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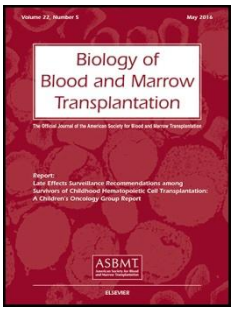

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PII: S1083-8791(17)30659-6
DOI: http://dx.doi.org/doi: 10.1016/j.bbmt.2017.08.024
Reference: YBBMT 54776

To appear in: *Biology of Blood and Marrow Transplantation*

Received date: 12-7-2017
Accepted date: 22-8-2017

Please cite this article as: Malgorzata Mikulska, Anna Maria Raiola, Federica Galaverna, Elisa Balletto, Maria Lucia Borghesi, Riccardo Varaldo, Francesca Gualandi, Livia Giannoni, Giordana Pastori, Daniele Roberto Giacobbe, Alessio Signori, Valerio Del Bono, Claudio Viscoli, Andrea Bacigalupo, Emanuele Angelucci, Pre-Engraftment Bloodstream Infections after Allogeneic Hematopoietic Cell Transplantation: the Impact of T-Repleted Transplant From Haploidentical Donors., *Biology of Blood and Marrow Transplantation* (2017), http://dx.doi.org/doi: 10.1016/j.bbmt.2017.08.024.

Title page

Title

Pre-engraftment bloodstream infections after allogeneic hematopoietic cell transplantation: the impact of T-repleted transplant from haploidentical donors.

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Short title

Pre-engraftment bloodstream infection after allogeneic HCT

Financial disclosure statement:

All the authors: none to declare.

Key words: bloodstream infection, sepsis, neutropenia, haploidentical, multidrug resistant (MDR) bacteria.

Highlights

- **Pre-engraftment bloodstream infections (BSI) affected 30% of allogenic HCT recipients**
- **The risk was the highest in case of T-repleted haploidentical transplants**
- **Gram-negative BSI, particularly if carbapenem-resistant, had negative impact on survival**

Abstract

Bloodstream infections (BSI) are frequent and important infectious complications after hematopoietic cell transplantation (HCT). The aim of this study was to analyze the incidence, risk factors and outcome of pre-engraftment BSI after allogeneic HCT.

A retrospective analysis of data from 553 consecutive patients transplanted in years 2010-2016 was performed. Sixty percent of patients received T-repleted unmanipulated haploidentical bone marrow with high dose post-transplant cyclophosphamide.

BSI rate was 30%; among isolated 213 pathogens, 54% were Gram-positive, 43% Gram-negative and 3% fungi. Independent risk factors for pre-engraftment BSI were transplant from haploidentical donor or from cord blood ($p<0.001$), active disease ($p=0.002$), age ($p=0.04$) and myeloproliferative disorders or aplastic anemia ($p<0.001$). Transplant from the haploidentical donor was an independent risk factor for both Gram-positive and Gram-negative BSI. The 7-day mortality after any BSI was 5% (n=9/178), and in multivariate analysis, BSI etiology was the only risk factor, with increased mortality in case of carbapenem-resistant Gram-negatives ($p<0.001$). Non-relapse mortality at day 60 after HCT was 3.8% (21/553); independent predictors were active disease ($p=0.045$), year of HCT ($p=0.027$), non-engraftment ($p=0.001$) and pre-engraftment BSI ($p<0.001$), with significantly higher risk in case of BSI due to Gram-negatives compared to Gram-positives, and BSI due to carbapenem-resistant Gram-negatives compared to susceptible ones.

Pre-engraftment BSI is a frequent complication after transplant from haploidentical donor or cord blood. Since the negative impact of pre-engraftment BSI on 60-day non-relapse mortality was mainly caused by carbapenem-resistant Gram negatives, particular attention should be given to appropriate empirical therapy and management of patients with high risk of Gram-negative BSI.

Introduction

Bloodstream infections (BSI) are an important complication in hematopoietic cell transplantation (HCT) recipients, particularly during the pre-engraftment neutropenia.[1-3] BSI affects from 16% to 40% patients,[1-8] with an associated mortality ranging from less than 5%, in case of Gram-positive bacteria, to up to 40% in case of multidrug resistant (MDR) *P. aeruginosa* and 64% in MDR *Klebsiella pneumoniae* infections in allogeneic HCT patients.[1, 3, 9, 10] In order to reduce negative outcomes of BSI, the knowledge of the current epidemiology is fundamental for deciding the most appropriate protocols of empirical therapy at every site.[11]

Few studies identified specific risk factors for pre-engraftment BSI in HCT, including the duration of neutropenia, severity of mucosal damage, type of conditioning regimen, source of stem cells, age, advanced or active underlying disease and some types of leukemia, such as chronic myelogenous leukemia.[4, 9] Little is known about specific risk factors for Gram-positive or Gram-negative BSI.

The main obstacles to successful allogeneic transplantation are the lack of matched sibling donor and the long time needed for searching in the registries and obtaining hematopoietic cells from matched unrelated donors. In fact, it has been estimated that at least 50% of patients with leukemia do not find a suitable unrelated donor in time.[12, 13] Although cord blood transplant (CBT) offers higher probability of finding a hematopoietic cell source and rapid availability of stocked units, the main limitations of choosing this cell source include low cell dose for adults and possible high risk of infectious complications.[14] Today, T-repleted haploidentical transplant with high dose post-transplant cyclophosphamide (PT-CY) represents a valid alternative for patients with hematological malignancies who do not have an HLA matched related donor.[15] Initially, non myeloablative conditioning regimens were used,[16] subsequently followed by protocols with myeloablative regimens.[17] The incidence and outcome of infections associated with this protocol remains to be determined.

The aim of this study was to analyze the incidence, risk factors and outcome of pre-engraftment BSI after allogeneic HCT, with particular attention to patients receiving a T-repleted unmanipulated transplant from haploidentical donors with high dose PT-CY.

Materials and methods

Patients and data

A retrospective analysis of 553 consecutive patients who underwent allogeneic HCT between 01/01/2010 and 30/04/2016 in S. Martino Hospital in Genoa, Italy was performed. All patients signed written informed consent for anonymous data collection before the transplant procedure according to EBMT and JACIE standards.

The collected information included age, sex, diagnosis, disease status at HCT, type of conditioning, type of donor, date of transplantation, day of engraftment, presence of pre-engraftment BSI, isolated pathogen, overall survival and cause of death. Data on all episodes of BSI occurring between onset of conditioning and engraftment, and on antibiotic susceptibility were obtained from the electronic hospital records of the Microbiology Service and cross-checked with patients' charts. BSI episodes occurring during neutropenia beyond the day 50 post-HSCT or after the day of the second HCT were excluded.

Definitions

In case of common skin contaminants, BSI was diagnosed if at least 2 consecutive blood cultures resulted positive for the same species. BSI was considered polymicrobial if 2 or more pathogens were isolated in a single blood culture.

Neutropenia was defined as an absolute neutrophil count below 0.5 x 10^9/L. Engraftment was defined as the first of 3 consecutive days of absolute neutrophil count of 0.5 x 10^9/L or greater.

The underlying diseases were divided into 5 groups: 1) acute myeloproliferative diseases, such as acute myeloid leukemia and myelodysplastic syndrome, 2) acute lymphoproliferative diseases, such as acute lymphoblastic leukemia (ALL) and aggressive non Hodgkin lymphomas that received

chemotherapy similar to LLA, 3) chronic lymphoproliferative diseases (LPD) such as chronic lymphocytic leukemia, multiple myeloma, other lymphomas, 4) chronic myeloproliferative diseases (MPD) such as chronic myeloid leukemia or primary myelofibrosis, and, 5) aplastic anemia or other immune-mediated diseases.

In patients with leukemia, the underlying disease was defined as active at transplant if more than 5% blasts were present in bone marrow [18]. In patients with lymphoproliferative disorders, the disease was defined as active according to CT or PET scan results. In all other cases the disease was defined as not active. For the analyses, patients with aplastic anemia were included in not active disease group.

Non relapse mortality (NRM) was defined as death due to any cause other than relapse of progression of the underlying disease.

Donors were divided into 4 groups: 1) matched related (MRD), 2) matched unrelated or related with 1 antigen mismatch (MUD/MMR), 3) cord blood and, 4) HLA-haploidentical related. Since 2014, CBT was chosen only if a haploidentical donor was unavailable.

Transplant-related procedures

Transplants were performed as reported previously.[19-21] Standard definitions of condition regimens were used.[17] The choice of the conditioning regimen was based on underlying disease, patient's age, and pre-existing comorbidities. Myeloablative conditioning regimens consisted either of total body irradiation (TBI) with 200 Gy twice daily for 3 days or 330 Gy for 3 days, associated with fludarabine or cyclophosphamide, or 3 doses of busulfan with thiotepa and fludarabine [17]. All other conditioning regimens were regarded as of reduced intensity. [17, 19]

GvHD prophylaxis differed according to donor. It consisted of cyclosporine A (CsA) and methotrexate for MRD recipients, anti-thymocyte globulin (ATG) was added in case of MUD/MMR. All CBT recipients received CsA, mycophenolate mofetil (MMF) and ATG. In case of haploidentical donors, post-transplant cyclophosphamide 50 mg/kg on days +3 and +5, CsA and MMF were administered. [17, 19]

Infection prophylaxis, monitoring and treatment

All patients received antibacterial prophylaxis with levofloxacin 500 mg/day from the onset of conditioning until engraftment, except for those colonized with MDR Gram-negatives. Prophylaxis, monitoring and treatment of fungal and viral infections were performed as previously reported.[21, 22] A single dose of 200mg of rituximab was administered as PTLD prophylaxis in case of GvHD prophylaxis which included ATG. [21] All patients were fitted with tunneled CVC and its management policy did not change overtime. Surveillance cultures were performed at admission to the HCT unit and then weekly.

In case of fever or any other signs or symptoms of infection two blood culture sets were drawn and antibiotic treatment was started. Other diagnostic procedures were performed according to clinical presentation. First choice empirical therapy was piperacillin/tazobactam, with vancomycin added as recommended by guidelines.[11, 23] Second choice empirical therapy was meropenem and vancomycin and it was prescribed in case of severe clinical presentation, or previous infection or current colonization with piperacillin/tazobactam-resistant Gram-negative bacteria. In patients colonized or previously infected with MDR Gram-negative pathogens, the empirical therapy was designed to target such a strain. De-escalation strategy was gradually introduced since 2011.[11]

Statistical analysis

Categorical variables were reported as numbers and percentages and continuous as median and interquartile range (IQR). For description of cohort characteristics and univariate analysis for 7-day mortality, they were compared with, respectively, chi-square test with Yeats' correction or the Fisher's exact and the Mann-Whitney U test. Age was reported in tercils for analyses on the whole patient population, and as a continuous variable for the subgroup analysis of patients with BSI.

Cumulative incidence of BSI according to the different types of donor was estimated with Aalen-Johansen method, with engraftment, death or second HCT as competing events. [24] Survivors who did not engraft and did not receive a second HCT were censored at day 50 after transplant.

The risk factors for pre-engraftment BSI were established in univariate and multivariate stepwise backward Cox regression models assessing the cause-specific hazard ratio (HR) for developing BSI (with time to any BSI, time to Gram-positive BSI, or time to Gram-negative BSI considered as the measured outcome in three different models). For these analyses, patients were censored at time of engraftment, the second transplant or death. If none of them occurred, patients were followed until day + 50 after transplantation.

In the subgroup of patients developing BSI, the impact of variables on 7-day and 30-day post-BSI mortality was assessed in a multivariate logistic stepwise backward regression model. For this analysis of survival after each BSI episode, multiple species BSI episode was defined as more than a single positive blood culture within 7 days, and the outcome at the 7^{th} and 30^{th} day after isolation of the last pathogen was considered.

The predictors of non-relapse mortality (NRM) at day 60 after transplant were analyzed in the entire cohort with univariate and multivariate stepwise backward Cox regression models. In both univariate and multivariate Cox regression models for NRM, development of BSI and engraftment were considered as time-dependent factors.

In all the multivariate analyses, variables with $p \leq 0.2$ in univariate models were included. All p values are two-sided, and p values < 0.05 were considered statistically significant. The cumulative incidence of BSI was calculated using R Statistical Software version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria). All the other analyses were performed using SPSS statistical package, version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Patients' characteristics and differences based on donor type

The characteristics, together with the outcome data on engraftment, of 553 patients included in the study are reported in Table 1.

During the study years, there was a significant shift in the use of different donor types: cord blood transplant decreased from 10% in years 2010-2012 to 1% in 2013-2016, while transplants from haploidentical donors increased from 42% to 76%, respectively. Among baseline characteristics, there were statistically significant differences for 4 donor types (Table 1).

Among 39 patients (7%) who did not achieve engraftment, 7 underwent a second HCT (in median 43 days after the first HCT), 14 were censored at the day +50 and were alive at day +60, while 18 died before achieving engraftment, in median 18 days after HCT (range: 6-54).

Incidence and timing of BSI

Among 553 patients, 166 (30%) developed at least one episode of BSI. The median time to the first BSI was 8 days after transplant, ranging from 7 days before to 45 after, and 71% of first BSI episodes developed within the day 10 days after HCT.

There was a significant difference in the median timing of the first BSI from the day of transplant according to the type of donor: 3 days for matched related, 5 for matched unrelated or mismatched related, 3.5 for CBT and 9 for haploidentical (p=0.014) (Table 1). Sex, age, type and phase of the underlying disease and conditioning regimen did not influence the time to the first BSI (data not shown). The cumulative incidence of BSI according to the donor is shown in figure 1. Taking into account that for all the types of donor the same proportion of recipients achieved engraftment between the day 10 and 20 after HCT, it is worth noting that the cumulative incidence of first BSI seemed to further increase after day 10 from HCT only in case of transplant from a haploidentical donor (Figure 1).

BSI etiology and antimicrobial resistance

Among 166 patients with BSI, 136 (24.5%) developed a single BSI, 22 (4%) two episodes and 8 (1.4%) 3 episodes of BSI, accounting for a total of 204 BSIs. Among single-agent BSI, 105 (51%) were caused by Gram-positives, 86 (42%) by Gram-negative rods and 6 (3%) by fungi; 8 (4%) were polymicrobial.

A total of 213 pathogens were isolated: 54% Gram positives (staphylococci 25%, enterococci 15%, viridans streptococci 14%), 43% Gram negatives and 3% fungi. The detailed etiology is reported in Table 2.

The only statistically significant difference in the etiology of bacterial BSI based on the type of donor consisted of viridans streptococci being more frequent after haploidentical donor transplant compared to other donor types (respectively, 18% of all isolates vs. 4%, $p < 0.019$).

Overall, 42% of Gram-negatives were resistant 3rd generation cephalosporins, 33% to piperacillin-tazobactam and 12% to carbapenems (Table 2).

Risk factors for BSI: any BSI, BSI due to Gram-positives and BSI due to Gram-negatives

The results of the univariate analysis of risk factors due to any BSI, and multivariate analyses of risk factors for any BSI, Gram-positive BSI and Gram-negative BSI are reported in Table 3.

Briefly, in univariate analysis, the risk of BSI was increased in case of older patients, myeloproliferative disorders or aplastic anemia, active disease at transplant, reduced intensity conditioning and transplant from donors other than MRD. The multivariate analysis confirmed the role of all these factors except for conditioning regimen. The risk of BSI was over 3.5 times higher in case of aplastic anemia, CBT and haploidentical donor.

BSI due to Gram-positive bacteria developed in 105 (19%) of patients. In multivariate analysis, reduced intensity conditioning regimen, CBT and transplant from a haploidentical donor were independent risk factors.

BSI due to Gram-negative bacteria developed in 83 (15%) of patients. The multivariate analysis confirmed an increased risk in case of older age and transplant from MUD/MMR or haploidentical donor.

Mortality after BSI

The overall mortality at day 7 after the onset of the first BSI was 3% (5/166). In all 5 patients infection was caused by a Gram-negative rod, which was carbapenem-resistant in 3 cases. The mortality at day +14 after BSI was the same as at day +7, whereas mortality at 30 days after the first BSI was 7% (12/166).

Multiple-species BSI (that is different species isolated within 7 days) occurred in 26 of 204 BSI. As a consequence, for the analyses of the influence of etiology on mortality, 178 separate BSI episodes in 166 patients were considered. The overall mortality at day 7 and 30 after each of 178 BSI episodes was, respectively, 5% (n=9) and 8% (n=15), and is reported according to the causing pathogen in Table 4. Briefly, no patient with a BSI caused only by Gram-positives died within 7 days from BSI. The mortality was 6% in case of single species Gram-negative BSI, and approximately 20% in case multiple-species episodes containing Gram-negatives.

The mortality was similar after BSI caused by Gram-negatives susceptible to both piperacillin/tazobactam and carbapenems (2/56, 4%) and those resistant to piperacillin/tazobactam but susceptible to carbapenems (1/21, 5%), but it was much higher in case of BSI episodes caused by a carbapenem-resistant Gram-negative (6/11, 55%). In 5 cases in which previous MDR infection or colonization had been known before BSI episode, empirical therapy targeting the MDR strain was provided and 3 patients survived. In 6 BSI episodes caused by a carbapenem-resistant strain, the appropriate therapy was provided after the results of susceptibility testing, and 2 patients survived.

These 9 episodes of BSI which resulted in patients' death with 7 from BSI occurred in median 8 day after HCT (range: 0-29), demonstrating unfortunately that the negative impact of MDR Gram-negatives was present in patients who otherwise might have succeeded in successful transplantation.

The results of univariate and multivariate analysis of variables associated with 7 day mortality after BSI episode are reported in Table 5. BSI etiology was the only factor which influenced the outcome of BSI, with significant excess mortality in case of carbapenem-resistant Gram negative bacteria.

Overall survival and non-relapse mortality

Overall survival at day +60 after HCT was 95.5%, with 25 patients deceased, in median 22 days after HCT, range: 6-54. Seven them had engrafted before the death. Four of them died of progression of the underlying disease, resulting in NRM at day +60 of 3.8% (21/553).

The factors associated with NRM at day +60 in univariate analysis were active disease at HCT, non-engraftment and occurrence of pre-engraftment BSI, particularly due to carbapenem-resistant Gram-negatives (Table 6). In multivariate analysis, NRM was higher in case of transplants performed in earlier years, active underlying disease at HCT, non-engraftment and pre-engraftment BSI, with significantly higher risk in case of Gram-negative BSI compared to Gram-positive BSI, and BSI due to carbapenem-resistant Gram-negatives compared to susceptible ones (Table 6).

Discussion

The main findings of this study in 553 HCT recipients are that: 1) the risk of pre-engraftment BSI was significantly increased in case of haploidentical donors and CBT, older age, myeloproliferative disorders or aplastic anemia and active disease at HCT; 2) BSI had a negative impact on 60-day NRM; 3) the mortality in case of BSI was almost exclusively influenced by the etiology, being the highest in case of carbapenem-resistant Gram negatives.

The overall rate of pre-engraftment BSI of 30% was similar to what reported in other cohorts: from 21% to 39%;[2, 6, 8, 9, 25] and to what observed in our center in years 1998-2002 (20.6% at the day 30 after transplant).[26] As reported in few other studies, older age and active disease at HCT were risk

factors for developing pre-engraftment BSI.[4, 7, 8] Additionally, the risk of BSI was higher in case of myeloproliferative disorders or aplastic anemia, compared to lymphoproliferative diseases. The role of the underlying disease probably depends on the previous episodes of prolonged neutropenia or poor neutrophil function, which are rare during chemotherapy for lymphoma, but universal in case of aplastic anemia. The association between RIC and the higher rate of BSI, particularly due to Gram-positives, might be a result of more prolonged pre-transplant therapies or more frequent patients' comorbidities, which were not included as separate variables in the analyses. Additionally, there might be also the influence of patients' age, since the median age of patients receiving myeloablative conditioning was 42 years, compared to 57 years in case of RIC (data not shown).

However, the most significant finding is the difference in the rate of BSI according to donor type, with the novel data on a particularly high risk (38%) in case of T-repleted transplant from haploidentical donor. Haploidentical transplant recipients in our cohort were usually older, with an active underlying disease and received more frequently a reduced intensity conditioning compared to other donors, which are all factors associated with an increase in BSI risk. Nevertheless, the haploidentical transplant remained consistently an independent risk factor in multivariate analysis, with 4-fold increased risk of BSI. This effect might be due to an important mucosal injury caused by post-infusion high dose of cyclophosphamide for in vivo T-depletion. In fact, the time to the development of the first BSI was significantly longer in haploidentical transplant (on day +9 compared to days 3-5 in case of other donors), confirming the probable role of post-transplant high dose cyclophosphamide administered in our protocol on days +3 and +5 after bone marrow infusion. In our clinical experience, almost all recipients of haploidentical transplants develop diarrhea of variable severity on approximately day +5 or +6, which in turn might result in increased permeability of mucosal surfaces. Other effects of cyclophosphamide, for example on host immunity, might also play a role. Finally, even some difference in the etiology of BSI might be attributed to the use of cyclophosphamide, since the development of mucosal injury would explain

an increase in viridans streptococci which were rarely isolated after transplant from other donors, and a high incidence of intestinal Gram-negatives.

One of the most important issues of management of BSI in neutropenic patients is establishing the risk of direct BSI-related mortality. Historically it was reported to be as high as 20% and 15% in case of, respectively, Gram-negative and Gram-positive bacteria.[27] In this study, the mortality at 7 days after the BSI was chosen to reflect the impact of different pathogens. Interestingly, none of patients with single species Gram-positive died within 7 days, and in case of multiple species BSI containing a Gram-positive, the mortality was 4%. These results suggest low mortality associated with Gram-positive infections, previously reported in the setting of HCT.[1, 6] In the past, BSIs due to viridans streptococci were reported as an important cause of mortality in neutropenic patients, particularly after treatment with high dose cyclophosphamide.[28] On the contrary, in our study, only 1 of 30 patients with viridans BSI died with 7 days, but his subsequent blood cultures were negative for streptococci and positive for MDR *P. aeruginosa*, demonstrating benign clinical course of viridans BSI in our setting.

BSI-associated mortality at day 7 in case of Gram-negatives susceptible to first or second line empirical therapy was 3.9%, suggesting that prompt and appropriate antibiotic therapy can efficiently limit the negative impact of BSI. In fact, there was no excess mortality in case of ESBL-producing or piperacillin/tazobactam-resistant Enterobacteriaceae, suggesting that the choice of meropenem in case of severe clinical presentation or risk factors may be warranted in settings with high rate of BSI caused by these strains.[29, 30] On the contrary, infections due to carbapenem resistant Gram-negatives, particularly *P. aeruginosa*, resulted in over 50% mortality rate. Such a high mortality rate in case of MDR Gram-negatives, which in most of the cases were adequately treated after 48 hours form the onset of BSI, highlights the importance of immediate active empirical therapy. The negative impact of carbapenem-resistant infections has been already reported in HCT setting in the context of carbapenem-resistant *K. pneumoniae.*[10] However, the problem is also

evident in case of *P. aeruginosa*, which continues to be associated with approximately 40% mortality rate in different cohorts.[1, 31, 32] Whereas novel therapeutic options, such as ceftazidime-avibactam, might help to resolve the problem of carbapenem-resistant *K. pneumoniae*, few therapeutic options are available for MDR *P. aeruginosa.* [33] Importantly, the episodes of BSI which resulted in patients' death with 7 from BSI occurred in median 8 day after HCT, demonstrating unfortunately that the negative impact of MDR Gram-negatives was present in patients who otherwise might have benefited from successful transplantation.

Finally, the results on NRM on day +60 after HCT are in line with a possible negative impact of developing a pre-engraftment BSI.[6] Also day +60 NRM was particularly high in case of Gram-negative BSI, particularly if carbapenem-resistant. Consistently with data from other cohorts, disease in remission and more recent transplant period were associated with lower NRM.[34] In fact, the management of patients at high risk of pre-engraftment BSI warrants particular attention in order to avoid BSI-associated mortality, and should include prompt empirical therapy based on the local susceptibility and individual patient's risk factors for Gram-negative bacteria. [11]

The limits of this study include a retrospective design and a possible important influence of local microbial epidemiology and antibiotic practices. However, the data on BSI were complete and cross-checked between patients' records and the central computerized microbiology database. Although the difference in antibiotic susceptibility might exist between geographical regions, the association of high dose post-transplant cyclophosphamide and a higher risk of BSI approximately 5-7 days later is likely generalizable to all the centers that use this type of GvHD prophylaxis. The impact of resistant Gram-negatives on mortality, highlights the importance of appropriate immediate empirical therapy, rather than resistance mechanisms, with the example of use of carbapenems and piperacillin/tazobactam in our center with high prevalence of ESBL-producing bacterial, while other antibiotic combinations might be necessary in centers with different epidemiology of resistant strains.

In conclusion, the risk of pre-engraftment BSI was particularly high in case of transplant from a T-repleted haploidentical donor, probably due to extensive mucosal damage caused by post-transplant high dose cyclophosphamide. Active empirical therapy might reduce the risk of infection-related mortality, as demonstrated by only a slight increase in mortality in case of BSI caused by pathogens susceptible to empirical therapy regimens. Effective treatment agents and management strategies are necessary to limit the negative impact of MDR Gram-negatives. Further studies should establish if the risk of BSI conferred by high dose cyclophosphamide would be similar in case of other donor types receiving transplant with this GvHD prophylaxis platform.

Acknowledgements.

None.

References

1. Collin BA, Leather HL, Wingard JR, Ramphal R. Evolution, incidence, and susceptibility of bacterial bloodstream isolates from 519 bone marrow transplant patients. *Clin Infect Dis.* 2001;33:947-953.

2. Gudiol C, Garcia-Vidal C, Arnan M, et al. Etiology, clinical features and outcomes of pre-engraftment and post-engraftment bloodstream infection in hematopoietic SCT recipients. *Bone Marrow Transplant.* 2014;49:824-830.

3. Mikulska M, Del Bono V, Raiola AM, et al. Blood stream infections in allogeneic hematopoietic stem cell transplant recipients: reemergence of Gram-negative rods and increasing antibiotic resistance. *Biol Blood Marrow Transplant.* 2009;15:47-53.

4. Almyroudis NG, Fuller A, Jakubowski A, et al. Pre- and post-engraftment bloodstream infection rates and associated mortality in allogeneic hematopoietic stem cell transplant recipients. *Transpl Infect Dis.* 2005;7:11-17.

5. Poutsiaka DD, Price LL, Ucuzian A, Chan GW, Miller KB, Snydman DR. Blood stream infection after hematopoietic stem cell transplantation is associated with increased mortality. *Bone Marrow Transplant.* 2007;40:63-70.

6. Blennow O, Ljungman P, Sparrelid E, Mattsson J, Remberger M. Incidence, risk factors, and outcome of bloodstream infections during the pre-engraftment phase in 521 allogeneic hematopoietic stem cell transplantations. *Transpl Infect Dis.* 2014;16:106-114.

7. Yuen KY, Woo PC, Hui CH, et al. Unique risk factors for bacteraemia in allogeneic bone marrow transplant recipients before and after engraftment. *Bone Marrow Transplant.* 1998;21:1137-1143.

8. Kikuchi M, Akahoshi Y, Nakano H, et al. Risk factors for pre- and post-engraftment bloodstream infections after allogeneic hematopoietic stem cell transplantation. *Transpl Infect Dis.* 2015;17:56-65.

9. Zheng C, Tang B, Zhu X, et al. Pre-engraftment bloodstream infections in acute leukemia patients undergoing unrelated cord blood transplantation following intensified myeloablative conditioning without ATG. *Ann Hematol.* 2016.

10. Girmenia C, Rossolini GM, Piciocchi A, et al. Infections by carbapenem-resistant Klebsiella pneumoniae in SCT recipients: a nationwide retrospective survey from Italy. *Bone Marrow Transplant.* 2015;50:282-288.

11. Averbuch D, Orasch C, Cordonnier C, et al. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia. *Haematologica.* 2013;98:1826-1835.

12. Ballen KK, Spitzer TR. The great debate: haploidentical or cord blood transplant. *Bone Marrow Transplant.* 2011;46:323-329.

13. Gragert L, Eapen M, Williams E, et al. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. *The New England journal of medicine.* 2014;371:339-348.

14. Ballen KK, Gluckman E, Broxmeyer HE. Umbilical cord blood transplantation: the first 25 years and beyond. *Blood.* 2013;122:491-498.

15. Ciurea SO, Zhang MJ, Bacigalupo AA, et al. Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. *Blood.* 2015;126:1033-1040.

16. Luznik L, Bolanos-Meade J, Zahurak M, et al. High-dose cyclophosphamide as single-agent, short-course prophylaxis of graft-versus-host disease. *Blood.* 2010;115:3224-3230.

17. Raiola AM, Dominietto A, Ghiso A, et al. Unmanipulated haploidentical bone marrow transplantation and posttransplantation cyclophosphamide for hematologic malignancies after myeloablative conditioning. *Biol Blood Marrow Transplant.* 2013;19:117-122.

18. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood.* 2017;129:424-447.

19. Raiola A, Dominietto A, Varaldo R, et al. Unmanipulated haploidentical BMT following non-myeloablative conditioning and post-transplantation CY for advanced Hodgkin's lymphoma. *Bone Marrow Transplant.* 2014;49:190-194.

20. Frassoni F, Gualandi F, Podesta M, et al. Direct intrabone transplant of unrelated cord-blood cells in acute leukaemia: a phase I/II study. *Lancet Oncol.* 2008;9:831-839.

21. Dominietto A, Tedone E, Soracco M, et al. In vivo B-cell depletion with rituximab for alternative donor hemopoietic SCT. *Bone Marrow Transplant.* 2012;47:101-106.

22. Mikulska M, Raiola AM, Bruzzi P, et al. CMV infection after transplant from cord blood compared to other alternative donors: the importance of donor-negative CMV serostatus. *Biol Blood Marrow Transplant.* 2012;18:92-99.

23. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2011;52:427-431.

24. Aalen OO, Johansen S. An empirical transition matrix for non-homogeneous Markov chains based on censored observations. *Scandinavian Journal of Statistics.* 1978:141-150.

25. Sanz J, Cano I, Gonzalez-Barbera EM, et al. Bloodstream infections in adult patients undergoing cord blood transplantation from unrelated donors after myeloablative conditioning regimen. *Biol Blood Marrow Transplant.* 2015;21:755-760.

26. Cappellano P, Viscoli C, Bruzzi P, Van Lint MT, Pereira CA, Bacigalupo A. Epidemiology and risk factors for bloodstream infections after allogeneic hematopoietic stem cell transplantion. *New Microbiol.* 2007;30:89-99.

27. Viscoli C, Varnier O, Machetti M. Infections in patients with febrile neutropenia: epidemiology, microbiology, and risk stratification. *Clin Infect Dis.* 2005;40 Suppl 4:S240-245.

28. Marron A, Carratala J, Gonzalez-Barca E, Fernandez-Sevilla A, Alcaide F, Gudiol F. Serious complications of bacteremia caused by Viridans streptococci in neutropenic patients with cancer. *Clin Infect Dis.* 2000;31:1126-1130.

29. Gudiol C, Tubau F, Calatayud L, et al. Bacteraemia due to multidrug-resistant Gram-negative bacilli in cancer patients: risk factors, antibiotic therapy and outcomes. *J Antimicrob Chemother.* 2011;66:657-663.

30. Tumbarello M, Sanguinetti M, Montuori E, et al. Predictors of mortality in patients with bloodstream infections caused by extended-spectrum-beta-lactamase-producing Enterobacteriaceae: importance of inadequate initial antimicrobial treatment. *Antimicrobial agents and chemotherapy.* 2007;51:1987-1994.

31. Mikulska M, Del Bono V, Bruzzi P, et al. Mortality after bloodstream infections in allogeneic haematopoietic stem cell transplant (HSCT) recipients. *Infection.* 2012;40:271-278.

32. Trecarichi EM, Tumbarello M, Caira M, et al. Multidrug resistant *Pseudomonas aeruginosa* bloodstream infection in adult patietns with hematological malignancies. *Haematologica.* 2011;96:e1-3.

33. Tatarelli P, Mikulska M. Multidrug-resistant bacteria in hematology patients: emerging threats. *Future microbiology.* 2016;11:767-780.

34. Sorror ML, Giralt S, Sandmaier BM, et al. Hematopoietic cell transplantation specific comorbidity index as an outcome predictor for patients with acute myeloid leukemia in first remission: combined FHCRC and MDACC experiences. *Blood.* 2007;110:4606-4613.

Figure 1. The cumulative incidence of the first BSI after allogeneic stem cell transplant from different donors.

CBT, cord blood transplant; Haplo, haploidentical donor, MRD, matched related donor; MUD/MMR, mismatched related donor.

Cumulative incidence was estimated with Aalen-Johansen method, with engraftment, death without BSI or second transplant were considered as competitive risks. Patients neutropenic and without any of the aforementioned events were censored at day 50 after transplant. No Gray's test for comparing subdistribution hazards across the different groups was performed because of violation of the proportionality assumption.

Table 1. Patients' baseline and outcome (engraftment and BSI) data, divided into the whole cohort and according to different donors.

Patients' characteristics	Total, n=553 (100%)	Matched related, n=115 (20.8%)	MUD/MMR, n=81 (14.6%)	CBT, n=27 (4.8%)	Haploidentical, n=330 (59.7%)	p
Baseline variables						
Sex						0.264
Male	**321 (58%)**	66 (57%)	55 (68%)	16 (60%)	184 (56%)	
Female	**232 (42%)**	49 (43%)	26 (32%)	11 (40%)	146 (44%)	
Age at HSCT, median, years (IQR)	**48 (31-57)**	44 (28-53)	47 (34-55)	49 (33-56)	50 (31-59)	0.036
Age, intervals in tercils						0.175
16-37	**188 (34%)**	42 (36.5%)	27 (33%)	8 (30%)	111 (33.6%)	
38-54	**185 (33.5%)**	46 (40%)	31 (38%)	10 (37%)	98 (29.7%)	
55-74	**180 (32.5%)**	27 (23.5%)	23 (28%)	9 (33%)	121 (36.7%)	
Year of HSCT						<0.0001
2010-2012	**259 (47%)**	72 (63%)	54 (67%)	25 (93%)	108 (33%)	
2013-2016	**294 (53%)**	43 (37%)	27 (33%)	2 (7%)	222 (67%)	
Diagnosis						<0.0001
AML/MDS	**248 (45%)**	53 (46%)	32 (40%)	17 (63%)	146 (44%)	
Acute LPD	**106 (19%)**	20 (17%)	14 (17%)	5 (19%)	67 (20%)	
Chronic LPD	**93 (17%)**	11 (10%)	6 (7%)	3 (11%)	73 (22%)	
Chronic MPD	**75 (14%)**	19 (17%)	14 (17%)	1 (4%)	41 (12%)	
Aplastic anemia	**31 (6%)**	12 (10%)	15 (19%)	1 (4%)	3 (1%)	
Phase of disease at HSCT						0.073
Not active	**346 (63%)**	84 (73%)	49 (61%)	17 (63%)	196 (59%)	
Active	**207 (37%)**	31 (27%)	32 (39%)	10 (37%)	134 (41%)	
Conditioning regimen						0.005
Myeloablative	**314 (57%)**	74 (64%)	47 (58%)	22 (81%)	171 (52%)	
Reduced intensity	**239 (43%)**	41 (36%)	34 (42%)	5 (19%)	159 (48%)	
Outcome variables						
Neutrophil engraftment						
Yes	**514 (93%)**	115 (100%)	78 (96%)	22 (82%)	299 (91%)	0.001
Median day of engraftment (range)	**17 (15-20)**	17 (10-47)	17 (9-37)	19 (13-42)	17 (12-44)	0.029
At least 1 BSI	**166 (30%)**	13 (11%)	17 (21%)	10 (37%)	126 (38%)	<0.0001
At least 1 BSI due to Gram-positives	**105 (19%)**	8 (7%)	6 (7%)	7 (26%)	84 (26%)	<0.0001
At least 1 BSI due to Gram-negatives	**83 (15%)**	5 (4%)	13 (16%)	3 (11%)	62 (19%)	0.001
Single BSI episode	**136 (25%)**	12 (10%)	17 (21%)	8 (30%)	99 (30%)	<0.09*
Two BSI episodes	**22 (4%)**	1 (1%)	0	1 (4%)	20 (6%)	
Three BSI episodes	**8 (1%)**	0	0	1 (4%)	7 (2%)	
Time to the first BSI after HSCT, median (IQR), days	**8 (2-11)**	3 (-1, 9)	5 (1, 10)	3.5 (-1, 9)	9 (5, 12)	0.014

AML/MDS, acute myeloid leukemia or myelodysplastic syndrome; BSI, bloodstream infection; CBT, cord blood transplant; IQR, interquartile range; LPD lymphoproliferative diseases; MPD myeloproliferative diseases; MUD/MMR, matched unrelated or mismatched related donor.
* p for single BSI vs. more than 1 BSI.

Table 2. Detailed etiology of pre-engraftment bloodstream infections.

	Total isolates, n= 213
Gram-positive bacteria	**116 (54%)**
Staphylococcus	52 (25%)
Staphylococcus aureus	4
Coagulase negative	48
Staphylococci resistant to oxacillin.	45 (87%)
Enterococcus	32 (15%)
E. faecalis	10
E. faecium	22
Enterococci resistant to vancomycin	5 (16%)
Viridans streptococci	30 (14%)
Other Gram-positive bacteria *	2 (1%)
Gram negative bacteria	**91 (43%)**
Gram-negative bacteria resistant to fluoroquinolones	81 (89%)
Gram-negative bacteria resistant to 3rd generation cephalosporins	38 (42%)
Gram-negative bacteria resistant to piperacillin/tazobactam	30 (33%)
Gram-negative bacteria resistant to carbapenems	11 (12%)
Escherichia coli	66 (31%)
Escherichia coli ESBL-producing	24 (36%)
Other Enterobacteriaceae	10 (5%)
K. pneumoniae	6
Enterobacter	4
Other Enterobacteriaceae ESBL-producing	9 (90%)
Other Enterobacteriaceae resistant to carbapenems	6 (60%)
Pseudomonas aeruginosa	8 (4%)
Pseudomonas aeruginosa resistant to carbapenems	4 (50%)
Other G-negative bacteria ***	7 (3%)
Fungi	**6 (3%)**
Candida	5 (2%)
C. krusei	3
C. parapsilosis	1
C. glabrata	1
Fusarium	1

ESBL, extended spectrum beta-lactamase.

Corynebacterium species, Gemella sanguinis*; * Acinetobacter baumannii* multidrug-resistant, *Pseudomonas fluorescens* ESBL-producing, *Pseudomonas* spp. resistant to aminoglycosides; other susceptible to all antibiotics tested: *Pseudomonas putida, Acinetobacter lowfii, Campylobacter jejuni and Routella planticola*.

Table 3. Analyses of risk factors for pre-engraftment BSI.

Variables	Any pre-engraftment BSI				Gram-positive BSI				Gram-negative BSI			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Incidence: 30%, n=166	P	HR (95% CI)*	p	Incidence: 19%, n=105	P	HR (95% CI)	p	Incidence: 15%, n=83	P	HR (95% CI)	p
Sex		0.787				0.37				0.35		
Male	95 (30%)				57 (18%)				52 (16%)			
Female	71 (31%)				48 (21%)				31 (13%)			
Age, intervals in tercils		<0.001		0.04		0.029		0.102		0.006		0.012
16-37	35 (19%)		1.00		23 (12%)		1.00		16 (9%)		1.00	
38-54	59 (32%)		1.75 (1.12-2.72)		38 (21%)		1.75 (1.04-2.95)		28 (15%)		1.80 (0.97-3.33)	
55-74	72 (40%)		1.67 (1.05-2.77)		44 (24%)		1.50 (0.88-2.56)		39 (22%)		2.42 (1.35-4.34)	
Year of HSCT		0.405				0.64				0.45		
2010-2012	74 (29%)				47 (18%)				36 (14%)			
2013-2016	92 (31%)				58 (20%)				47 (16%)			
Diagnosis		0.045		<0.001		0.24				0.30		
AML/MDS	82 (33%)		1.00		50 (20%)				45 (18%)			
Acute LPD	24 (23%)		0.84 (0.52-1.36)		15 (14%)				13 (12%)			
Chronic LPD	19 (20%)		0.49 (0.29-0.82)		13 (14%)				8 (9%)			
Chronic MPD	31 (41%)		1.25 (0.82-1.91)		21 (28%)				12 (16%)			
Aplastic anemia	10 (32%)		3.84 (1.74-8.45)		6 (19%)				5 (16%)			
Phase of disease at HSCT		0.001		0.002		0.019	-	NS		0.03	-	NS
Not active	85 (25%)		1.00		54 (16%)				42 (12%)			
Active	81 (39%)		1.71 (1.22-2.39)		51 (25%)				41 (20%)			
Conditioning regimen		0.007	-	NS		0.006		0.039		0.24		
Myeloablative	77 (25%)				45 (14%)		1.00		41 (13%)			
Reduced intensity	89 (37%)				60 (25%)		1.58 (1.02-2.43)		42 (18%)			
Donor		< 0.001		<0.001		< 0.001		<0.001		0.015		0.022
Matched related	13 (11%)		1.00		8 (7%)		1.00		5 (4%)		1.00	
MUD/MMR	17 (21%)		1.51 (0.73-		6 (7%)		1.04 (0.36-2.98)		13 (16%)		3.69 (1.31-	

CBT Haploidentical	10 (37%) 126 (38%)		3.15) 3.88 (1.66- 9.07) 4.45 (2.47- 8.02)		7 (26%) 84 (26%)		4.06 (1.45-11.36) 3.66 (1.78-7.58)		3 (11%) 62 (19%)		10.36) 2.02 (0.48-8.54) 3.96 (1.59-9.89)	

* Cause specific HR for BSI. AML/MDS, acute myeloid leukemia or myelodysplastic syndrome; BSI, bloodstream infection; CBT, cord blood transplant; LPD lymphoproliferative diseases; MPD myeloproliferative diseases; MUD/MMR, matched unrelated or mismatched related donor; NS, not statistically significant and not retained in the final model.

Table 4. Seven- and 30-day mortality after 178 separate BSI episodes.

For the purposes of this analysis, in case of blood cultures positive for more than one pathogen within 7 days, it was considered a multiple-species BSI episode, and the mortality at the 7th day after isolation of the last pathogen was considered.

	Mortality at day 7 after BSI, n=9/178 (5%)	Mortality at day 30 after BSI, n=15/178 (8%)
Single species BSI episodes	**4/146 (3%)**	**8/146 (5%)**
Gram-positive	**0/78**	**1/78 (1%) ***
Gram-negative	**4/64 (6%)**	**7/64 (11%)**
Escherichia coli	1/50 (2%)	2/50 (4%)
Klebsiella	2/6 (33%)	3/6 (50%)
Enterobacter	0/1	0/1
Pseudomonas aeruginosa	1/3 (33%)	2/3 (67%)
Other Gram-negative	0/4	0/4
Fungal	**0/4**	**0/4**
Multiple-species BSI episodes	5/32 (16%)	7/32 (22%)
Only Gram-positives	0/8	1/8 (13%)
Gram-positive and Gram-negative	4/19 (21%)	5/19 (26%)
Only Gram-negatives or including fungi	1/5 (20%)**	1/5 (20%)**
Etiology of all BSI episodes		
BSI due to at least one Gram-positive	4/106 (4%)	7/106 (7%)
BSI due to at least one *Enterococcus*	3/30 (10%)***	5/30 (17%)***
BSI due to at least one Gram-negative	9/88 (10%)	13/88 (15%)
BSI due to *P. aeruginosa*	3/8 (38%) ****	4/8 (50%)
BSI due to at least one Gram-negative susceptible to P/T and carbapenems	2/56 (4%)	4/56 (8%)
BSI due to at least one Gram-negative resistant to P/T and susceptible to carbapenems	1/21 (5%)	2/21 (10%)
BSI due to at least one Gram-negative resistant to carbapenems	6/11 (55%)	7/11 (64%)
Carbapenem-resistant *Pseudomonas aeruginosa*	3/4 (75%)	3/4 (75%)
Carbapenem-resistant Enterobacteriaceae and Acinetobacter	3/7 (43%)	4/7 (57%)

P/T, piperacillin/tazobactam; VRE, vancomycin-resistant enterococci.

*Died of legionellosis, 16 day after BSI due to *Streptococcus viridans*; ** *Fusarium spp.* and *P. aeruginosa*; *** including 1/5 VRE, mortality for VRE 20% at day 7 and 30; **** all resistant to carbapenems.

Table 5. Univariate and multivariate analysis of predictors of all-cause 7-day mortality after 178 BSI episodes in 166 patients.

For the purposes of this analysis, in case of blood cultures positive for more than one pathogen within 7 days, it was considered a mixed species BSI episode, and the mortality at the 7th day after isolation of the last pathogen was considered.

Variables	Univariate analysis		Multivariate analysis	
	Overall mortality at day +7 after BSI, n=9 (5%)	P	OR (95% CI)	p
Sex		0.309		
Male	7 (6.7%)			
Female	2 (2.7%)			
Age, years, median vs. survival group	44 vs. 53	0.14	-	NS
Date of HSCT,		0.183	-	NS
2010-2012	6 (8%)			
2013-2016	3 (3%)			
Diagnosis		0.268		
AML/MDS	6 (7%)			
Acute LPD	2 (8%)			
Chronic LPD	0			
Chronic MPD	0			
Aplastic anemia	1 (9%)			
Phase of disease at HSCT		0.745		
Not active	4 (4.4%)			
Active	5 (5.7%)			
Donor		0.77		
Matched related	0 (0%)			
MUD/MMR	1 (6%)			
CBT	1 (9%)			
Haploidentical	7 (5%)			
Conditioning		0.188	-	NS
Myeloablative	6 (7.6%)			
Reduced intensity	3 (3%)			
Previous BSI		0.133	-	NS
No	7 (4.2%)			
Yes	2 (15.4%)			
Etiology of BSI		< 0.001		<0.001
Only Gram positive or *Candida*	0		1.00*	
Including carbapenem-susceptible Gram negative	3 (3.9%)		1.00*	
Including carbapenem-resistant Gram negative	6 (54.5%)		85.6 (13.6-537.9)	

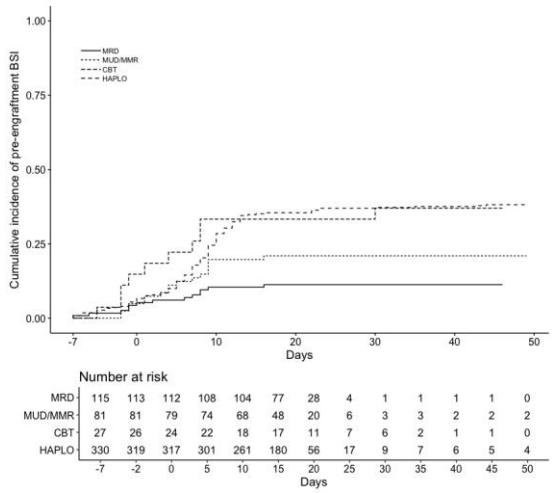
* For OR calculation, the two first categories were considered together, since there were no events in the first one.
AML/MDS, acute myeloid leukemia or myelodysplastic syndrome; BSI, bloodstream infection; CBT, cord blood transplant; LPD lymphoproliferative diseases; MPD myeloproliferative diseases; MUD/MMR, matched unrelated or mismatched related donor; NS, not significant.

Table 6. Univariate and multivariate analysis of predictors of non-relapse mortality (NRM) at day +60 after transplantation.

	Univariate analysis		Multivariate analysis	
	NRM at day +60, n=21 (3.8%)	**p**	**Hazard ratio with 95%CI**	**p**
Sex		0.096	-	NS
Male	16 (5%)			
Female	5 (2.2%)			
Age, intervals in tercils		0.189	-	NS
16-37	3 (1.6%)			
38-54	9 (4.9%)			
55-74	9 (5%)			
Date of HSCT,		0.072		0.027
2010-2012	14 (5.4%)		1.00	
2013-2016	7 (2.4%)		0.35 (0.14-0.89)	
Diagnosis		0.821		
AML/MDS	10 (4%)			
Acute LPD	2 (1.9%)			
Chronic LPD	4 (4.3%)			
Chronic MPD	4 (5.3%)			
Aplastic anemia	1 (3.2%)			
Phase of disease at HSCT		0.008		0.045
Not active	7 (2%)		1.00	
Active	14 (6.8%)		2.55 (1.02-6.37)	
Donor		0.103	-	NS
Matched related	1 (0.9%)			
MUD/MMR	2 (2.5%)			
CBT	3 (11.1%)			
Haploidentical	15 (4.5%)			
Conditioning		0.623		
Myeloablative	13 (4.1%)			
Reduced intensity	8 (3.3%)			
Engraftment*		<0.001		0.001
Yes	7 (1.8%)		1.00	
No	14 (8.4%)		7.45 (2.21-25.12)	
BSI*		<0.001		<0.001
No	7 (1.8%)		1.00	
Yes	14 (8.4%)		5.32 (2.08-13.58)	
BSI		<0.001		<0.001***
No	7 (1.8%)		1.00	
BSI due to Gram-positive	2 (2.5%)		1.56 (0.32-7.64)	
BSI due to Gram-negative**	12 (14.5%)		9.71 (3.68-25.61)	
BSI		<0.001		<0.001***
No	7 (1.8%)		1.00	
BSI due to Gram-positive	2 (2.5%)		1.54 (0.32-7.51)	
BSI due to carbapenem-susceptible Gram-negative	6 (8.2%)		4.83 (1.56-14.98)	
BSI due to carbapenem-resistant Gram-negative	6 (60%)		72.88 (23.37-227.28)	

* Analyzed as time dependent variable in the univariate and multivariate analysis. ** With a Gram-positive BSI in 5 cases. *** Hazard ratio and p established when entered separately in the multivariate model, hazard ratios for other variables reported for the model with BSI and not significantly different from other models.

AML/MDS, acute myeloid leukemia or myelodysplastic syndrome; BSI, bloodstream infection; CBT, cord blood transplant; LPD lymphoproliferative diseases; MPD myeloproliferative diseases; MUD/MMR, matched unrelated or mismatched related donor; NS, not significant.



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