Original Article

# Prevalence of Fungemia in Pediatric Patients with Febrile Neutropenia

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## Abstract

**Background:** Increasing use of different chemotherapy regimens, organ transplants, etc., has led to the increasing number of neutropenic patients. Overall, 10% of patients affected by cancer who are under treatment with anticancer drugs, regardless of the tumor type, are susceptible to febrile neutropenia. The study was performed to evaluate the frequency of bloodstream fungal infections in pediatric patients with febrile neutropenia in Sayed Al-Shohada Hospital (Cancer Referral Center in Isfahan) in 2010–2012. **Materials and Methods:** This cross-sectional study was performed on pediatric patients with febrile neutropenia who were referred to Sayed Al-Shohada Hospital (Cancer Referral Center in Isfahan) in 2010–2012. Blood samples were obtained from all the patients and were loaded into Bactec 9050 blood culture instruments (Bectone Dickinson, Baltimore, Md., USA), and organisms responsible for causing fever were detected. **Results:** Sixty-seven patients (51.3 males, 48.7 females) with a mean age of 12.3 ± 15.8 years were included. The blood cultures of 48 patients (71.6%) were negative. Seven samples of the isolates (10.4%) were fungi, and twelve of them (18%) were bacteria. Thus, the prevalence of fungal infection was 10.4%. **Conclusion:** Due to the high relative prevalence of fungal infections in our study, it is necessary to take precautions for fungal infection prevention and choose the best way management to obtain optimal results in these patients.

**Keywords:** *Fever, fungemia, neutropenia, pediatrics*

## Introduction

Increasing use of different chemotherapy regimens, organ transplants, etc., has led to the increasing number of neutropenic patients.[1,2] Overall, 10% of patients affected by cancer who are under treatment with anticancer drugs, regardless of the tumor type, are susceptible to febrile neutropenia.[3] Developing fungal infection in neutropenic patients is one of the most dangerous side effects.[4] Febrile neutropenic patients who receive antibiotics are at risk for fungal infections. This risk increases greatly with the length and severity of neutropenia.[5] Studies have shown that approximately 13.8% of febrile neutropenic children are infected with fungal infections.[6] Fricker-Hidalgo *et al*. in a study in 2004 in France conducted to evaluate the use of the medium of BACTEC Plus Aerobic/F and Anaerobic/F system with BACTEC 9240 for detection of yeasts paid according to results; this method has high sensitivity and reliability for the diagnosis of fungemia.[7] Due to the high incidence of febrile neutropenic patients and the importance of diagnosis and early treatment of fungal infections in patients, this study was performed to evaluate the frequency of fungal infections in febrile neutropenic patients hospitalized in Sayed Al-Shohada Hospital (Cancer Referral Center in Isfahan) in Isfahan, Iran.

## Materials and Methods

This study is a cross-sectional study that was done in Sayed Al-Shohada Hospital (Cancer Referral Center in Isfahan) from 2010 to 2012 in Isfahan. The study was approved by the Medical University's Ethics Committee Isfahan University of Medical Sciences. The studied population was pediatric patients with febrile neutropenia who were hospitalized during this period at this center or have to go to the hospital because of fever. The sampling method was census sampling ($n$ = 67), and during this period, all febrile neutropenic cases admitted to hospital were investigated. Inclusion criteria were under the age of 15 years. Fever was defined as a single oral temperature of ≥38.3°C (101°F) or a temperature of ≥38.0°C (100.4°F) for ≥1 h, under condition that the patient did not receive



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blood products. Neutropenia is defined as a neutrophil count of <500 cells/mm$^3$ or a count of <1000 cells/mm$^3$ with a predicted decrease to <500 cells/mm$^3$.[1] Neutropenic is considered as a neutrophil count of <3 mm/500 or <3 mm/1000 expected to decline by 3 mm/500.[1] In this study, patients who used mouthwash, nystatin but not taking prophylactic antifungal drug were not excluded. By contrast, the patients who received antifungal before culture sampling or those who got fever subsequently after receiving the blood transfusion and blood products were excluded from the study. On the other hand, patients who received antibiotics were not considered part of the exclusion criteria. To determine fungal infections, the blood samples of the studied population taken under laboratory conditions and cultured by Bactec 9050 automated Blood culture system and microorganisms responsible for causing fever were detected.

### Statistics

Laboratory and patients' demographic data were entered in a particular form and were prepared for analysis. Eventually, the data were obtained by computer and statistical software SPSS (SPSS Version 16.0, 2007, SPSS Inc., Chicago, IL, USA) and Student's *t*-test and Chi-square test were analyzed.

## Results

From the year 2010 to the end of the first half of 2012, 67 patients with the inclusion criteria were hospitalized in this hospital. The mean age of the patients was 6/5 ± 3/5 years with a range of 1–15 years. Twenty-four (30/8%) of these patients were under 5 years of age, 29 patients (37/2%) at age 5–9 years, and 14 (20/9%) were 10 years or older. The sex distribution was as follows: 32 (51/3%) were males and 35 (52/2%) were females. The mean age of males and females, respectively, was 6/1 ± 3/6 and 6/9 ± 3/5 years, and *t*-test showed no significant difference between the sexes ($P$ = 0/38). According to the results of blood cultures for patients by Bactec 9050 automated Blood culture system, 48 patients (71/6%) had no growth of microorganisms, seven samples of the isolates (10.4%) were fungi, and twelve of them (18%) were bacteria. Hence, the prevalence of infection in these patients was 10/4%. The mean disease duration was 9/8 ± 7/5 months, with a range from 2 to 36 months. The duration of fever was 7/4 ± 3/1 days, with a range from 2 to 15 days. Eight patients (11/9%) had venous catheter, and two patients (3%) had a Foley catheter. In Table 1, the distribution of microbial growth in terms of demographic variables is shown. According to this table, the mean age of patients and duration of disease depending on the type of microorganisms had a significant difference, although microbial growth had no significant difference in the duration of fever and sex. The growth of microorganisms by an intravenous catheter and Foley catheter had no significant difference.

The mean neutrophil count in the studied patients was 341.7 ± 173.5 per mm$^3$. The mean neutrophil count in patients who did not grow microorganisms in blood culture was 195/7 ± 365/8, in patients with bacterial growth in blood culture was 154 ± 311/2, and in patients with fungi in their blood cultures was 61/5 ± 242/2, and the one-way variance analysis test showed that the mean number of neutrophils in the three groups has significant difference ($P$ = 0/037). Furthermore, Scheffe's test showed that the mean number of neutrophils in both groups of no microbial growth and fungal growth was statistically significant ($P$ = 0.04)) but between two groups of bacterial growth and no microbial growth and between the two groups of fungal growth and bacterial growth there was no significant difference. In addition, no cases with bacterial and fungal growth were seen[Figure 1].

## Discussion

The overall purpose of this study was to determine the frequency of fungal infections in pediatric patients with febrile neutropenia in Sayed Al-Shohada Hospital (Cancer Referral Center in Isfahan) from 2010 to 2012. According to the results of this study, the prevalence of fungal infections in febrile neutropenic patients was

**Table 1: The frequency distribution of demographic variables in terms of microbial growth**

| Variable | Units | Fungi | Bacteria | No growth | *P* |
|---|---|---|---|---|---|
| Age | Mean±SD | 7.9±5.8 | 4.3±2.3 | 6.9±3.2 | 0.36 |
| Duration of disease (months) | Mean±SD | 4.6±1.8 | 6.3±2.8 | 11.5±8.2 | 0.012 |
| Duration of fever (months) | Mean±SD | 8.9±3.4 | 8.3±2.7 | 7±3.1 | 0.18 |
| Sex *n* (%) | Male | 2 (6.2) | 8 (25) | 22 (68.8) | 0.24 |
| | Female | 5 (14.3) | 4 (11.4) | 26 (74.3) | |
| Intravenous catheter, *n* (%) | Don't have | 6 (10.2) | 12 (20.3) | 69.5 (41) | 0.37 |
| | Have | 1 (12.5) | 0 | 7 (87.5) | |
| Foley catheter, *n* (%) | Don't have | 7 (10.8) | 11 (16.9) | 47 (72.3) | 0.46 |
| | Have | 0 | 1 (50) | 1 (50) | |

SD: Standard deviation

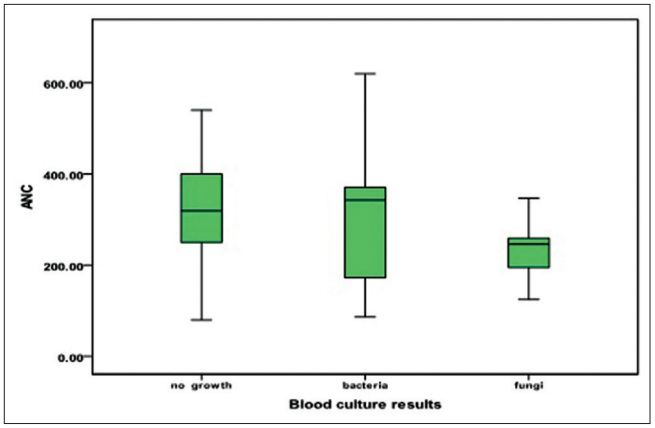


**Figure 1: Median, range, and percentiles 25% and 75% of neutrophil counts in terms of microbial growth in blood culture**

10/4%, while the prevalence of fungal infections in nonneutropenic patients is much lower. Previous studies on cancer patients who were treated with chemotherapy have shown that due to immunosuppression that occurs due to chemotherapy, the extreme debility, and cachexia, these patients showed severe reduction in the levels of immune factors including neutrophils, in that they can provide incidence of opportunistic infections mostly, fungal infections. However, there are different reports on the prevalence of fungal infections. Badiee *et al*. in Shiraz Medical Sciences University in 2008 studied the prevalence of systemic candidiasis and efficacy of polymerase chain reaction-PCR method for early diagnosis in patients with hematologic malignancy has *Candida* spp. This study was conducted from 2004 to 2006 and a total of 194 patients with hematologic malignancies were evaluated for systemic candidiasis in 25 patients (12/9%), with systemic candidiasis which included 21 patients *Candida albicans*, 3 for *Candida tropicalis*, and 1 was *Candida krusei*.[8] Mess and Daar's study conducted in California in 1997 investigated the clinical utility of fungi blood cultures for AIDS. During a 25-month study period, 1162 fungal blood cultures were obtained for 322 patients. These cultures with bacterial blood cultures lead to the isolation of fungi from 26 patients (8/1%); 15 cases (4/7%) of them were true pathogens.[9] In Meidani *et al*.'s study in Sayed Al-Shohada Hospital from 2005 to 2010 on febrile neutropenic patients with conventional blood culture methods, only 2/6% disease had positive blood cultures.[10] In another study by Meidani *et al*. from 2010 to 2012 in Sayed Al-Shohada Hospital on febrile neutropenic patients older than14 years on the basis of blood cultures with Bactec 9050 automated Blood culture system, 28/4% of patients had positive blood cultures. According to this method for blood culture, the prevalence of fungal infections was 4.9%.[11] Regardless of the health-care process in neutropenic patients for preventing infection, the other reason for the higher prevalence of fungal infections in our study in comparison with studies in other countries is probably related to the sensitivity and type of devices used in different centers; additional factors such as duration of fever and duration of disease are involved in fungal infections. Another notable issue in patients who have higher stage of disease and have taken more frequent chemotherapy is that they have higher risk of developing neutropenia and they will have higher chances of fungal infections. Moreover, given the fact that patients treated at Sayed Al-Shohada Hospital (Cancer Referral Center in Isfahan) received a full course of chemotherapy and patients are under follow-up, the relative survival rates are higher, and these individuals compared with patients who have a shorter survival received more chemotherapy and have a higher stage of the disease and therefore the chances of fungal infections in such patients are more; in other words, between fungal infection and survival time of patients, there is a direct relationship. According to the results of our study, there was a significant relationship between the count of neutrophils and fungal infections, and patients with fungal infections compared to noninfected patients had lower count of neutrophils per mm.[3] Studies have shown reduced neutrophil count <1000 per $mm^3$ which significantly increases the risk of fungal infection; this risk increases greatly with the length and severity of neutropenia.[5] According to Saeidpour *et al*.'s study, which was conducted in 2008 in Mashhad University of Medical Sciences, the survey of 100 neutropenic febrile children under 12 years showed 13/8% fungal infections and 62/1% of the people were infected with Gram-negative infections and 24/1% were infected with Gram-positive infections.[6]

The main limitations of our study were:

1. Small sample size
2. We could not specify the type of fungal species.

## Conclusion

A general conclusion that can be found from this study is that due to a weak immune system, febrile neutropenic patients are at risk of any kind of infection, including opportunistic fungal infections that may be life threatening. Given the relatively high prevalence of fungal infections in our study, it is necessary to take precautions for fungal infection prevention and choose the best way management to obtain optimal results in these patients.

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### Conflicts of interest

There are no conflicts of interest.

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