ORIGINAL REPORT

Evaluation of Febrile Neutropenia in Patients Undergoing Hematopoietic Stem Cell Transplantation

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Abstract- The aim of this study was to determine the incidence and causes of fever as a major problem contributing to transplantation related mortality among patients undergoing hematopoietic stem cell transplantation (HSCT) and evaluation of antibiotic use, according to reliable guidelines.We retrospectively reviewed hospital records of 195 adult patients who underwent HSCT between 2009-2011 at hematology-oncology and bone marrow transplantation research center. Baseline information and also data related to fever and neutropenia, patient's outcomes, duration of hospitalization and antibiotic use pattern were documented.A total of 195 patients were analyzed and a total of 268 febrile episodes in 180 patients were recorded (mean 1.5 episodes per patient). About 222 episodes (82%) were associated with neutropenia which one-fourth of them were without any documented infection sources. Microbiologic documents showed that the relative frequencies of gram positive and gram negative bacteria were 62.5% and 37.5%, respectively. The hospital stay duration was directly related to the numbers of fever episodes (P<0.0001).The rate of febrile episodes in autologous stem cell transplantation was significantly higher compared to allogeneic type (P<0.05).It is necessary to determine not only the local profile of microbiologic pattern, but also antibiotic sensitivities in febrile neutropenic patients following hematopoietic stem cell transplantation, and reassess response to antibiotic treatment to establish any necessity for modifications to treatment guidelines in order to prevent any fatal complications from infection.

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Introduction

Hematopoietic Stem Cell Transplantation (HSCT) has been used primarily for hematologic and lymphoid cancers and for many other disorders (1).

Infection is one of the most life threatening complications after HSCT and is still a major problem contributing to transplantation related mortality (2,3).About one-half of all infectious complications occur early in the first 4-6 weeks following HSCT. Neutropenia as a direct result of the myeloablative transplantation regimens is almost certainly the predominant risk factor for infection during this early period (1).

Even though, fever can be the only sign of infection in neutropenic patients, but the infection cannot be documented by cultures in a large numbers of febrile patients (4,5). However empirical antibiotic therapy right after fever detection can prevent morbidity and mortality (6,7). There are some reliable guidelines that have determined which antibiotics must be initiated in patients with fever and neutropenia (8,9), nevertheless access to local microbiological epidemiology and susceptibility and clinical experience especially in absence of distinct etiology can help to choose more appropriate therapeutic regimen.

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In order to optimize the antimicrobial therapy and prevent infections, this study has been designed to evaluate the epidemiology of infections in HSCT recipients.

Patients and Methods

We retrospectively reviewed hospital records of 197 adult patients between July 2009 and March 2011 at hematology-oncology and bone marrow transplantation research center, Shariati Teaching Hospital, one of the major medical centers of Tehran University of Medical Sciences (TUMS).

For each patient, we collected data from the time of admission until discharge. We also collected the data from records of patients who had died during treatment in the hospital.Two patients were excluded from the study, because their records were not complete.

Baseline information (including age, gender, underlying diseases and type of the HSCT), and also data related to fever and neutropenia, patient's outcomes, duration of hospitalization and antibiotic use pattern were documented.

According to the guideline of the Infectious Diseases Society of America (IDSA), fever defined as a single oral temperature of 38.3ºC or an oral temperature of38 ºC lasting one hour, and neutropenia 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 within the next 48-72 hours (8).

Patients who had fever and neutropenia after transplantation were included in the study and each fever detection in neutropenic phase considered as one fever episode.

We reviewed and analyzed the clinical and microbiological evidences for each febrile episode in patients. Clinical evidence defined as clinicians' reports in medical patient chart like catheter inflammation or respiratory symptoms such as cough. Cultures from blood, urine, sputum throat and other suspected sites for bacteria and fungus were evaluated for microbiological findings. We also recorded the types of antibiotic use for each fever episode and administration pattern compared to IDSA guideline.

Results

One hundred and ninety five subjects were evaluated in this study. The patients' baseline information is shown in table 1.The mean age of the patients was 27 years old which sixty five percent of them were male. Acute myelogenous leukemia (AML) was the most common underlying disease and 63% of patients received allogeneic transplant.

In table 2, the characteristics of all febrile episodes are illustrated. Out of 195 patients, only180 of them (92% of all recipients) had fever; and169 patients had fever with neutropenia (87% of all recipients).

A total of 268 febrile episodes in 180 patients were recorded (mean 1.5 episodes per patient), from which 222 episodes (82%) were associated with neutropenia, 48 episodes (18%) were without neutropenia and 57 episodes (25%) were associated with blood transfusion. The mean length of hospital stay after transplantation and the mean time for the first fever detection were 18.9± 7.8 and 5.9± 3.9days respectively. The hospital stay duration was directly related to the numbers of fever episodes (P<0.0001).The rate of febrile episodes in autologous stem cell transplantation was significantly higher compared to allogeneic type (P<0.05).

A total of 56 episodes (25%) of febrile neutropenia were without any documented infection sources. Clinical, microbiological and radiological evidence of infection were seen in 36(16.2%), 102 (45.9%) and 21(9.4%) of episodes, respectively.

Table 1. Patients' characteristics.

Characteristics	No. (%)
Total number of patients	195
Median age at transplantation (range), years	27 (13-65)
Gender	
Male	126(65)
Female	69(35)
Disease	
AML	49(25)
Thalassemia	30(15)
HD	29(15)
ALL	22(11)
MM	17(9)
CML	4(2)
NHL	14(7)
AA	12(6)
Others	18(9)
Transplantation type	
Allogeneic	123(63)
Autologous	72(37)
Median duration of hospitalization (range), days	18.93±7.83

AML (acute myelogenous leukemia), HD (Hodgkin disease), ALL (acute lymphoblastic leukemia), MM(multiple myeloma), CML(chronic myelogenous leukemia), NHL (non-Hodgkin's lymphoma), AA(aplastic anemia).

Table 2. Characteristics of fever and febrile episodes of patients.

Total number of patients	197
Total no. of patients with fever	180 (92)
Total no. of patients with fever and neutropenia	169(87)
No. of patients with One fever episode	127(75)
No. of patients with Two fever episode	35(20)
No. of patients with 3+ fever episode	7(5)
Total number of febrile episodes	268
Episodes associated with neutropenia	222(82)
Episodes associated with blood transfusion	57(25)
Median duration of neutropenia (range), days	11(4-49)
Median duration of febrile episodes (range), days	2(1-33)
Median duration of febrile episodes associated with neutropenia (range), days	2(1-21)

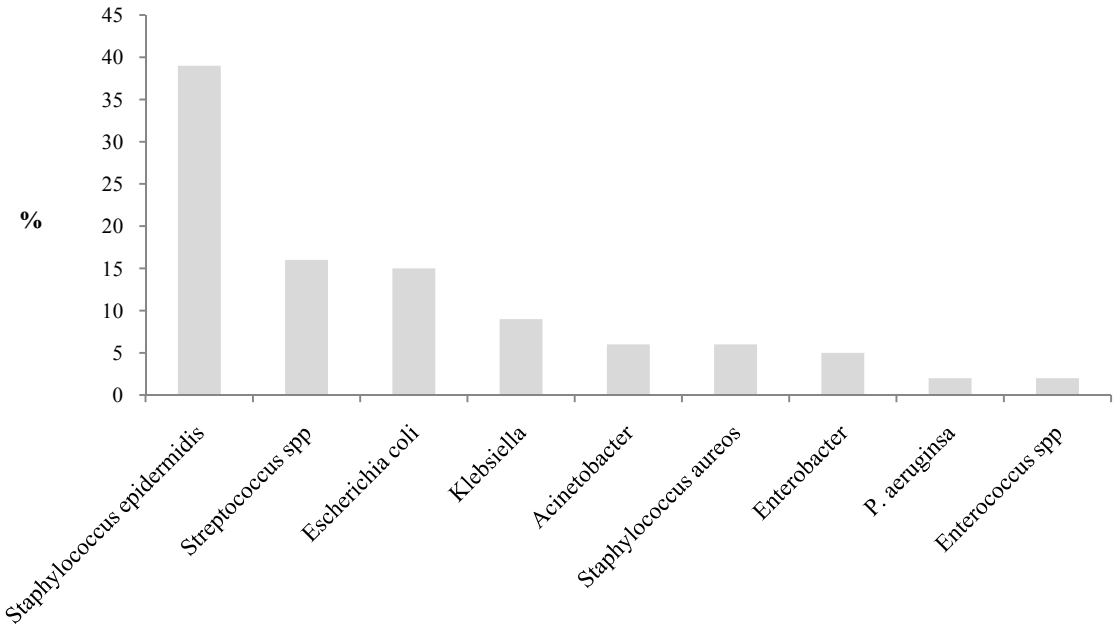

Figure 1. The incidence of causative pathogens.

Table 3. Number of clinical and radiological evidence of infectionin febrile neutropenic episodes.

Document of infection	**No.**
Clinical sites of infection	36
Respiratorytract	23
Catheter	8
Urinary tract	1
Gastrointestinaltract	4
Radiological documents	22
Chest X-ray	19
CT scan	3

Among neutropenic patients, respiratory symptoms were the most common clinical evidence that were reported by clinicians. All descriptions about clinical and radiological evidences are shown in table 3.

Among positive cultures, the relative frequencies of Gram-positive and Gram-negative bacterial infections were 62.5% and 37.5% respectively. Incidence of causative pathogen is shown in figure 1.

The mortality rate of patients during hospitalization was 3.5 % (7 patients) that 71% of them died due to infection. It should be mentioned that despite the small numbers of death among patients, three patients died due

to gram negative bacteremia. Gram-negative organisms associated with death were *Pseudomonas aeruginosa* and *Escherichia coli*.

Antibiotics were administrated in all patients with febrile episodes. A combination of ceftazidime and amikacin was used in 27 patients (15%) and carbapenems (imipenem and meropenem) were started in 142 patients (78.8%). 134 patients (74.4%) received vancomycin, which was added to antibiotic regimen either empirically or based on microbiological or clinical evidences. Antifungal agents were also administrated to 25 patients (13.8%).

Discussion

Fever is the most important sign of infection during the early post transplantation before engraftment (4,5). Duration and severity of neutropenia are the predominant risk factors for infection in this period (1,10). In present study, median duration of neutropenia (range) was 11 days and fever occurred within 5-6 days of transplantation in neutropenic patients. However, the numbers of febrile episodes were related with the type of transplantation and the length of neutropenia. In contrast, a retrospective cohort studies by Ninin*et al.* didn't show any differences between allogeneic and autologous transplantation type in incidence of febrile neutropenia (11).

In some published studies, regarding the epidemiology of infections following fever and neutropenia, evidences for infections had been reported in about half of the febrile episodes (12-14). However in our study, two thirds of febrile episodes had at least one documented etiology for infection. Microbiologic evidence was detected in 45.9% of episodes and also Gram-positive organisms were more prevalent than Gram-negative organisms (approximately 2/3 vs. 1/3). In a study by Klasterskyet *al*., the relative frequencies of Gram-positive and Gram-negative bacterial infections were the same as present study (15). Even though in our study, the most isolated bacteria were Gram-positive, but only Gram-negative organisms lead to death in the cases that expired with microbiologic evidences. In addition, *Staphylococcus* species as the most common isolated pathogen did not result in any mortality. This result is in accordance with Collin report in 2001, which *P. aeruginosa* was pathogen with the highest mortality despite adequate antibiotic therapy (16).

Similar to Orasch *et al*. report, respiratory signs of infection in our study were the predominant clinical evidence in patients with febrile neutropenia (17).

Starting early empiric antibiotic treatment after fever detection can decrease morbidity and mortality (6,7). Initial therapy in febrile neutropenic patients should cover prevalent pathogens. In our institute, antibiotic coverage generally consisted of monotherapy with a carbapenem or in some cases, combination of ceftazidime plus an aminoglycoside. These selections are compatible with recommendations of some reliable guidelines (8,9). Better coverage of Gram-positive microorganisms with administration of vancomycin should be limited to some specific situations such as IV catheter-related infections, clinical instability, and known colonization with *Methicillin-Resistant Staphylococcus aureus*(MRSA) bacteria. Because of the emergence of vancomycin-resistant organisms, the drug should be discontinued in 2-3 days if a resistant Gram-positive organism (e.g. MRSA) was not identified. Even in some studies, which had compared the empirical regimens with or without vancomycin as part of the initial empirical regimen, there was nosignificant reduction in either fever duration or overall mortality (18-20). In our cases, we observed excessive administration of vancomycin which was not compatible with guidelines' recommendations, and just one thirds of our patients received this drug appropriately. Common causes of irrational usage of vancomycin were selection of vancomycin in initial treatment without any indications and continuation of the drug without any proven evidence that could justify such treatment. The selection of initial antibiotic regimen, in addition of guideline's recommendation, should consider the type, frequency of occurrence, and antibiotic susceptibility pattern of bacterial isolates in any institute.

One of the limitations of our study was data being gathered from patients' medical records retrospectively; it was likely that this information might be incomplete; so we could not be certain about appropriate use of antibiotics. Likewise, we could not make conclusion accurately about response rate and the reason for initial selected regimen.

In conclusion, the mortality rate was low in our study; however infectious etiology was the most known cause of death that we observed. It was mentioned that the hospitalization period was directly related to the numbers of fever episodes, so it is necessary to determine not only the local profile of microbiologic pattern but also antibiotic sensitivities in febrile neutropenic patients following HSCT, and also to reassess response to antibiotic treatment.

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