Microbiologically documented infections following peripheral blood stem cell transplantation: single center experience

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ABSTRACT

This study was performed to assess the incidence of infectious complications in patients undergoing autologous and allogeneic hematopoietic stem cell transplantation (HSCT). The characteristics of microbiologically documented infections in 114 consecutive patients undergoing HSCT (84 autologous, 30 allogeneic) were analyzed. Conditioning and the pre-engraftment period until one month was defined as the early period; the post-engraftment period until one year was defined as the late period. All patients received antibiotic prophylaxis and hematopoietic growth factors during neutropenia. Febrile patients received imipenem-cilastatin or cefepime plus amikacin or ceftazidime plus amikacin. A total of 117 episodes with microbiologically documented infections were seen 90 of 114 patients and 79% of the patients experienced at least one febrile episode during their post-transplant course. Of these episodes, 69 (59%) were in the early period and 48 (41%) were in the late period. In the early period, 38.8% of causative organisms were gram-positive, 51.5% were gram-negative and 7.7% were fungi. The most common pathogens were coagulase-negative Staphylococcus (CoNS) and E. coli in the early period. In the late period, 44.6% of causative organisms were gram-positive, 44.6% were gram-negative and 6.8% were fungi. CoNS and E. coli were also the most commonly isolated agents in this period. Resistance to methicillin was detected in 47.4% of S. aureus and 86.5% of CoNS isolates. The isolation rate was in accordance with previous reports; similar percentages of gram-positive and gram-negative isolates were found in patients undergoing HSCT in both periods. However, a remarkably low rate of viridans streptococci and fungi were observed. The spectrum of pathogens detected in these cases serves as the basis for recommendations on the choice of empiric antimicrobial treatment regimens. Therefore, studies reporting local microbiological findings are necessary. We suggest that local microbiologic surveillance should be known before empiric antimicrobial therapy is started in each institution.

Key Words: Infection, Peripheral blood stem cell, Transplantation, Bacterial, Fungal.

ÖZET

Periferik kök hücre naklinde mikrobiyolojik kanıtlanmış infeksiyonlar: Tek merkez deneyimi

Bu çalışma otolog ve allogeneik kök hücre nakli yapılan hastalarda infeksiyöz komplikasyonları değerlendirmek için yapılmıştır. Kök hücre nakli yapılan 1/4 hasta (84 otolog, 30 allogeneik) incelendi. Hazırlama ve birinci ayı içine alan pre-engrafman dönemi erken dönem, birinci yıla kadar engrafman sonrası dönem ise geç dönem olarak tanımlandı. Tüm hastalar nötropenik dönemde antibiyotik profilaksisi ve büyüme faktörü aldılar. Ateşli hastalar imipenem-silastatin veya sefepim + amikasin yada seftazidim + amikasin aldılar. Yüzondört olgunun 90'ında 117 mikrobiyolojik tanımlanmış infeksiyon atağı izlendi. Nakil sonrası dönemde hastaların %79'u en az bir febril epizod gösterdi. Bunların 69 (%59)'u erken, 48 (%41)'i geç dönemde idi. Erken dönemde etken mikroorganizmaların %38.8'i gram-pozitif %51.5'i gram-negatif ve %7.7'si mantar idi. Erken dönemde en sık rastlanan patojenler koagülaz-negatif stafilokok (KNS) ve *E. coli* idi. Geç dönemde ise etken mikroorganizmaların %44.6'sı gram-pozitif, %44.6'sı gram-negatif ve %6.8'i mantardı. Bu dönemde de KNS ve *E. coli* en sık rastlanan mikroorganizmalardı. *S. aureus*'ta %47.4, KNS de ise %86.5 metisilin direnci saptandı.

Mikroorganizma izolasyon oranları daha önce bildirilenlerle benzerdir. Ancak viridans streptokok ve mantarlar nispeten düşük bulunmuştur. Bu olgulardaki etken spektrumun bilinmesi ampirik tedavi rejimlerinde antibiyotik seçiminde yol gösterici olmaktadır. Bu nedenle lokal sonuçların bildirimi önemlidir ve her kurumda ampirik antibiyotik başlamadan önce lokal mikrobiyolojik sürveyans sonuçlarının bilinmesi yararlı olur.

Anahtar Kelimeler: İnfeksiyon, Periferik kök hücre nakli, Bakteriyel, Fungal.

INTRODUCTION

Intensive chemotherapy with hematopoietic stem cell transplantation (HSCT) is increasingly used to treat several malignancies[1]. Defects in both humoral and cellular immunity are the strongest risk factor for infection in patients undergoing HSCT[2,3]. The risk factors may differ in different time periods. For example, in the early pre-engraftment period, neutropenia and mucositis are major risk factors and T-cell mediated immunodeficiency is much less important. Infectious complications are major causes of morbidity and mortality in these patients[4,5]. They have been largely described in patients with allogeneic HSCT[6]. Most reports describing infections following autologous HSCT include patients who received bone marrow as well as peripheral blood stem cells[7-9]. There is a substantial incidence of bacteremia after peripheral blood stem cell transplantation (PBSCT)[10,11]. Observational and descriptive studies are important because they show variation over time and provide clues about the probable etiology of infection in the early and late period. On the basis of reports of this type, local groups will be better prepared to decide on further antimicrobial combination, or monotherapy. Therefore, we retrospectively analyzed microbiologically defined infections including bacterial and fungal during the conditioning, transplantation, engraftment and post-engraftment period.

MATERIALS and METHODS

Patients and Methods

The transplanted population was between 12 years to 63 years of age. The underlying disease for transplantation was 46 (40.4%) lymphoproliferative disease, 25 (21.9%) acute leukemias, 16 (14%) multiple myeloma, 14 (12.3%) chronic myeloproliferative disease and 13 (11.4%) solid tumors. Between 1997 and 2003, 114 PBSCTs were performed, autologous and allogeneic transplants accounted for 73.7% (84 patients) and 26.3% (30 patients) of all procedures, respectively. All patients undergoing allogeneic transplantation

received continuous infusion of cyclosporine 5 mg/kg as prophylaxis for graft-versus-host disease (GVHD) from day -2 to day +3, then 3 mg/kg, IV, from day +4 to day +15, and then 2.75 mg/kg, IV, from +16 to day +35; doses were adjusted to maintain serum levels of 150-450 ng/mL. Therapy was continued to oral cyclosporine 5-10 mg/kg from day +36 to day +180. Allogeneic transplant recipients also received methotrexate (15 mg/m^2 intravenously on day +1 and 10 mg/m^2 intravenously on days +3, +6 and +11; the last dose was omitted for patients with severe mucositis). Patients with moderate or severe GVHD were treated with high-dose intravenous methylprednisolone (1 g/m^2/d). Haemopoiesis was stimulated with G-CSF given as a continuous infusion from day +1 after graft infusion until stable leukocyte engraftment. Granulocyte and platelet engraftment was accepted when the patients have neutrophil counts more than 0.5 x 10^9/L and platelet counts more than 20 x 10^9/L.

Antibiotic Use Policy and Other Preventive Measures

All patients received ciprofloxacin 500 mg/day from day -8 to engraftment, fluconazole 200 mg/day from day -8 to day +100 and acyclovir 1g/day from -8 to day +100 as prophylaxis. Trimethoprim-sulfamethoxazole (160/800 mg) is given twice a day from -8 to 0 and reinitiated upon engraftment until day +100. When a neutropenic patient (absolute neutrophil count < 500 neutrophils/mm^3 or trending down) became febrile, antibiotics were switched from prophylactic regimens to empiric therapeutic regimens. Antibiotic coverage generally consisted of monotherapy with carbapenems or combination therapy with cefepime plus an aminoglycoside. Vancomycin was used extensively in patients for persistent fevers, or when a gram-positive pathogen was isolated from the blood, and when a catheter-associated infection was suspected. Amphotericin B was further given on day 7 or 8 of fever. A Hickman-type intravenous catheter was used for intravenous access. Patients were nursed in a single room with restricted entry. Careful washing of the hands with antiseptic solutions were mandatory.

Definition of Infection and Data Collection

As baseline information, we recorded each patient's age, gender, underlying diseases, temperature, absolute neutrophil count, Karnofsky performance status and type of transplant on admission. Patients undergoing HSCT were evaluated daily until discharge and then monthly until post-transplant one year. In the event of febrile neutropenia or fever, patients were evaluated by physical examination and cultures from urine and suspected sites. Blood cultures were obtained through the two lumens of the catheter and a peripheral vein. This protocol was repeated daily if fever persisted and each time when there was a new febrile episode. Infection was defined as the presence of signs and/or symptoms of inflammation at anatomic sites and classified as microbiologically documented when pathogenic microorganisms were recovered. Patients with a clinical diagnosis of infection who had no microbiological documentation and with viral infection were not included to study. Standard definitions of bacteremia, sepsis and catheter-related infections were used[12-14]. For microbiological documentation, we required positive culture of a specimen from the site. At least two positive blood cultures were required to diagnose a coagulase-negative *Staphylococcus* (CoNS) bacteremia. Fungal infections were defined according to EORTC-MSG definitions[15].

Conditioning and the pre-engraftment period were defined as the early period; the post-engraftment period until one year was defined as the late period. Febrile neutropenia was defined as a neutrophil count less than 500/mm^3 and oral temperature greater than 38.5°C once or 38°C on two or more occasions in 24 h.

Specimen Handling

Before empiric treatment of antibiotics was initiated, at least three blood cultures were obtained through the two lumens of the catheter and a peripheral vein. In cases of fever or suspicion of infection, additional cultures were taken from blood, urine, sputum or bronchoalveolar lavage (BAL) and skin lesions.

Blood cultures were performed in an automated system (BacT/Alert; Organon, Durham, NC, USA). *Mycobacterium tuberculosis* and fungi were identified by inoculating the specimens into bottles with Lowenstein-Jensen medium or onto Sabouraud and/or micosel media plates, respectively. Candifast (International Microbio, Signes, France) was used for *Candida* typing. A preliminary examination of samples, sputum and BAL fluid was done through one Gram-stained smear and a 10% potassium hydroxide-stained smear. As specimens were obtained, they were inoculated onto blood agar, MacConkey agar, and Sabouraud and Lowenstein-Jensen media. Bacterial identification was performed by standard biochemical methods. Antimicrobial susceptibility of the isolates was tested by disc diffusion (Kirby-Bauer) method.

Statistical Analysis

Data were analyzed using an SPSS statistical package (SPSS, Chicago, IL, USA). The independent t-test or Mann-Whitney U test was used for the comparison of continuous variables between two groups, and datasets with more than two subgroups were compared by multivariate analysis. Categorical data analyzed using the Fisher exact test or a chi-square test. All p values are two-tailed. Significance indicated by a $p< 0.05$.

RESULTS

One-hundred-fourteen patients with hemato-oncological malignancies underwent PBSCT (84 autologous PBSCT, 30 allogeneic PBSCT) from 1997 to 2003. The median age of the patients was 38 years (range; 12-63 years). Patients' characteristics are shown in Table 1. Median follow up time was 332 days (range; 60-670 days) and median duration of neutropenia was 12 days (range; 4-35 days). The median number of days with fever was 3 (range; 0-23). Allo-patients had a longer median duration of fever than auto-patients [4 days (range; 0-23 days) vs. 3 days (range; 0-12 days), respectively; $p< 0.004$]. Characteristics of the episodes with microbiologically documented infections in early and late period are shown in Table 2.

A total of 117 episodes with microbiologically documented infections were seen in 90 of 114 (78.9%) patients from conditioning until post-transplantation one year. Of these episodes, 69 (59%) were diagnosed in the early period and 48 (41%) were in the late period. The episodes of infection were more frequent in early period than late period ($p= 0.05$). Pathogens isolated were a higher rate in allo-patients 93.3% (28/30) than auto-patients 73.8% (62/84) ($p= 0.035$). Gram-positive bacteria were isolated in 62.4% (73/117) of all documented infection episodes. The rate of gram-positive bacteria isolation were more frequent in autologous HSCT (44/67; 65.7%) than in allogeneic HSCT (29/50; 58%) ($p> 0.05$). CoNS were the most commonly isolated agents in all infection episodes (37/117, 31.6%). Gram-negative bacteria were isolated in 72.6% (85/117) of all documented infection episodes [allogeneic 96% (48/50) and autologous 55.2% (37/67), ($p= 0.0001$)]. *E. coli* was the most frequent gram-negative bacteria isolated in all episodes (39/117, 33.3%). There were 14 (12%) microbiologically defined fungal infections in all patients; 12 were *Candida albicans* (four urinary tract infection, four candidemia, two catheter related infections and two pneumonia), two were *Aspergillus fumigatus* (two pneumonia). There was no statistically significant difference in the incidence of fungal infections between al-

Table 1. Clinical characteristic of PBSCT patients

Characteristic	All patients (n= 114)	Patient group	
		Auto-patient (n= 84)	Allo-patient (n= 30)
Sex (male/female)	74/40	55/29	19/11
Median age (range)	38 (12-63)	54 (12-63)	34 (19-52)
Karnofsky index, median (range)	1 (0-2)	1 (0-2)	1 (0-1)
Diagnosis			
Lymphoproliferative disorders (n)	46	44	2
Acute leukemias (n)	25	12	13
Multiple myeloma (n)	16	15	1
Chronic myeloproliferative disorders (n)	14	0	14
Solid tumors (n)	13	12	1
Neutrophil engraftment, median day (range)	12 (4-35)	12 (4-24)	14 (8-35)
Status of primary diseases at the time of transplant			
Complete remission	68	44	24
Partial remission	32	30	2
Stable or progression	14	10	4
Acute GVHD			
None	3		3
Grade 1-2	21		21
Grade 3-4	6		6
Chronic GVHD			
Limited	8		8
Extensive	6		6

Table 2. Characteristics of the episodes with microbiologically documented infections in the early and late periods

	Early period		Late period	
	Auto-patient (n= 84)	Allo-patient (n= 30)	Auto-patient (n= 83)	Allo-patient (n= 23)
Microbiologically documented infections	43 (62.4%)	26 (37.6%)	24 (50%)	24 (50%)
Febrile days, median (range)	3 (0-12)	4 (0-23)	2 (0-4)	4 (2-8)

lo-patients and auto-patients [12% (6/50 episodes) vs. 11.9% (8/67 episodes), respectively]. *Mycobacterium tuberculosis* was isolated in a patient with auto-transplant.

Microbiologically Documented Infections in the Early Period

In the early period, 69 episodes with microbiologically documented infections were

seen 64 of 114 (56.1%) patients (26 allogeneic, 43 autologous PBSCT) (Table 3). There were significant differences in the number of microbiologically documented infection episodes between the autologous PBSCT and allogeneic PBSCT in the early period (26 episodes in 30 allogeneic vs. 43 episodes in 84 autologous PBSCT; p= 0.0005). According to sources of infections, 52.2% of microbiologically documented infections episodes (36/69) were bacteremia, 31.9% (22/69) was urinary infection, 21.7% (15/69) was pneumonia and 15.9% (11/69) was catheter-related infection. The incidence of bacteremia was higher than the other infections in multivariate analysis (p= 0.0002). Overall, gram-positive organisms accounted for 58% of the episodes, gram-negative organisms for 75.4%, and fungi for 13% and polymicrobial for 2.9%. All fungi were *C. albicans*. CoNS and *E. coli* were the predominant pathogen cultured in this period. Microbiologically documented infections are shown in Table 3 in the early period.

Microbiologically Documented Infections in the Late Period

In the late period, 48 episodes with microbiologically documented infections were seen 26 of 106 (24.5%) patients (24 allogeneic, 24 autologous PBSCT, Table 4). There were significant differences in the number of microbiologically documented infection episodes between the autologous PBSCT and al-

Table 3. Microbiologically documented infections in patients following PBSCT in the early period

		Patient group	
Type of infection	**All patients (n= 114)**	**Auto (n= 84)**	**Allo (n= 30)**
Microbiologically documented infections	69	43	26
Sources of infection			
Primary bacteremia	36	21	15
Urinary infection	22	10	12
Pulmonary infection	15	9	6
Catheter-related infection	11	9	2
Other infections	12	8	4
Type of organism			
Gram-positive organisms	40	27	13
CoNS	22	15	7
Staphylococcus aureus	6	5	1
Streptococcus pneumoniae	5	2	3
Other	7	5	2
Gram-negative organisms	52	23	29
Escherichia coli	27	11	16
Acinetobacter baumannii	4	2	2
Enterobacter cloacae	4	1	3
Other	17	9	8
Polymicrobial	2	1	1
Candida albicans	9	7	2

logeneic PBSCT in the late period (24 episodes in 23 allogeneic vs. 24 episodes in 83 autologous PBSCT; p< 0.0001). Twenty-two of 48 (45.8%) of the episodes were bacteremia, 33.3% urinary infection, 27.1% pneumonia and 16.7% catheter-related infection. The incidence of catheter-related infection was lower than the other infections in multivariate analysis (p= 0.001). Overall, gram-positive organisms accounted for 68.8% of the episodes, gram-negative organisms for 68.8% and polymicrobial isolates for 4.2%. Microbiologically documented agents are shown in Table 4. CoNS and *E. coli* were also the predominant pathogen cultured in this period. There were five microbiologically defined fungal in-

Table 4. Microbiologically documented infections in patients following PBSCT in the late period

		Patient group	
Type of infection	**All patients (n= 106)**	**Auto-patients (n= 83)**	**Allo-patients (n= 23)**
Microbiologically documented infections	48	24	24
Sources of infection			
Primary bacteremia	22	12	10
Urinary infection	16	5	11
Pulmonary infection	13	6	7
Catheter-related infection	8	3	5
Other infections	3	3	0
Type of organism			
Gram-positive organisms	33	17	16
CoNS	15	5	10
Staphylococcus aureus	13	11	2
Streptococcus pneumoniae	2	0	2
Other	3	1	2
Gram-negative organisms	33	14	19
Escherichia coli	12	4	8
Klebsiella pneumoniae	3	2	1
Haemophilus influenzae	3	2	1
Citrobacter spp.	3	0	3
Pseudomonas aeruginosa	2	1	1
Acinetobacter baumannii	2	1	1
Proteus spp.	2	1	1
Others	6	3	3
Polymicrobial	2	0	2
Fungus	5	1	4
Candida albicans	3	1	2
Aspergillus fumigatus	2	0	2
Mycobacterium tuberculosis	1	1	0

fections in the late period; three *C. albicans* and two *Aspergillus fumigatus*. In addition, *Mycobacterium tuberculosis* was isolated in the late period from one case that underwent autologous PBSCT.

Bacteremia

Fifty-eight episodes of bacteremia were diagnosed in all 117 episodes (49.6%); 36 (62.1%) episodes were in the early period, 22 (37.9%) episodes were in the late period (p= 0.018). In patients with autologous PBSCT, gram-positive and gram-negative organisms were isolated in 21 and 10 episodes of bacteria, respectively. The most common organisms isolated were CoNS (12 isolates) and *E. coli* (5 isolates). In patients with allogeneic PBSCT, gram-positive and gram-negative organisms were isolated in 14 and 9 episodes of bacteria, respectively. The most common organisms isolated were also CoNS (11 isolates) and *E. coli* (4 isolates). The characteristic of bacteremia was detailed in Table 5.

C. albicans was isolated from blood cultures in four episodes; two of which in patients with allogeneic PBSCT and two autologous PBSCT.

Catheter-Related Infections

Infections related to the intravascular central line were documented in 19 of 117 episodes (16.2%). Of these episodes, 57.9% (11/19) were in the early period (10 autologous PBSCT and 1 allogeneic PBSCT) and 42.1% (8/19) were in the late period (3 autologous PBSCT and 5 allogeneic PBSCT). There was no statistically significant difference between the early and late periods (p= 0.40). Overall, catheter-related infections were documented in 7 of 30 (23.3%) patients with allogeneic PBSCT and 12 of 84 (14.3%) patients with autologous PBSCT (p= 0.39). CoNS was the most common microorganism in catheter related infections both early and late periods.

Antibiotic Resistance of Microbiologically Documented Infection Episodes

Despite the use of ciprofloxacin for antimicrobial prophylaxis, 36 episodes related with *E. coli* were documented in all periods (9/36; 25% bacteremia). Twenty-six of 36 (77.8%) *E. coli* isolates were resistant to ciprofloxacin. Eight of 36 (22.5%) isolates were resistant to ampicillin. Imipenem and amikacin were the most active (100% susceptible) agents

Table 5. Description of episodes of bacteremia

Type of infection	All patients (n= 114)	Patient group: Early period (n= 114)	Patient group: Late period (n= 106)	p
Episodes of bacteremia	58	36	22	0.018
Gram-positive organisms	35	20	15	0.3
CoNS	23	14	9	
Staphylococcus aureus	7	1	6	
Others	5	5	0	
Gram-negative organisms	19	14	5	0.03
Escherichia coli	9	8	1	
Acinetobacter spp.	3	1	2	
Others	7	5	2	
Candida albicans	4	3	1	
Polymicrobial	4	2	2	

against all gram-negative organisms. Antimicrobial susceptibility testing for gram-positive isolates showed that methicillin resistance of *S. aureus* and CoNS isolates rates were 47.4% (9/19) and 86.5% (32/37), respectively.

Infection-Related Mortality

The overall mortality rate from any cause was 17.5% (20/114). Infection-related mortality rate was 5.3% (6/114). Infection was responsible for 30% (6/20) of all deaths. All of the patients who died because of infection were allo-patients. Three patients died because of *Acinetobacter baumannii* infections (two sepsis and one pneumonia) in the early period. Two patients died because of invasive pulmonary aspergillosis and one patient died due to sepsis with *Pseudomonas aeruginosa* in the late period.

DISCUSSION

Fifty-six percent (64/114) of the patients experienced at least one infectious episode during chemotherapy-induced neutropenia. However, when appropriate supportive care measures were applied the severity of these infections was moderate. In previous reports, microbiologically documented infections varied between 32.5% and 48%[16-21]. In this study, febrile episodes are more common in the early period compared to the late period (59% vs. 41%, respectively, p= 0.05). The majority of early infectious complications consisted of bacterial infections, with a significant difference in incidence between auto-patients and allo-patients, which was reflected in a tendency to more complications in the later group (p= 0.0006). In one-year period, there was also a statistically significant difference between groups (p= 0.0001).

Early studies show that gram-negative microorganisms were the most frequently isolated pathogens during the neutropenic period[22]. Since the 1980s, gram-positive isolates have become more frequent, presently accounting for 55-66% of bacteremia episodes in patients during febrile neutropenic period after transplantation[9,19,23,24]. Despite a reduction in gram-negative sepsis with the use of fluoroquinolone prophylaxis in the peritransplant setting, an increase has been observed in the incidence of infection with viridans streptococci and other gram-positive cocci. Gram-positive bacteria, especially CoNS and *S. aureus*, were the predominant pathogens cultured in cases of microbiologically documented infections[25,26]. Similarly, the EORTC Group showed an increase in gram-positive infections from 29% to 67% and decrease in gram-negatives from 71% to 31%[27]. However, this study demonstrates that infections are less likely to be caused by gram-positive organisms in the early period after PBSCT (58% gram-positive vs. 75.4% gram-negative). This can be explained by a high frequency urinary infection with gram-negative bacteria (especially, *E. coli*) in our patients.

CoNS and *S. aureus* were the most commonly isolated gram-positive organisms, comparable with the literature. As in previous reports, viridans streptococci are a major cause of bacteremia after transplantation, representing 15% to 44% of isolated pathogens[19,28,29]. We found a low incidence of viridans streptococci.

The high incidence of the late infections is concerning. There were 48 (45.3%) microbiologically documented infections, with a significant difference in incidence between auto-patients and allo-patients (p= 0.0001). There was a similar incidence of gram-negative and gram-positive microorganisms in this period. In addition, *Salmonella typhi* was documented in two patients and *Mycobacterium tuberculosis* was isolated in one case among 48 infection episodes. According to several series reported, the frequency of *M. tuberculosis* infections in HSCT recipients has varied from less than 0.1 to 5.5[30-34].

There were significant differences in the number of microbiologically documented infections between the early and late period (69 vs. 48; p= 0.05). Late febrile episodes are less common mainly because of the short period of neutropenia.

Traditionally, bloodstream infections in patients undergoing PBSCT are mainly thought to be complication of neutropenia. In our series, 58 episodes of bacteremia were diagnosed in study period. The incidence of bacteremia was found 30.8% in the early period, despite antimicrobial prophylaxis. Kolbe et al found a similar incidence of neutropenia-associated complications with a 39% incidence of bacteremia among 66 patients[10]. Bacteremia predominantly with gram-positive bacteria, especially CoNS was the most frequent infectious syndrome in these patients. This may be because of protracted and aggressive chemotherapy, prophylactic treatment with ciprofloxacin, and empiric treatment with antibiotic directed primarily against gram-negative microorganisms and disruption of gastrointestinal mucosa[35-42].

The incidence of infections caused by fungi in patients with PBSCT is approximately 7-25% and they have also been reported with increasing frequency, and are important contributors to morbidity and mortality in these patients[43-48]. In this study, the incidence of fungal infections was 12% in study period. Of 14 episodes with fungi, 9 were in the early period and 5 in the late period. Our results confirm the strong correlation between the incidence of invasive fungal infections and the duration of neutropenia. Despite the high predisposition to fungal infection induced by neutropenia, we observed nine (13%) invasive fungal infections with *C. albicans* within the first 30 days[47,48]. Antifungal prophylaxis with fluconazole has demonstrated efficacy in reducing the incidence of both colonization and infection with *Candida* species in PBSCT[49]. The spectrum of isolated fungal pathogens was not different between allo-patients and auto-patients. We did not encounter problems with fluconazole resistant *C. albicans*. It is curious that all cases of candidiasis were due to *C. albicans*, especially in a cohort of patients receiving fluconazole prophylaxis. Although the dose of 200 mg/day in all patients is low to prevent infection, the prolonged use of fluconazole may be associated with a shift to non-albicans species.

Methicillin-resistance of *S. aureus* and CoNS isolates varies between 20-66% and 40-85%, respectively[44,50]. In the present study, methicillin-resistance was detected in 86.5% of CoNS, but in 47.4% of *S. aureus* isolates. Methicillin-resistance in staphylococci was also very high in our general hospital and these endemic infections were not effectively controlled. Specific strategies to reduce the rate of nosocomial infections and antimicrobial resistance in this high-risk population must be evaluated.

Although quinolones have reduced the incidence of gram-negative bacteremia, they have not decreased the incidence of febrile episodes or the morbidity and mortality of infection[40,41]. Moreover, the extensive use of this class of antibiotics has exerted a strong selective pressure that contributed to the emergence of resistant gram-negative bacteria (especially *E. coli*). We have expressed concern regarding the emergence of quinolone resistance with its continued use as prophylaxis for patients with neutropenia. Because quinolone prophylaxis may provide only limited benefits to this patient population and may promote resistance, it remains uncertain whether quinolone prophylaxis should be routinely administered. Perhaps by stopping the present prophylactic management policy we can avoid selection of resistant gram-negative isolates in the future, which is a current problem in the developed word. In this study, because all gram-negative bacilli showed good sensitivity to imipenem, piperacillin-tazobactam (except *Pseudomonas aeruginosa*) and amikacin, empirical treatment of antibiotics against gram-negative microorganisms should include these antibiotics.

Despite the high response rate of infections to antimicrobial therapy, infections remain a predominant cause of death in pati-

ents undergoing PBSCT. Unlike previous reports, our data clearly show that infection-related mortality is very low (5.3%, 6 of 114). Empirical administration of broad-spectrum intravenous antibiotics at the onset of fever, whether a β-lactam or a carbapenem alone, or a combination of a β-lactam and aminoglycoside, have considerably reduced the morbidity and mortality of infection. In contrast to six infection related deaths in the allo-patients, none of the auto-patients with infections died. Among gram-negative pathogens, *Acinetobacter baumannii* had the highest associated mortality rate (3/6, 50%) followed by *Pseudomonas aeruginosa* (1/6, 16.7%). Therefore, empirical treatment of antibiotics against gram-negative microorganisms should be initiated because they are associated with a high risk of mortality. A 33.3% mortality rate of invasive aspergillosis was observed, similar to that reported in the series of auto-patients[51]. The therapy of invasive fungal infections is often unsuccessful, and fungal infections have been reported to have a mortality of > 90 allo-patients[28]. Similarly, two patients (100%) undergoing allogeneic PBSCT died because of invasive pulmonary aspergillosis in the late period. This can be explained by potentially impaired immunreconstitution and/or continued immunosuppressive therapy[19,52].

This report describes the routine work-up followed in our patients with febrile neutropenia and febrile but non-neutropenia during post-engraftment periods, including bacterial and fungal isolates. It is necessary to know what is happening worldwide, but it is more important to know what takes place in our patients and to accurately assess our own microbiological findings. Therefore, it is mandatory to obtain basal studies showing local ecological epidemiology. On the basis of reports of this type, local groups will be better prepared to decide on further antimicrobial, combination, or monotherapy.

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