Fungemia in Immunocompromised Patients (Hematological Malignant and Hematopoietic Stem Cell Transplant Patients during Febrile Neutropenia)

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ABSTRACT

Background: Fungal infections are a major cause of morbidity and mortality among febrile neutropenic patients. The choice of empiric antifungal regimen is based on susceptibility pattern of locally prevalent pathogens.
Objectives: to determine fungemia, identify fungal spectrum and their antifungal susceptibility pattern.
Methods: From 150 hematological malignant and hematopoietic stem cell transplant patients during febrile neutropenia, blood cultures (B.C) were processed. **Results:** Eight fungal isolates (5.3%) were recovered which found to be represented by *candida* spp. Five of them were non albicans *Candida (*62.5%) and three of them were *Candida albicans* (37.5%). *C. parapsilosis* resulted in the most frequent *Candida non albicans* (CnA) species (37.5%). All *C. parapsilosis* strains were isolated from patients with vascular catheters. *C. krusei* fungemia generally occur in patients with previous exposure to fluconazoles. All species of *Candida* were sensitive to amphoterecin B, echinocandins and voriconazole. Persistent fever for prolonged duration and prolonged broad spectrum antibiotic use were statistically significant risk factors for developing fungemia. Also extent of neutropenia, duration of chemotherapy, immunosuppressive therapy, altered mucosal barriers and presence of central venous lines were considered major risk factors for development of fungemia. **Conclusion:** The current study was limited by method of diagnosis and low sample size in a single center experience. Furthermore review of the epidemiology of fungemia which was represented by candidemia at our institution revealed the percentage of candidemia was 5.3% and *non albicans Candida* species were the predominant isolates. **Recommendations:** The choice of therapy in neutropenic patients should be formulated based on local antimicrobial susceptibility of these organisms. Close monitoring of fungal infection in patients receiving broad-spectrum antibiotics is mandatory.

Keywords Febrile neutropenia, Fungemia, Aetiology, Risk factors.

INTRODUCTION

The general term fungemia describes the presence of a fungal species in the blood. A positive culture may indicate a widespread infection or commonly, the infection of an intravenous catheter. Often the term fungemia is used synonymously with candidemia because Candida species are more prevalent [1]. Neutropenia is defined as an absolute neutrophil count (ANC) of less than or equal to 500 cells per mm^3 or a count which is expected to fall to that level within the next 1-2 days [2]. It is a common complication in patients receiving immunosuppressive therapy for any cause such as those with acute leukemia, other hematological malignancies and after bone marrow transplantation [3]. Infection is an important complication of neutropenia and is associated with a high morbidity and mortality. Common amongst these infections are those involving the blood stream and lower respiratory tract. In febrile neutropenic patients, the attack rate of blood stream infection (BSI) is reported to be between 11 and 38% [4]. BSI in this population should be closely monitored and optimal management of established infection is mandatory to improve outcome in neutropenic patients and prevent complications [5]. Yeasts have been increasingly present as aethiological agents of fungemia, including *Candida albicans* and other species such as *Candida* non-*albicans* [6]. The prevalence of candidemia among patients with hematological malignancy has been found to vary widely between 1.6% and 22.9% depending on the patient profile studied, geographical location involved, and diagnostic criteria used [7]. Blood cultures (BCs) remain the gold standard for fungemia diagnosis and are recommended in current guidelines. As they are culture-based techniques, the isolation of yeasts from a blood sample is delayed until the microorganism growth becomes detectable (median time to positivity is 2–3 days, ranging from one to more than 7 days). In addition, their sensitivity is low: only 50–75% [8]. The present study was conducted to determine incidence of fungemia in immunocompromised patients (with

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hematological malignancies mainly acute leukemia and bone marrow transplant during febrile neutropenia), to identify fungal species and to evaluate the susceptibility pattern of the isolated fungi to antifungal drugs in vitro.

PATIENTS AND METHODS

Patients:

The study was carried out on one hundred and fifty immunocompromised patients chosen from Oncology and Hematology Hospital at Maadi Military Compound between March 2016 and January 2018. The practical work was carried out in Microbiology Laboratory Department of Maadi Military Compound, Cairo. These immunocompromised patients were defined as; patients with hematological malignancies and bone marrow transplant during febrile neutropenia; Antifungal prophylaxis is not exclusion criteria. An informed consent was obtained from each patient before enrollment in this study. For each patient in this study, the following data were collected (code, age, sex, underlying original immunodeficiency disease, dose and duration of immunosuppressive therapy, antifungal prophylaxis, chemotherapy and catheterization).

According to Infectious Diseases Society of America (IDSA) and the National Comprehensive Cancer Network (NCCN) guidelines; fever is defined as a single oral temperature of > 38.3°C (101°F) or a temperature measurement of 38.0°C (100.4°F) for ≥ 1 hour. Neutropenia is defined as an absolute neutrophilic count (ANC) of < 500 cells/μL or an ANC of < 1000 cells/μL with a predicted decrease to < 500 cells/μL over the next 48 hours and profound neutropenia is an ANC < 100 cells/μL [9].

The study was approved by the Ethics Board of Al-Azhar University.

Microbiology

During the febrile episode, two blood samples per patient were drawn from two separate sites including central venous catheter [CVC] if present and directly injected to Bact/Alert® 3D bottles and incubated in BacT/ALERT system instrument (bioMérieux Diagnostics, Lyon, France).

Aerobic blood culture bottles were incubated for 7 days at 37°C. Positive cultures were Gram stained and subcultured onto on two Sabouraud's dextrose agar (SDA) with chloramphenicol plates and CAN2 chromogenic agar (bioMérieux Diagnostics, Lyon, France). One SDA plate was be incubated at 36 ± 1 °C and the other SDA plate was incubated at 28°C (for yeasts and filamentous isolation respectively).

CAN2 chromogenic agar (BioMérieux Diagnostics, Lyon, France) plates were incubated at 36 ± 1 for *candida* isolation. All isolates were identified according to conventional methods of *De Hoog et al.* [10] as follow; Identification of yeasts was performed with morphological, color of the colonies on CAN2, cultural characters and sugar assimilation profiles obtained using the automated VITEK-2 System (BioMérieux).

Filamentous fungi were identified on the basis of their macroscopic and microscopic morphological and cultural characters, in accordance with conventional methods. Antifungal susceptibility testing was performed against Amphoterecin B, Fluconazole, Voriconazole, Caspofungin, Micafungin and Flucytosine to measure minimal inhibitory concentration (MIC) by the automated VITEK-2 System for yeast according to CLSI [11] and disc diffusion method for filamentous fungi as described by *CLSI* [12].

Statistical analysis

Data were collected, revised and entered using the statistical package SPSS. The collected data were tabulated and analyzed with the suitable statistical methods using mean value ± standard deviation, t-test and chi square test. P value of less than 0.05 was considered statistically significant.

RESULTS

This study was conducted to one hundred and fifty febrile neutropenic patients with hematological malignancies and fifteen of them underwent hematopoietic stem cell transplantation from Oncology and Hematology Hospital at Maadi Military Compound between March 2016 and January 2018.

The main characteristics of the patients are described in (**Table 1**).

Table 1: Baseline characteristics of the 150 studied patients

Variable	Number (%)
Total patients	**150 (100)**
Male	107 (71.3)
Female	43 (28.7)
Age (years)	**mean** 38.7 (2-76) years
Hematological malignancies without HSCT	**135 (90)**
Acute leukemia	98 (65.3)
Acute myeloid leukemia	78 (52)
Acute lymphoid leukemia	20 (13.3)
Non-Hodgkin lymphoma	17 (11.3)
Hodgkin lymphoma	7 (4.7)
Chronic lymphocytic leukemia	6 (4)
Multiple myeloma	6 (4)
Burkitt's lymphoma	1 (0.7)
Hematological malignancies with HSCT	**15 (10)**
Allogeneic	9 (6)
Autologous	6 (4)
Central venous catheter	131 (87.3)
Blood stream infection	**66 (44)**
Bacteremia	58 (38.7)
Fungemia	8 (5.3)

The mean temperature was higher in the patients with fungemia than in other patients without fungemia and this difference was statistically significant (P=0.016), mean duration of fever was higher in the patients with fungemia than in other patients without fungemia, but the difference was statistically significant (P=0.014), mean duration of prophylactic/empirical antibiotic before B.C was higher in the patients with fungemia than in other patients without fungemia and this difference was statistically significant (P=0.001). The comparison between patients who had fungemia and those without fungemia regarding absolute neutrophilic count revealed insignificant decrease in absolute neutrophilc in fungemic patients (P=0.266) as in (**Table 2**).

Table 2: characteristics of hematologic malignant and HSCT patients during febrile neutropenia according to fungemia

Variable	Patients with fungemia (n=8)	Patients without fungemia (n=142)	P. value
	Mean ± SD	Mean ± SD	
Fever	**39.44 ± 0.68**	**38.93 ± 0.57**	**0.016**
Duration of fever/hr	**39.13 ± 28.31**	**23.78 ± 16.30**	**0.014**
Duration of antibiotic before B.C	**105 ± 70.19**	**41.83 ± 41.71**	**0.001**
ANC	**76 ± 98.17**	**129.05 ± 132.02**	**0.266**

Fungemia was higher in patients with acute myeloblastic leukemia, in patients underwent allogeneic bone marrow transplant and in blood cultures taken from both central venous catheter and peripheral, and most common fungi isolated from blood cultures were *Candida non albicans* mainly *Candida parapsoliosis* (all of which were isolated from patients with central venous catheter) followed by *Candida albicans*. Indwelling CVC has been identified to be a risk factor for candidemia in patients with malignancy where it represents (62.5%) of positive cases. The treatment modification of candidemia done by removing of CVC in the presence of bloodstream infections (**Table 3**).

Table 3: Fungal pathogens and treatment responses of patients with bloodstream infections

Case	Age	Sex	H.M	BMT	Source of B.C	Fungal pathogen	Antifungal resistant	Empirical antifungal treatment before identification	Treatment modification
1	5	male	AML	Allogeneic	2 Peripheral	*C.krusi*	FLC-5FC	FLC	From FLC to AmB
2	50	female	AML	-	2 Peripheral	*C. albicans*	-	-	-
3	51	female	AML	-	CVC-Peripheral	*C. parapsoliosis*	-	-	Central line removed
4	65	male	NHL	-	CVC-Peripheral	*C. parapsoliosis*	-	-	Central line removed
5	6	female	BL	-	CVC-Peripheral	*C. parapsoliosis*	-	-	Central line removed
6	65	male	MM	-	2 Peripheral	*C. albicans*	-	-	-
7	46	male	HL	-	CVC-Peripheral	*C. albicans*	-	-	Central line removed
8	20	male	AML	Allogeneic	CVC-peripheral	*C. tropicalis*	-	-	Central line removed

Abbreviations: H.M: Hematologic malignancy, AML: acute myeloblastic leukemia, NHL: non-hodgkin lymphoma, BL: Burkitt's lymphoma, MM: multiple myeloma, HL: Hodgkin lymphoma, FLC: fluconazole, 5FC: flucytosine, CVC: central venous catheter, BMT: bone marrow transplant.

Fungemia was found higher in blood cultures which were taken from CVC and peripheral sites by (62.5%), in comparison to that taken from peripheral sites only (37.5%). But this difference was statistically insignificant (p = 0.732) (**Table 4**).

Table 4: Distribution and frequency of blood culture fungemia in relation to Source of positive blood cultures.

Source of blood cultures		Fungemia, N (8)	P value
CVC+ Peripheral	**N**	**5**	**0.732**
	%	**62.5**	
2 Peripheral	**N**	**3**	
	%	**37.5**	

Fungemia was found higher in hematological malignant patients underwent hematopoietic stem cell transplantation (13.3%) in comparison to hematological malignant patients without HSCT (4.4%). But this difference was statistically insignificant (P=0.146) as in (**Table 5**).

Table 5: Distribution and frequency of blood culture fungemia in relation to hematopoietic stem cell transplantation.

hematopoietic stem cell transplantation	Fungemia N (%)	No fungemia N (%)	P value
Hematological malignancies without HSCT (135)	6 (4.4)	129 (95.6)	0.146
Hematological malignancies with HSCT (15)	2 (13.3)	13 (86.7)	

Fungemia was found higher in allogeneic transplant patients in comparison to autologous transplant patients. But this difference was statistically insignificant (P=0.215) as in (**Table 6**).

Table 6: Distribution and frequency of blood culture fungemia in relation to type bone marrow transplant.

Type of bone marrow transplant	Fungemia N (%)	No fungemia N (%)	P value
Allogeneic (9)	2 (22.2)	7 (77.8)	0.215
Autologous (6)	0 (0)	6 (100)	

Regarding the susceptibility of the studied isolates, all sensitive to amphotericin B, voriconazole and echinocandin and our proportion of fluconazole resistant isolates was (12.5%) against *C. kreusi* as in (**Table 7**).

Table7: Antifungal susceptibility pattern among fungal isolates (*n*=8) recovered from blood cultures of febrile neutropenic patients.

Fungal isolates (*n*=8)	Susceptibility %					
	Amphotricin B	Fluconazole	Caspofungin	Flucytosine	Voriconazole	Micafungin
C. krusei (1)	1 (100)	0 (0)	1 (100)	1 (100)	1 (100)	1 (100)
C. albicans (3)	3 (100)	3 (100)	3 (100)	3 (100)	3 (100)	3 (100)
C. parapsilosis(3)	3 (100)	3 (100)	3 (100)	3 (100)	3 (100)	3 (100)
C. tropicalis (1)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)

DISCUSSION

Neutropenia is defined as an absolute neutrophil count (ANC) of less than or equal to 500 cells per mm³ or a count which is expected to fall to that level within the next 1–2 days and profound neutropenia is an ANC < 100 cells/μL [2]. It is a common complication in patients receiving immunosuppressive therapy for any cause such as those with acute leukemia, other hematological malignancies and after bone marrow transplantation [3]. Infection is an important complication of neutropenia and is associated with a high morbidity and mortality. Common amongst these infections are those involving the bloodstream. In febrile neutropenic patients, the attack rate of bloodstream infection (BSI) was reported to be between 11 and 38% [4]. In our study the total number of studied patients was 150, 66 (44%) of them with bloodstream infections in form of bacteremia in 58 patients (38.7%) and this was correspond to *Al-Mulla et al.* [13] who reported that, total number of cancer patients analyzed was 185; with 111 BSI episodes, the number of patients with bacteremia was

70 (38.7%). In this study, we report a prevalence of 5.3% for fungemia which was represented by candidemia among febrile neutropenic hematological malignancy and hematopoietic stem cell transplant patients attending a tertiary-care Oncology & Hematology Hospital at Maadi Military Compound in Cairo. These results were found to agree with the results of 57357 Hospital studies in Cairo that pooled rates of fungemia was 5.7%, where blood culture fungemia was 7% in 2015, 5.6% in 2016 and 4.5% in 2017, respectively **(personal communication, 2017)**, while the study done by *Gedik et al.* **[14]** reported that the episodes of fungemia were 8%. *El-Masry et al.* **[15]** reported that the percentage of fungemia in patients was (37.5%), *Morace et al.* **[16]** found that 43% of patients had fungeamia, also *El-Mahallawy et al.* **[17]** mentioned that 35% of the studied patients had fungeamia. The difference between our study and these studies is due to different type of methods used in diagnosis of fungemia. Also patients within previously recorded studies were more likely to be severely neutropenic. The majority of them received aggressive chemotherapy, which is associated with significant oral and lower gastrointestinal mucositis that lead to easy blood invasion. *Rókusz et al.* **[18]** reported that fungi are a common cause of secondary infection among neutropenic patients who have been treated with broad-spectrum antibiotics for the primary bacterial infection and this is similar to our study, where we reported that the percentage of fungemia in patients on preventive broad spectrum antibiotic was found to be higher (8.8%) with (p value= 0.134). In our study, we reported a prevalence of 5.3% for fungemia which was represented by candidemia and the prevalence of candidemia among patients with hematological malignancy was found to vary widely between 1.6% and 22.9% depending on the patient profile studied, geographical location involved, and diagnostic criteria used **[7]**. Blood culture (BC) remains the gold standard for fungemia diagnosis and are recommended in current guidelines. As they are culture-based techniques, the isolation of yeasts from a blood sample is delayed until the microorganism growth becomes detectable (median time to positivity is 2–3 days, ranging from one to more than 7 days). In addition, their sensitivity is low: only 50–75% **[8]**. In our study, the incidence of Candida non-albicans species among candidemia was 62.5% which run with the work done by *Gokcebay et al.* **[19]** and *Colombo and Guimarães* **[6]**, which revealed that an incidence of *non-albicans Candida* spp among candidemia more frequently in 63% of cases for both works. Among yeasts in our study, *Candida non albicans* (CnA) species particularly *C. parapsilosis* were the most frequently isolated, according to a retrospective study carried out for 6 years at a university hospital in Southern Italy by *Caggiano et al.* **[20]** and prospective study carried out over a period of 18 months in multicenter involving nine nosocomial facilities in Southern Italy to evaluate the incidence of invasive fungal infections (IFIs) in adult and pediatric patients with hematologic malignancies done by *Montagna et al.* **[21]**. Also in our study *C. parapsilosis* resulted in the most frequent CnA species (37.5%). These results were found to agree with the results of a multicenter survey of nine nosocomial facilities in Southern Italy that rates of *C. parapsilosis* was 38.5% **[22]**. Although this yeast is one of the less virulent species of Candida, its role in epidemiology of blood stream infections is very important because it is often responsible for healthcare-associated infections (e.g., intravascular catheters) **[23]**. The most prominent species in our study that have been reported were *C. parapsilosis* in patients with CVC-related infections and this finding is in confirmation with the earlier report done by *Gokcebay et al.* **[19]**. Like the previous findings of *Villarroel et al.* **[23]** who reported that fever persisting for prolonged duration significantly (P = 0.0001) increased the risk for invasive fungal infections (IFI) in cancer febrile neutropenic patients, we found significant difference (P = 0.014) between patients with fungemia and patients without fungemia regarding the mean duration of fever. Neutropenia, prolonged multiple antibiotic use, and other medical conditions were more likely to result in a higher incidence of fungemia in our cases. Colonization with yeast is commonly seen in hematology patients due to compromised immune status, use of broad-spectrum antibiotics, colonization of several body sites, disruption of physiological barriers in the digestive tract, and other factors. AML, which poses a high risk for fungemia, was diagnosed in 4 of 8 cases with fungal BSIs. *Non-albicans Candida* species caused most of the fungemia episodes in our cases. *C. parapsilosis* was isolated in about of one third of fungemia episodes (37.5%) in our cases. Whilst *C. parapsilosis* is commonly isolated from patients with vascular catheters. *C. krusei* fungemia generally occurs in patients with previous exposure to azoles. These finding are in confirmation with the report done by *Gedik et al.* **[14]**. In our study, we report that risk factors for the development of fungemia were an ANC of less than 100 (Mean ± SD=76 ± 98.17) with no

significance (P = 0.266) and this is similar to *Swati et al.* [24] who reported that, risk factors for the development of fungal sepsis were an ANC of less than 100. Also *El-Ashry and Ragab* [25] reported that there was no significant difference (P = 0.681) between positive and negative PCR cases of fungemia regarding the absolute neutrophil count. Most of our patients with candidemia had CVC (62.5%) and the treatment modification of candidemia done by removing of CVC from these patients. In the current study, prolonged antibiotic therapy was found to be a significant risk factor for fungemia in FN patients (P = 0.001), this was correspond to *Swati et al.* [24] who reported that risk factor for the development of fungal sepsis were prolonged antibiotic therapy (P = 0.032). Regarding the susceptibility of the studied isolates, antifungal resistance was an infrequent finding in our study and was restricted to a few isolates, and none of them were resistant to amphotericin B, voriconazole and echinocandin and our proportion of fluconazole-resistant isolates was (12.5%) against *C. kreusi.*

CONCLUSIONS AND RECOMMENDATIONS

Conclusion

- The current study was limited by method of diagnosis and low sample size in a single center experience.
- Furthermore review of the epidemiology of fungemia which was represented by candidemia at our institution revealed the percentage of candidemia is 5.3% and a predominance of non-*albicans* species as the cause of these infections.
- As long as the medical condition permits, CVC removal should be considered in patients with hematological diseases and Candida-associated bloodstream infections.

Recommendations

- Close monitoring of fungal infection in patients receiving broad-spectrum antibiotics is mandatory
- The choice of therapy in neutropenic patients should be formulated based on local antimicrobial susceptibility of these organisms.
- Further different diagnostic methods (such as antigen detection and molecular techniques) on large-scale studies are warranted to detect large-scale of fungal isolates that cause fungemia and evaluate the contribution of the other risk factors, such as preexistent medical condition.
- The last situation may be to consider *C. parapsilosis* as an exogenous pathogen and breaches of catheter care and of infection control practice should be investigated and revised within institutions where this species has become a common blood culture isolate.

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