

## Bloodstream infection in hematopoietic stem cell transplantation outpatients: risk factors for hospitalization and death

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### ABSTRACT

We described 235 bloodstream infection (BSI) episodes in 146 hematopoietic stem cell transplantation (HSCT) outpatients and evaluated risk factors for hospitalization and death. Records of outpatients presenting with positive blood cultures over a 5-year period (January 2005 to December 2008) were reviewed. Variables with  $p < 0.1$  in bivariate analysis were used in a regression logistic model. A total of 266 agents were identified, being 175 (66.7%) gram-negative, 80 (30.3%) gram-positive bacteria and 9 (3.4%) fungi. The most common underlying disease was acute leukemia 40 (27.4%), followed by lymphoma non-Hodgkin 26 (18%) and 87 patients (59.6%) were submitted to allogeneic hematopoietic stem cell transplant (HSCT). BSI episodes were more frequent during the first 100 days after transplantation (183 or 77.8%), and ninety-one (38.7%) episodes of BSI occurred up to the first 30 days. Hospitalization occurred in 26% of the episodes and death in 10% of cases. Only autologous HSCT was protector for hospitalization. Although, central venous catheter (CVC) withdrawal and the Multinational Association of Supportive Care in Cancer (MASCC) score up to 21 points were protector factors for death in the bivariate analysis, only MASCC remained as protector.

**KEYWORDS:** Bacteremia. Hematopoietic stem cell transplantation. Outpatients. Outcome. Resistance.

### INTRODUCTION

Bloodstream infection (BSI) is the most relevant infections in patients undergoing hematopoietic stem cell transplant (HSCT) with high morbidity and mortality<sup>1</sup>. Until recently, gram-positive bacteria (GPB) were the most common agents causing BSI in these patients; moreover, in the last years there has been an increase of gram-negative bacteria (GNB) in several hospitals<sup>2</sup>.

Despite the increase in the number of allogeneic (allo) HSCT patients with early discharge and outpatient autologous (auto) transplantation programs; there is a lack of studies evaluating the safety of treating infections in HSCT outpatients.

The objective of this study was to evaluate the etiological agents causing BSI in HSCT outpatients as well as the risk factors associated with hospitalization and 30-day mortality.

### METHODS

The Hospital das Clínicas is a teaching hospital with 2,200-beds and is a reference

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center for auto and allo- HSCT in Brazil. The outpatient unit is open from 7 am to 7 pm, every day of the week, including weekends. All patients submitted to HSCT were hospitalized at the time of transplantation.

Records of outpatients presenting with positive blood cultures over a 5-year period (January 2005 to December 2008) were reviewed. This study was approved by the Ethics Committee of the Hospital das Clínicas of University of Sao Paulo.

The BSI definition used were patients with positive blood culture collected through the central venous catheter (CVC) or a peripheral access during a period in which patients had fever and physicians had described antibiotics. The end points evaluated were hospitalization and 30-day mortality BSI onset. Clinical and demographic variables at the time of BSI, such as gender, age, underlying disease, length of hospitalization, type of HSCT, CVC (type and withdrawal), the presence of mucositis or graft-versus-host disease (GVHD) and Multinational Association of Supportive Care in Cancer (MASCC) risk index score were evaluated. Hospitalizations depended on the clinical status, and when possible, the treatment was administered in the outpatient unit in which blood cultures were indicated in the presence of fever, hemodynamic instability or any infectious symptoms.

Microorganism identification and antimicrobial susceptibility test was performed using Vitek® (laboratory BioMérieux) and disk diffusion test followed the updated recommendations of CLSI (Clinical and Laboratory Standards Institute).

Data were analyzed using the softwares Epi Info version 3.5.1 and STATA. The two-tailed Fisher's exact test was used for categorical variables and the Wilcoxon test was used for continuous variables. Logistic regression models were developed to identify factors associated with hospitalization within 21 days onset of BSI and 30-day mortality onset BSI. All non-overlapping variables with  $p < 0.1$  on bivariate analysis were entered into a stepwise forward model. A  $p$ -value  $< 0.05$  was considered statistically significant.

## RESULTS

A total of 743 HSCT outpatients were evaluated during the study period and the records of 146 of them were analyzed. A total of 235 BSI episodes were identified among the 146 patients evaluated, being 207 (88%) monomicrobial and 28 (12%) polymicrobial. The hospitalization occurred in 61 (26%) episodes, the more frequent reason was septic shock, 18/61 (31%) (Table 1). A total of 266 agents were isolated, being 175 (66.7%) gram-negative bacteria (GNB),

80 (30.3%) gram-positive bacteria (GPB) and 9 (3.4%) fungi (Table 1).

Resistance to cefepime in *P. aeruginosa* was identified in only 2/15 (13%) of the isolated agents, to imipenem in 2/14 (14%), and to meropenem in 3/10 (27%). Among *Enterobacter cloacae*, resistance to cefepime occurred in 3/11 (27%) cases, no carbapenem resistance was identified. Among *Acinetobacter spp*, resistance to cefepime occurred in 3/24 (14%) and resistance to imipenem in 2/24 (8%). Resistance to levofloxacin occurred in 1/39 (3%) and to trimethoprim-sulfamethoxazole in 3/39 (8%) of *S. maltophilia* isolates. Resistance to vancomycin was identified in 7/9 (78%) of *E. faecium* BSI. Gram-negative bacteria accounted for 72% of bloodstream infections in allogeneic transplants and 62% of autologous ones ( $p=0.12$ ). The mean time between transplantation and BSI was higher among allogeneic than autologous HSCT patients (145.5 and 44.1 days, respectively), probably because allogeneic patients remain hospitalized for longer periods after transplantation and at higher risk of infection after discharge. Death in 30 days were 8.5% in autologous and 15.2% in allogeneic HSCT ( $p=0.17$ ). Median time between positive culture and death in days were 56 days in gram-negative and 27 days in gram-positive infections.

The bivariate analysis showed that previous use of levofloxacin, MASCC score higher than 21 and autologous (auto)-HSCT were protector factors and neutropenia was a risk factor for hospitalization. Moreover, only auto-HSCT remained as protector in the multivariate analysis (Table 2). The bivariate analysis showed that the CVC withdrawal, and MASCC higher than 21 points were protector factors for death (Table 2). Moreover, only MASCC score remained as protector (Table 2).

## DISCUSSION

We observed a high proportion of GNB-BSI in our HSCT outpatient unit. The predominance of GNB has been reported by Brazilian studies that evaluated HSCT inpatients<sup>3</sup>. In our casuistic, BSI episodes occurred mainly in the first 100 days after the transplantation, similarly to other studies in the literature<sup>1,2</sup> and *S. maltophilia* was the most frequent agent in both monomicrobial and polymicrobial BSI. In general, this agent causes outbreaks in BMT settings<sup>4</sup>. Moreover, as in our hospital, a recent study has shown that *S. maltophilia* and *P. aeruginosa* were the most commonly isolated GNB in HSCT patients<sup>5</sup>. We observed a high frequency of infection caused by waterborne bacteria (18%). Infection by these agents is rare even in neutropenic patients<sup>6</sup>. However, our service recommends the protection of the CVC's lumen with a

**Table 1** - Clinical characteristic of 235 bloodstream infection episodes in 146 HSCT outpatients in Hospital das Clinicas, Brazil

Characteristic	N (%)	Characteristic	N (%)
<b>Mucositis</b>	63 (25)	<i>Micrococcus spp</i>	9 (3%)
<b>Grade of mucositis (%)</b>		<i>Staphylococcus aureus</i>	7 (3%)
I	25 (48)	<i>Streptococcus pneumoniae</i>	4 (1%)
II	15 (29)	Most frequent Gram-negative bacteria	175 (67)
III	10 (19)	<i>Stenotrophomonas maltophilia</i>	39 (15%)
IV	2 (4)	<i>Acinetobacter spp</i>	24 (9%)
<b>GVHD (%)</b>		<i>Pseudomonas aeruginosa</i>	15 (6%)
Skin	58 (70)	<i>Burkholderia cepacia</i>	13 (5%)
Gut	48 (60)	<i>Klebsiella spp</i>	12 (4%)
Lung	5 (6)	<i>Enterobacter cloacae</i>	11 (4%)
<b>Grade of GVHD (%)</b>		<i>Serratia marcescens</i>	9 (3%)
I	12 (44)	<i>Agrobacterium spp</i>	8 (3%)
II	4 (15)	Fungi	9 (3)
III	8 (30)	<i>Candida spp</i>	6 (2%)
IV	3 (11)	<b>Cultures (%)</b>	
Severe neutropenia (<100 cells/mm <sup>3</sup> ) (%)	63 (28)	Monomicrobial	207 (88)
<b>Neutropenia</b>		Polymicrobial	28 (12)
ANC, median (range) (cells/mm <sup>3</sup> )	2,300 (0-37,600)	<b>Hospitalization up to 21 days after culture (%)</b>	61 (26)
Length of neutropenia, median (range) (days)	6 (1-30)	<b>Hospitalization reasons (%)</b>	
<b>Immune recovery after transplant (%)</b>		infection complications	8 (14)
Until 30 days after BMT	91 (39)	Sepsis	12 (14)
30 days to 100 days after BMT	92 (39)	Sepsis shock	18 (31)
After 30 days of BMT	52 (22)	Others	20
<b>CVC (%)</b>		<b>New infection (%)</b>	84 (36)
Non-tunneled	2 (1)	<b>Length of positive culture until hospitalization, media (range) (days)</b>	3.3 (0-21)
Tunneled	191 (84)	<b>MASCC, median (range)</b>	22 (8-26)
Totally implantable	9 (4)	<b>Death up to 30 days (%)</b>	22 (10)
Absence	25 (11)	<b>Time between positive culture and death, median (range) (days)</b>	42 (0-995)
<b>CVC infection (%)</b>	19 (9)		
<b>CVC withdrawal (%)</b>	66 (33)		
<b>Previous usage of antimicrobials (%)</b>	190 (81)		
Until 30 days before collection (%)	187 (80)		
On time of collection (%)	139 (60)		
Cefepime	113 (58)		
Levofloxacin	52 (27)		
Meropenem	105 (54)		
Teicoplanin	136 (70)		
<b>BSI agents (%)</b>			
Most frequent Gram-positive bacteria	80 (30)		
<i>Staphylococcus coagulase negative</i>	31 (12%)		
<i>Enterococcus faecium</i>	9 (3%)		

CVC: central venous catheter; MASCC: Multinational Association for Supportive Care in Cancer Risk Index, GVHD: Graft-Versus-Host Disease. Others BSI agents: *Leuconostoc spp*, *Bacillus spp*, *Sphingomonas paucimobilis*, *Chryseobacterium spp*, *E.coli*, *Leuconostoc spp*, *Aeromonas spp*. Other: myelodysplastic syndrome (25%), Fanconi anemia (25%), myelofibrosis (12.5%), Ewing' sarcoma (6.25%), Krabbe disease (6.25%), germinal cells tumor (6.25%), adrenoleukodystrophy (6.25%), seminoma (6.25%).

plastic dressing to prevent exposure to tap water, a potential source of waterborne agents but it was not possible to assess patients' compliance with this recommendation. Thus, inappropriate care of CVC at home during baths might explain this finding<sup>7</sup>.

In our study the 30-day mortality onset BSI was 10% and hospitalization occurred in 26% of patients. Moreover, the multivariate analysis showed that autologous HSCT was the only independent protector factor for hospitalization.

MASCC score and CVC withdrawal were protective factors for death in the bivariate analysis. In addition, only MASCC score higher than 21, remained as protector factor in the multivariate analysis. Unfortunately, in our study the catheter removal was not carried out as recommended in the literature because of the difficulty of venous access.

In the literature the presence of infection is a major cause of death in HSCT patients<sup>1</sup>. Ortega et al showed that 10% of HSCT inpatients with infection evolved to death<sup>6</sup>.

**Table 2** - Risk factors for hospitalization and death in 30 days among 235 episodes of BSI in HSCT outpatients patients.

Variables	Hospitalization N (%)		Bivariate Analysis RR (CI 95%)	P- value	Multivariate analysis OR (CI 95%)	p-value
	No	Yes				
Previous usage of levofloxacin (%)	44 (85)	8 (16)	0.82 (0.70-0.97)	0.030	0.56 (0.23-1.40)	0.22
Autologous BMT (%)	74 (88)	10 (12)	0.75 (0.65-0.86)	0.0001	0.23 (0.11-0.68)	0.005
Bacteremia due to gram-positive* (%)	46 (66)	24 (34)	1.17 (0.97-1.41)	0.050	1.16 (0.51-2.65)	0.71
Mucositis (%)	43 (68)	20 (32)	1.11 (0.91-1.33)	0.16		
Severe neutropenia (%)	38 (60)	25 (40)	1.28 (1.02-1.60)	0.007	1.67 (0.71-3.92)	0.24
CVC withdrawn (%)	52 (79)	14 (21)	0.91 (0.77-1.07)	0.19		
Length of BMT until bacteremia, median (range) (days)	174	61	60 (6-746)	0.21		
ANC. median (range) cels/mm <sup>3</sup>	164	61	220 (0-23,400)	0.12		
MASCC. median	174	59	18 (8-26)	< 0.0001		
MASCC score higher than 21 (%)	101 (82)	23 (18)	0.82 (0.70-0.96)	0.008	0.55 (0.27-1.13)	0.10
	Death N (%)		Bivariate Analysis RR (CI 95%)	P- value	Multivariate analysis OR (CI 95%)	p-value
	Yes	No				
Age. (median)	32	38		0.29		
Previous usage of levofloxacin (%)	26 (93)	2 (7)	0.89 (0.77-1.03)	0.17		
Autologous BMT (%)	54 (92)	5 (8)	0.93 (0.86-1.01)	0.17	3.73 (0.90-15.28)	0.06
Bacteremia Gram- positive* (%)	39 (81)	9(19)	1.11 (0.95-1.29)	0.10		
Bacteremia Gram-negative (%)	81(90)	19 (9)	0.91 (0.79-1.0)	0.15		
Fungi	4 (100)	0	0.87 (0.81-0.92)	0.58		
Mucositis (%)	38 (83)	8 (17)	1.02 (0.92-1.12)	0.41		
GVHD (%)	34 (83)	7(17)	1.07 (0.92-1.25)	0.21		
Severe neutropenia (%)	32 (82)	7 (18)	1.06 (0.90-1.23)	0.28		
CVC withdrawal (%)	34 (97)	1 (3)	0.87 (0.79-0.97)	0.050	40 (0.07-2.38)	0.32
ANC, median (range) (cels/mm <sup>3</sup> )	2,350	1,250		0.54		
Duration of neutropenia. (days, mean)	3.4	4.5				0.43
MASCC. median	21	16		0.0001	0.78 (0.68-0.90)	0.001
MASCC score higher than 21 (%) **	127 (88)	18 (12)	0.90 (0.83-1.02)	0.07		
Shock	11 (27)	29 (73)	1.70 (0.43-6.69)	0.34		

CVC: central venous catheter; MASCC: Multinational Association for Supportive Care in Cancer Risk Index. GVHD: Graft-Versus-Host Disease

Therefore, the proportion of deaths in the present study in outpatients was similar to that described in BSI HSCT inpatients<sup>8</sup>. Vancomycin-resistant enterococcus (VRE) mortality in HSCT patients ranges from 7% to 34%<sup>9</sup> similar to our findings. In contrast, authors have reported a high mortality of BSI caused by carbapenem-resistant GNB in HSCT<sup>10</sup>.

In conclusion, GNB were the most frequent agents causing BSI in HSCT outpatients in our hospital; hospitalization rate was low and auto-HSCT was a protector

factor for hospitalization and the MASCC score higher than 21 points for 30-day mortality.

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## CONFLICT OF INTERESTS

None to declare.

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