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BRIEF REPORT

Candidemia in Febrile Neutropenic Patients; a Brief Report

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Abstract: **Introduction:** Febrile neutropenic patients are at risk of serious infections. The aim of the present study is to identify the frequency, species, and susceptibility patterns of candidemia in febrile neutropenic patients. **Methods:** This cross-sectional study was conducted on febrile neutropenic patients suspected with candidemia who had been referred to 3 educational hospitals during 9 months. **Results:** The blood samples of 80 febrile neutropenic patients with the mean age of 48±16.6 years were studied (60% female). Five (6.25%) episodes of candidemia were identified. The underlying disease was acute myeloid leukemia in 4 (80%) cases and all 5(100%) cases had central venous catheter and were receiving prophylactic ciprofloxacin and acyclovir. 100% of isolates were found to be susceptible to Voriconazole, 80% to Caspofungin, 60% to Amphotericin B, and 40% to Fluconazole. **Conclusion:** The frequency of candidemia among the studied febrile neutropenia patients was 6.25%, with 80% mortality rate, and the most frequently identified yeast was Candida albicans (100% susceptible to Voriconazole).

Keywords: Candidemia; febrile neutropenia; antifungal agents; drug resistance, multiple, fungal

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1. Introduction

Febrile neutropenic patients are at risk of serious infections (1). Generally, bacteria are responsible for bloodstream infections (BSIs), but, 8% of all cases of infectious agents are Candida spp. (2, 3). Candida spp. that cause candidemia are the fourth most common agent of BSIs and the fifth most common cause of nosocomial infection (4, 5). Candida albicans is the most important cause of BSIs; however 45% are caused by non-albicans species such as Candida glabrata, Candida krusei, Candida parapsilosis, and Candida tropicalis (6, 7).

It appears that infection caused by species of Candida is associated with a high crude mortality rate, globally (40% in the United States)(8). The epidemiology of candidemia has been extensively studied in developed countries, but there is a lack of data in developing ones. The aim of the present study is to identify the frequency, species, and susceptibility patterns of candidemia in febrile neutropenic patients.

2. Methods

2.1. Study design and setting

This cross-sectional study was conducted on febrile neutropenic patients who had been referred to Khatam-al-Anbia, Shohadaye Tajrish, and Taleghani educational hospitals, Tehran, Iran, from November 2016 to August 2017. The Ethical Committee of Shahid Beheshti University of Medical Sciences approved this study under the code: IR.SBMU.RETECH.REC.1396.192. All enrolled participants were informed about the study and written informed consent was obtained from them.

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2.2. Participants

Febrile neutropenic patients suspected of candidemia (based on clinical symptoms), referred to emergency departments or hospitalized in intensive care units (9) of the mentioned hospitals were enrolled to the study. Patients who had prolonged fever in spite of receiving broad-spectrum antibiotics for more than four days were considered as suspicious to candidemia. Patients with chronic neutropenia were excluded from this study since the incidence of neutropenia is unpredictable, and difficult to clearly identify and determine. There was not any sex or age limitation.

2.3. Data gathering

Demographic and clinical data were collected including age, sex, duration of stay in ICU, current history of broad-spectrum antibiotic therapy (for > 4 days), antifungal therapy, underlying diseases, and outcomes of sur–gical procedures. Source of data was the patient's profile. An Assistant professor of infectious diseases (Dr. Yousefi) was responsible for selecting suspected cases. Neutropenia was defined as neutrophil count <500/mm^3 or <1000/mm3 with a predicted decrease to <500/mm^3 and fever was defined as single elevation in oral temperature to ≥ 38.30 °C or a temperature of ≥ 38 ÂřC for ≥ 1 hour (10).

2.4. Cultures

10 ml of venous blood sample were obtained for each patient aseptically via venipuncture according to a standard technique by using a sterile syringe after skin disinfection. Culture vials were placed in the BACTEC 9120 System (Becton Dickinson Microbiology Systems, Maryland, DE, USA), and were controlled automatically every 10 minutes. The BACTEC bottles that showed a sign of fungal growth were sub-cultured on the plates with the BHI agar (Merck, Germany) and Sabouraud Dextrose Agar with Chloramphenicol (SC) (Merck, Germany), separately. CHROM agar Candida medium (CHROM agar Microbiology, Paris, France) was used for sub-culture of isolates, incubated at 35 °C for 48 h and for preliminary species identification, production of specific colony colors were analyzed. ITS1 and ITS4 universal primers were used for polymerase chain reaction (PCR) and DNA sequencing was also performed.

2.5. Susceptibility testing

In vitro antifungal susceptibility test of the Candida iso–lates against amphotericin B (AMB) (Sigma-Aldrich, USA.), fluconazole (FLU) (Sigma-Aldrich, USA.), voriconazole (VOR) (Pfizer Central Research, UK), and caspofungin (CAS) (Merck, USA.) were performed using micro-dilution method.

2.6. Statistical analysis

Statistical analyses were performed using SPSS software version 21.0. The findings were reported using descriptive statistics such as mean ± standard deviation or frequency and percentage.

3. Results:

153 blood samples were collected from 80 febrile neutropenic patients (38 blood samples from emergency departments and 115 from ICUs). The mean age of the patients was 48±16.6 years (60% female).

Five (6.25%) episodes of candidemia were identified during the study period. Baseline characteristics and outcome of patients with positive blood Culture are summarized in table 1. The underlying disease was acute myeloid leukemia in 4 (80%) cases and all 5(100%) cases had central venous catheter and were receiving prophylactic ciprofloxacin and acyclovir. The mean dura-tion of hospital and ICU stay in patients with candidemia were 42±5.4 and 26±4.9 days, respectively.

Table 2 shows the in vitro susceptibility of 5 Candida spp. strains against antifungal agents. 100% of isolates were found to be susceptible to Voriconazole, 80% to Caspofungin, 60% to Amphotericin B, and 40% to Fluconazole.

4. Discussion

Based on the findings, the frequency of candidemia among the studied febrile neutropenia patients was 6.25%, with 80% mortality rate, and the most frequently identified yeast was Candida albicans (100% susceptible to Voriconazole).

The fourth most common pathogen isolated from the blood of ICU patients is Candida albicans, with an attributed mortality range between 20–30%. (11-13). However, during recent years, the incidence of Candida spp. infections other than Candida albicans has significantly increased and Candida parapsilosis is currently one of the main causes of invasive candidiasis (14-16).

The estimated rate of candidemia among ICU admitted patients is between 0.5–32 cases per 1,000 admissions (17, 18). Ghahri et al. identified Candida parapsilosis as the most prevalent Candida spp. from the blood samples of patients with candidemia in Iran; but this was not the case in our study (14).

According to antifungal susceptibility tests, the most active antifungal drug in isolated candida species was VOR; this result was similar to a study by Labbe et al. (19).

A study by Pfaller et al. on in vitro susceptibility results for 1,184 isolates showed that VOR was considerably more potent than FLU (4). We also found similar results showing that 100% of candida isolates were sensitive to VOR.

Table 1: Baseline characteristics and outcome of patients with positive blood Culture

Variables	Case 1	Case 2	Case 3	Case 4	Case 5
Sex	Female	Female	Female	Male	Male
Age (year)	61	34	26	48	71
Hospitalization (day)	44	50	34	43	38
ICU admission (day)	28	35	23	24	21
Underlying disease	AML	AML	AML	AML	ALL
Prophylaxis					
Ciprofloxacin	+	+	+	+	+
Acyclovir	+	+	+	+	+
Fluconazole	+	–	+	–	+
Itraconazole	–	+	–	+	–
Co-trimoxazole	–	–	–	–	+
Medical device	CVC	CVC	CVC	CVC	MV, CVC
Candida Spp.	C. albicans	C. albicans	C. albicans	C. albicans	C. glabrata
Outcome	Died	Died	Survived	Died	Died

ICU: intensive care unit; CVC: central venous catheter; MV: mechanical ventilation; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia.

Table 2: In vitro susceptibility test results of the 5 Candida spp. strains against 4 antifungal agents.

Antifungal agent	Susceptible	Dose dependent	Resistant
Fluconazole	2 (40)	3 (60)	0 (0)
Voriconazole	5 (100)	0 (0)	0 (0)
Amphotericin B	3 (60)	1 (20)	1 (20)
Caspofungin	4 (80)	0 (0)	1 (20)

Data were reported as number (%).

This investigation showed that FLU has the highest MIC GM (2.3); this result is similar to the study by Lobbe et al. that reported the highest MIC for FLU compared to other azole antifungal drugs such as VOR, ravuconazole, itraconazole, and posaconazole (19).

A study by Pappas PG et al. proposed that in patients with positive blood cultures that become positive more than 48 hours after collection, FLU should probably be avoided; and it is more likely that patients are infected by Candida glabrata (20).

A delay of ≥12 hours in the initial empiric antifungal treatment was associated with higher hospital mortality (21). It seems that empiric antifungal therapy needs to be started early in order to decrease morbidity and mortality.

5. Limitations

This study had several limitations including the short duration of survey followed by a low number of positive patients. Therefore, it was difficult to compare and interpret the findings, especially antifungal susceptibility patterns. However, based on the findings of this study, candidemia should be considered a significant problem in febrile neutropenic patients.

6. Conclusion

Based on the finding, the frequency of candidemia among the studied febrile neutropenia patients was 6.25%, with 80% mortality rate, and the most frequently identified yeast was Candida albicans (100% susceptible to Voriconazole).

7. Appendix

7.1. Acknowledgements

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7.2. Author contribution

Ensieh Lotfali, Davood Yadegarynia, Meysam Yousefi designed the study. Zahra Arab-Mazar participated in acquisition of data. Ali Ghajari and Alireza Fatemi participated in management of data. All authors approved the final version of the manuscript to be published.

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7.4. Conflict of interest

The authors declare that they have no conflicts of interest.

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