiotic combinations especially containing glycopeptides, carbapenems, aminoglycosides and beta lactam- beta lactamase inhibitors were found to be independently associated with an increased risk of candidemia.

Crude mortality of candidemia cases at 30th day was 43.9% in our study. In comparison, mortality at 30th day was 37.9% in ECMM study which is slightly lower than our study.[7] However, in some other studies 30 day mortality rates were reported between 41.5 and 61.8 %.[17,19,21,29] *Candida* infections are mostly related to a failure in host defence mechanisms rather than the pathogenicity of

microorganism. Patients with severe underlying diseases are at high risk for candidemia and also have poor prognosis.[2,3,18] Attributable mortality, which estimates the increase in mortality just because of fungal infection is more clinically relevant parameter than crude mortality. This parameter can only be investigated in patient groups matched for underlying diseases and risk factors. In our study, such a match was not done and therefore we could not determine attributable mortality rate.

Mortality was significantly higher for patients infected with *C. albicans* than the others infected with non-*albicans Candida* species in the study presented here. This is in contrast to the study by Bassetti et al.[23] who found that crude mortality was 55% in all patients with candidemia although, there was no statistically significant difference between the mortality rates of *albicans* and non-*albicans* candidemia patients. Similarly, Chow et al.[30] found the mortality rates of BSIs due to *C. albicans* and non-*albicans Candida* species 58% and 57% respectively. In contrast, Dimopoulos et al.[18] reported significantly high mortality for BSIs due to non-*albicans* species. In our study , the most common non-*albicans Candida* isolate was *C. parapsilosis* which has relatively low mortality among others and this could influence on mortality rates.

CONCLUSION

In conclusion, candidemia is an important and life threatening infection in the ICU. According to our study, in our hospital *C. albicans* is the predominant species and we found no increase in annual rates of azole resistant non-*albicans Candida* species during the study period. Important risk factors were invasive procedures and medications. Candidemia should be suspected in patients with these risk factors and diagnostic/therapeutic interventions should be performed immediately.

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