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Comparison between Risk Factors for Candidemia and Bacteremia in a Tertiary Intensive Care Unit

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ABSTRACT

Objective: Candidemia is the most common type of invasive fungal infections. It is essential to initiate early and appropriate treatment. In this study, we aimed to compare the potential risk factors of candidemia and aerobic bacteremia.

Methods: In this study, 21 patients with candidemia and 101 patients with bacteremia were retrospectively compared with 1567 patients who were admitted to a tertiary intensive care unit between January 2011 and January 2014. Potential risk factors for the patients were evaluated statistically.

Results: The rate and incidence density of candidemia were, respectively, 1.34% and 1.62, whereas those for bacteremia were 9.38% and 11.37, respectively. According to our results, having a previous gastrointestinal system (GIS) surgery, solid organ tumor (p=0.0001), hemodialysis catheter (p=0.001), continuous hemodiafiltration (p=0.005), bogota bag (p=0.009), colostomy (p=0.033), abdominal drain (p=0.001), need for blood transfusion (p=0.025), and total parenteral nutrition (TPN) (p=0.0001) were found to be associated risk factors for candidemia in comparison with bacteremia.

Conclusion: Patients who have blood stream infections have higher risk for morbidity and mortality in intensive care units. According to the results of our study, previous GIS surgery, having a surgical implement, solid organ tumor, end-stage renal disease, need for blood transfusion, and TPN were found to be risk factors of candidemia.

Keywords: Candidemia, bacteremia, intensive care unit

Introduction

Bloodstream infections (BSI) are the major causes of morbidity and mortality worldwide (1). BSIs are common in intensive care units (ICU) and are considered prognostic factors for severe sepsis cases (2). The most frequent etiological microorganisms are aerobic Gram-positive cocci and Gram-negative bacilli followed by Candida at rank 4 or 5 (3).

Invasive fungal infections (IFI) are a progressively increasing problem worldwide. The most frequently detected agent is Candida as a type of yeast (4). Candida-related BSIs have the highest incidence rate among admitted patients, especially in the ICU. Furthermore, they are the most prevalent form of IFI (3, 4). In the United States, candidemia-related infections are ranked fourth among in-patients and tertiary ICU patients (3).

Early diagnosis of fungal infections is not always possible. Therefore, initiation of antifungal treatment may be delayed. The delays in onset of empirical treatment in candidemic patients may result in longer hospitalization durations and

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higher mortality rates (3, 5). Consequently, detection of risk factors for invasive Candida infections and the associated type of Candida is critical in planning an early and appropriate antifungal treatment. Many different risk factors contributing to candidemia and bacteremia have been reported in several studies (3-10). Some of these risk factors may be similar in both candidemia and bacteremia.

In this study, we aimed to compare the risk factors among adult ICU patients with Candida spp. or aerobic bacteria-related BSIs. The risk factors for candidemia were assessed in this comparison, and the epidemiological characteristics of these candidemia and bacteremic patients were also evaluated.

Methods

Patient population and design

Istanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital has 612 beds, including 26 beds for adult patients in the ICU. In the ICU of our hospital, there is a mixed composition of adult patients mostly referred from surgery departments.

This study included patients older than 14 years of age who were admitted to the ICU between January 2011 and January 2014. Of 1567 patients, 21 candidemia and 101 bacteremia patients were retrospectively compared. Seven patients who had no follow-up data were excluded from the study. Data were summarized using a standard data collection form. The clinical course, underlying diseases, laboratory results, risk factors, and other data were retrospectively obtained from hospital files of the patients. The surveillance rate of BSI was determined in accordance with Centers for Disease Control and Prevention criteria and calculated on the basis of bedside visits (11). The literature was reviewed and potential risk factors contributing to BSIs were identified regarding patient characteristics. The estimated risk factors, demographic characteristics of the patients, and characteristics of the isolated microorganisms were transferred to data forms on Excel. The research protocol was approved by the hospital ethics committee (decision date/number: 11-04-2016/2016-03-01). Written consent was not obtained from patients because the research was done retrospectively.

Definitions

This study included the patients with candidemia (Group 1) or bacteremia (Group 2) who stayed in the ICU for more than 48 h between January 2011 and January 2014. Patients with clinical symptoms of infection were distributed into the candidemia or bacteremia group only if they had one or more positive cultures for Candida spp. or another bacterial agent.

Only one positive blood culture with skin flora bacteria (coagulase-negative Staphylococcus, diphtheroid bacilli, etc.) was not accepted as a BSI. Patients who stayed in the ICU for less than 48 h were excluded from the study. In our study period, no patient with neutropenia or past organ transplant in medical history was admitted to the ICU.

"Infection rates" were calculated using the formula: 100×infection number/patients in the ICU, whereas "incidence densities" were calculated using the formula: 1000×infection number/patient-day.

Microbiological identification

BACTEC 9120 (Becton Dickinson, USA) blood culture system was used in our laboratory. Blood was taken from positive culture tubes (maximum incubation period was 7 days) and streaked on 5% sheep blood agar and chocolate agar. In case of growth after 24 to 48 h of incubation at 37°C, Gram staining was performed. In presence of yeast cells, germ tube test and phenotypic typing on CHROMagar Candida medium (Becton Dickinson, USA) were performed. For bacteria phenotyping on chromogenic agar, conventional methods or identification systems such as PHOENIX and API20NE were used.

Statistical analysis

Statistical analysis was performed using NCSS 2007 (Number Cruncher Statistical System) software. The data set was evaluated using descriptive methods (such as mean, median, frequency distribution, standard deviation, and percentage distribution); independent samples t-test was used for binary variables, whereas Chi-square test and Fisher's exact test were performed for the evaluation of quantitative data. The results below 0.05 ($p<0.05$) were accepted statistically significant.

Results

In this study, 1567 patients who stayed in the ICU for more than 48 h were followed up. The total hospitalization period was 12.918 d. Of 21, 12 (57.1%) candidemic patients were also bacteremic. A total of 135 bacteremia episodes were found among the 101 patients of Group 2. The rate and incidence density of candidemia were, respectively, 1.34% and 1.62, whereas those of bacteremia were 9.38% and 11.37, respectively. The total BSI rate was 10.72%, whereas the incidence density was 13.01.

Of the 168 BSIs, Candida-associated BSIs ranked 5th during the 3-year study period. *C. albicans* was the most frequently isolated species of Candida, whereas the most frequently isolated species in the bacteremia group was coagulase-negative Staphylococcus (Table 1).

The statistical comparison between the two groups, including demographic characteristics of the patients, numbers of catheters, Glasgow coma score (GCS), hospitalization duration, comorbidity, and mortality rates has been represented in Table 2. In Group 1, statistically significant factors were numbers of present hemodialysis catheter ($p=0.003$), central venous catheter (CVC) ($p=0.044$), ratio of gastrointestinal system surgery group ($p=0.001$), and presence of gastrointestinal pathology and solid organ tumor ($p<0.001$). The time until transfer to the ICU was found to be statistically significant in Group 2 ($p=0.02$). No statistically significant difference was observed between the two groups with respect to age, gender, GCS, days spent in the ICU,

Table 1. Distribution of Candida and bacteria species

Distribution of Candida species		Distribution of Bacteremia	
Name	n (%)	Name	n (%)
Candida albicans	12 (57.1)	*Coagulase-negative staphylococcus*	39 (26.5)
Candida parapsilosis	4 (19.0)		
Candida tropicalis	3 (14.3)	*Enterococcus spp.*	30 (20.4)
Candida krusei	2 (9.5)	*Staphylococcus aureus*	25 (17)
		Acinetobacter spp.	22 (15)
		Pseudomonas spp.	8 (5.4)
		Klebsiella spp.	8 (5.4)
		Escherichia coli	7 (4.8)
		Others	8 (5.4)

days spent in the hospital, Chronic Obstructive Pulmonary Disease (COPD), respiratory failure, cardio-pulmonary resuscitation, renal failure, diabetes mellitus (DM), chronic hepatic disease, presence of infection on admission, cardiac disease, general body trauma, decubitus ulcer, and mortality rates.

The impact of invasive procedures and other interventions was compared between the candidemia and bacteremia groups (Table 3). Patients who were using a bogota bag, hemodialysis catheter, colostomy or abdominal drain and were also receiving transfusion of blood and/or blood products, continuous hemodiafiltration, TPN, or immunomodulators had significantly higher risk for candidemia. There was no statistically significant difference between the two groups with respect to risk factors such as use of nasogastric tube, oral feeding, enteral feeding, gastroscopy, percutaneous endoscopic gastrostomy, rectal tube, tracheostomy, tube thoracotomy, administration of inhaled or systemic steroids, and pentaglobin.

The use of antibiotics before positive blood cultures was also evaluated. There was no significant difference between the two groups except with respect to glycopeptides usage (Table 4).

Discussion

Candidemia is one of the most critical fungal hospital infections that is commonly presented in the ICU. The prevalence of candidemia ranges between 1% and 8% (3, 7, 12, 13). In our study, rate and incidence density of candidemia were calculated to be 1.34% and 1.62, respectively. In a study conducted in Greece, a country in the same geographic region as Turkey, rate and incidence density of candidemia in the non-neutropenic patients admitted to the ICU were found to be 3.8% and 2.4, respectively (7). When the previous studies conducted in Turkey were reviewed, we found a similar study that was conducted in Gulhane Military Medical Faculty Haydarpasa Training Hospital. In this study, rate and incidence density of candidemia were 1.59% and 1.38, respectively (14). The study was conducted in the branch hospital on Chest Diseases where most of the complicated patients were admitted to the ICU, the rate of candidemia was 3.1%, which was approximately 3-fold higher than our results (9).

Because of higher morbidity and mortality rates of candidemia patients, every hospital must determine and analyze their specific surveillance data based on Candida species and their antifungal sensitivities (15). The most frequently isolated Candida species in our ICU was *C. albicans* (57.1%), whereas *C. parapsilosis*, *C. tropicalis*, and *C. krusei* were other

Table 2. Comparison between the two groups with respect to demographic and clinical characteristics of the patients

Features	Group 1 (n=21) Mean SD	Group 2 (n=101) Mean SD	p
Age	52.6±20.7	56.09±19.8	0.469
Glasgow Coma Scale	6±2.58	4.91±2.29	0.397
Numbers of hemodialysis catheter	0.62±0.87	0.2±0.49	0.003
Numbers of central venous catheter	2.14±1.59	1.54±1.14	0.044
Days spent in the ICU	37.1±31.83	35.53±24.08	0.779
Days spent in the hospital	45.57±41.63	36.96±24.37	0.202
Days spent in the hospital before ICU	8.48±29.03	36.96±24.3	0.02
	Number (%)	Number (%)	p
Gender (male)	12 (57.1)	65 (64.4)	0.390
Central nervous system pathology	8 (38.1)	51 (50.5)	0.301
Chronic obstructive pulmonary disease	5 (23.8)	13 (12.9)	0.198
Respiratory failure	8 (38.1)	55 (54.5)	0.172
Gastrointestinal system surgery	12 (57.1)	21 (20.8)	0.001
Gastrointestinal pathology	13 (61.9)	24 (23.8)	0.001
Solid organ tumor	7 (33.3)	5 (5.0)	<0.001
Renal failure	6 (28.6)	17 (16.8)	0.211
Diabetes mellitus	5 (23.8)	18 (17.8)	0.523
Chronic hepatic disease	0 (0.0)	3 (3.0)	0.424
Presence of infection at admission	8 (38.0)	26 (25.7)	0.251
Cardiac disease	3 (14.3)	35 (34.7)	0.067
Cardio-pulmonary resuscitation	6 (28.6)	30 (29.7)	0.918
General body trauma	3 (14.3)	17 (16.8)	0.774
Decubitus ulcer	8 (38.1)	33 (32.7)	0.632
Mortality	14 (66.7)	46 (45.5)	0.078

SD: standard deviation; GCS: glasgow coma scale; ICU: intensive care unit

Table 3. Comparison between the two groups with respect to receiving invasive procedures and other interventions

Factors	Group 1 (n=21) n (%)	Group 2 (n=101) n (%)	p
Central venous catheter (jugular or subclavian)	17 (81.0)	78 (77.2)	0.708
Hemodialysis catheter (femoral)	7 (33.3)	14 (13.9)	0.031
Hemodialysis catheter (jugular)	4 (19.0)	2 (2.0)	0.001
Continuous hemodiafiltration	9 (42.9)	16 (15.8)	0.005
Nasogastric tube	19 (90.5)	92 (91.1)	0.929
Oral feeding	0 (0.0)	7 (6.9)	0.214
Enteral feeding	19 (90.5)	93 (92.1)	0.807
Gastroscopy	11 (52.4)	42 (41.6)	0.364
Percutaneous endoscopic gastrostomy	8 (38.1)	40 (39.6)	0.898
Rectal tube	0 (0.0)	8 (7.9)	0.182
Bogota bag	5 (23.8)	6 (5.9)	0.009
Colostomy	6 (28.6)	11 (10.9)	0.033
Abdominal drain	12 (57.1)	22 (21.8)	0.001
Tracheostomy	7 (33.3)	50 (49.5)	0.177
Tube thoracotomy	2 (9.5)	14 (13.9)	0.592
Blood transfusion	20 (95.2)	73 (72.3)	0.025
Total parenteral nutrition	17 (81.0)	33 (32.7)	<0.001
Inhaler steroid	18 (85.7)	88 (87.1)	0.861
Systemic steroid	15 (71.4)	74 (73.3)	0.863
Pentaglobin	1 (4.8)	3 (3.0)	0.675
Immune modulators	13 (61.9)	32 (31.7)	0.009

Table 4. Use of antibiotics before positive blood culture

Antibiotics	Group 1 (n=21) n (%)	Group 2 (n=101) n (%)	p
Quinolone	5 (23.8)	14 (13.9)	0.253
3rd generation cephalosporin	11 (52.4)	54 (53.5)	0.928
Aminoglycosides	2 (9.5)	4 (4.0)	0.283
Metronidazole/Ornidazole	7 (33.3)	23 (22.8)	0.307
β-lactam/β-lactamase inhibitors	7 (33.3)	30 (29.7)	0.742
Carbapenem	2 (9.5)	7 (6.9)	0.679
Glycopeptide	4 (19.0)	4 (4.0)	0.011

prevalent isolates. Similar results were found in other studies from Turkey. *C. glabrata* and *C. guilliermondii* were the other isolated rare species mentioned in other studies in our country (6, 10, 16-18). Another study conducted in a university hospital of Turkey revealed a distribution of Candida species as *C. albicans* (51.5%), *C. sake* (12.5%), *C. inconspicua/norvegensis* (8.8%), and *C. tropicalis* and *C. parapsilosis* (5.1%) (19). High rates of *C. sake* and *C. inconspicua/norvegensis* were said to be associated with an outbreak in the neonatal ICU. Similar results were found in studies from other countries (20, 21). One of those studies has presented the following incidence rates: *C. albicans* (60.2%), *C. tropicalis* (18.6%), *C. glabrata* (7.6%), *C. parapsilosis* (6.8%), and *C. krusei* (5.1%) (19). A multicenter study from France revealed a similar species distribution (*C. albicans*, 57.0%; *C. glabrata*, 16.7%; *C. parapsilosis*, 7.5%; *C. krusei*, 5.2%; *C. tropicalis*, 4.9%; and *C. kefyr*, 3.6%) (21).

Our ICU patient population was generally composed of patients referred from the Department of Gastrointestinal Surgery and this situation might be the cause of higher rates of endogenous Candida species such as *C. albicans* observed. A study completed in North America stated that gastrointestinal surgery has no contribution in the development of candidemia (5). In contrast with this study, another study on the ICU patients in North America presented a counter-conclusion (8). However, further studies are needed for a more accurate conclusion.

The impact of renal failure as a risk factor varies in several studies. In many studies, the impact of renal failure was found to be statistically non-significant, whereas another study from North America evaluated the impact of renal failure in favor of bacteremia and candidemia (3, 5-10). In our study, renal failure was not found to be a risk factor, whereas hemodialysis catheter and continuous hemodiafiltration were found to be risk factors for candidemia. Renal failure could be a risk factor for candidemia if dialysis is needed.

In another study from our country, use of colostomy or an abdominal drain was not found to be a risk factor for candidemia (6). In our study, in the candidemia group, risk factors such as having a bogota bag, colostomy, or abdominal drain were more prevalent compared with the bacteremia group.

Similar to our results, blood transfusion was reported as a significant risk factor for candidemia in some studies (8, 10). Use of TPN was assessed as an important predisposing risk factor in many studies as well as our study (1, 5, 9, 10). There was no significant effect of central nervous system pathologies and general body trauma on the incidence of candidemia and bacteremia in our study. The presence of CVC was usually accepted to be associated with candidemia in many studies; however, it was not observed in this study (6, 7).

Mortality rates of candidemia and bacteremia in the ICU were 66.7% and 45.5%, respectively, in our study, and there was no statistically significant difference between them; however, the mortality rates of candidemia were observed to be significantly higher in many studies (1, 3, 6-9).

The control group of our study was the bacteremia group, and this could be a reason as a specific characteristic of our study different from other studies.

Many antibiotics that were used before the onset of bacteremia or cadidemia were investigated; however, only the use of glycopeptides was found to increase the incidence of candidemia as shown in Table 4. In another study, increased incidence of candidemia was found to be associated with vancomycin and piperacillin/tazobactam. The rate of patients who were receiving immunomodulators was statistically significantly higher in the Group 1 compared with Group 2 with rates 61.9% and 31.7%, respectively (p=0.009). Immunomodulators are usually used to prevent the development of infections by elevating the immune status of the patients in the ICU. We found that the use of immunomodlators is more effective in preventing bacteremia compared with candidemia. There is no other study that disproves or supports this suggestion. Further studies are needed that report the use of immunomodulators to prevent nosocomial infections.

Conclusion

The most important limitation of our study was the small number of candidemia cases. In conclusion, use of a bogota bag, colostomy bag, abdominal drain, receiving blood and/or blood products and TPN, presence of solid organ tumors, need to conduct hemodialysis or continuous ambulatory hemodialysis (CAHD), and a past medical history including a previous operation for a GIS pathology indicated an increased risk for candidemia rather than bacteremia in ICU patients. This finding should be taken into account during the planning of empirical treatment.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (2016-94).

Informed Consent: Patient approval is not required because of retrospective file scanning.

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