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ORIGINAL ARTICLE

G-CSF-primed haplo-identical HSCT with intensive immunosuppressive and myelosuppressive treatments does not increase the risk of pre-engraftment bloodstream infection: a multicenter case–control study

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Abstract

A multicenter retrospective study in 131 patients (44 females/87 males) with hematological disorders who underwent G-CSF-primed/haplo-identical (Haplo-ID) ($n = 76$) or HLA-identical (HLA-ID) HSCT ($n = 55$) from February 2013 to February 2016 was conducted to compare the incidence and risk factors for pre-engraftment bloodstream infection (PE-BSI). In the Haplo-ID group, 71/76 patients with high-risk ($n = 28$) or relapsed/refractory hematological malignancies ($n = 43$) received FA5-BUCY conditioning (NCT02328950). All received trimethoprim–sulfamethoxazole (TMP–SMX) prophylaxis. Blood cultures and catheter tip cultures were obtained to confirm the BSI. PE-BSI was detected in 24/131 HSCT patients (18/76 in Haplo-ID and 6/55 in HLA-ID) after 28 febrile neutropenic episodes. Among 28 isolates for the 24 patients, 21 (75%) were G^{neg} bacteria, 6 (21.4%) G^{pos} and 1 (3.6%) fungi. Bacteria sources were central venous line infection (7/29.2%), gastroenteritis (6/25%), lower respiratory tract infection (LRTI; 5/20.8%), perianal skin infection (4/16.7%), and unknown (2/8.3%). The duration of neutropenia ($P = 0.046$) and previous G^{neg} bacteremia ($P = 0.037$) were important risk factors by univariate analysis, while the type of HSCT was not. A trend of TMP–SMX-resistant BSI in both groups may be due to routine antibacterial prophylaxis strategies. Our data show that G-CSF-primed Haplo-ID HSCT did not increase the risk of PE-BSI, even with intensive immunosuppressive treatments.

Keywords Haplo-identical · HSCT · Immunosuppressive and myelosuppressive treatments · Pre-engraftment · Bloodstream infection

Introduction

Bloodstream infection (BSI) is one of the common and fatal complications of hematopoietic stem cell transplantation (HSCT), which mainly occurs during the pre-engraftment period between the initiation of the conditioning regimen and the resolution of neutropenia. The negative effects of pre-engraftment BSI (PE-BSI) on the outcome of allo-HSCT are being the major cause of 100-day mortality and acute GvHD II–IV with cause-specific hazard ratios (HR) of 2.17, which may be due to the release of cytokines during BSI [1, 2] or the bacterial components that can contribute to the activation of donor T cells via antigen-presenting cells [3].

Previous reports have shown that the presence of neutropenia, a central venous catheter (CVC), and severe mucositis resulting from the intensive immunosuppressive and myelosuppressive treatments are important risk factors for PE-BSI [4, 5]. In the light of these evidence-based risk factors, the risk of PE-BSI may be related to the types of transplant and/or the source of the grafts. It has been reported that patients who underwent allogeneic HSCT (allo-HSCT) had a significant increase in the risks for bacterial BSI compared to those who underwent autologous HSCT (auto-HSCT) [6, 7], and higher

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rates of BSI were reported in patients receiving umbilical cord blood (UCB) transplants than in bone marrow (BM) or peripheral blood stem cell (PBSC) transplants [8–10]. However, with respect to the impact of the source of the allograft, conflicting data were reported. Some reported that the risk was greater with a matched unrelated donor (MUD) than with a matched sibling donor (MSD) [7, 10–12]. Others recently reported that the allograft from a MUD or MSD had no impact on the risk of BSI [6, 8]. Nevertheless, it is believed that the intensive immunosuppressive agents for the prevention of acute GVHD might result in higher incidence of PE-BSI.

Haplo-identical HSCT (Haplo-ID) with a graft from a partially matched family member is an alternative approach when HLA-identical (HLA-ID) siblings are not available, and is widely performed nowadays in China due to the one-child policy of the past 30 years. Based on the difference from the types of transplant as reported [6], we hypothesized that Haplo-ID HSCT with an intensive immunosuppressive regimen would be associated with a greater risk of PE-BSI than HLA-ID transplantation. To the best of our knowledge, only few studies have examined this question. More specifically, there are no other published multicenter studies, which may confer advantages over single-center studies and allow for increased generalizability of the results. Moreover, the current management guidelines recommend using general antibiotic prophylaxis regardless of the HSCT types and procedures [13–16], which raises the question of whether extensive prophylactic antibiotic therapy should be provided in the Haplo-ID setting to reduce the risk of PE-BSI.

Thus, the aim of this study was to compare the pre-HSCT disease status, impact of risk factors, epidemiological characteristics, and clinic outcome of PE-BSI in recipients undergoing Haplo-ID or HLA-ID transplantation. The data indicate that the risk of PE-BSI is not increased in the G-CSF-primed Haplo-ID group, even with intensive immunosuppressive and myelosuppressive treatments for advanced hematological malignancies.

Methods

Study design

This is a non-randomized, multicenter retrospective study in a cohort of patients with active hematological disorders who underwent Haplo-ID or HLA-ID in the Fujian Province, China, during a 3-year period (Feb. 2013 to Feb. 2016). Informed consent was obtained from all patients and donors before they were included in the study. This study was conducted in accordance with the ethical standards of the local institutional review board (the Medical Ethics Committee of Fujian Medical University Union Hospital and the Helsinki Declaration). All subjects were cared for in the laminar airflow hospital units by nurses specializing in HSCT.

Patient characteristics

Patient characteristics are summarized in Table 1. One hundred and thirty-one consecutive patients (44 females, 87 males) with a median age of 23 years (range 1.1–60) were included in the study. Transplantation indications were guided by the China recommendations from the Chinese Society of Hematology as published in JHO [17]. The diagnoses were as follows: acute myeloid leukemia (AML, $n = 52$), AML secondary to myelodysplastic syndrome (sAML, $n = 12$), acute lymphoblastic leukemia (ALL, $n = 37$), advanced myelodysplastic syndrome (aMDS, $n = 5$), chronic myelogenous leukemia in blast crisis (CML-BC, $n = 9$), Hodgkin lymphoma (HL, $n = 2$), non-Hodgkin lymphoma (NHL, $n = 5$), and severe aplastic anemia (SAA, $n = 9$).

Seventy-six patients received Haplo-ID ($n = 29$ AML; 11 sAML; 23 ALL; 3 advanced MDS; 5 CML-BC, 2 HL, 1 NHL, 2 AA), and 55 patients underwent HLA-ID ($n = 23$ AML; 1 sAML; 14 ALL; 2 advanced MDS; 4 CML-BC, 4 NHL, 7 AA). At the time of the transplant procedure, 66 patients (46 Haplo-ID, 20 HLA-ID) were in relapse or primary refractory status, and 56 patients (28 in Haplo-ID, 28 in HLA-ID) were in remission, but had a high risk of relapse based on cytogenetics and/or molecular markers as defined by the National Comprehensive Cancer Network (NCCN) practice guidelines [18].

Primary refractory AML was defined as blast persistence in bone marrow (BM) aspirates on day 28 after the first or second induction treatment. Relapsed AML was defined as > 5% blasts in BM aspirates in patients who had achieved complete hematological remission after the first or second induction treatment.

All 7 patients with lymphoma (HL and NHL) attained a partial response (PR), which was defined as described [19].

The 9 patients with SAA, including 2 cases of EB virus-associated SAA and 5 cases of post-hepatitis AA (HAA), were all unresponsive to the previous immunosuppressive agents including CSA, ATG, and androgens.

As pre-transplant serum ferritin may have an impact on the incidence of pre-engraftment BSI [20, 21], we included pre-transplant serum ferritin, which was available in 101 patients. Fifty patients in the Haplo-ID group and 30 in the HLA-ID group had serum ferritin levels lower than 1000 ng/ml, while it was higher than 1000 ng/ml in 14 Haplo-ID patients and 7 HLA-ID patients.

HLA typing and donors

Patients and their donors were tested for HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 by high-resolution

Table 1 Patient characteristics prior to HSCT compared by transplantation types

	Haplo-ID (76 cases)	HLA-ID (55 cases)	*P* value
Median age, years (range)	20.5 (1.11–53)	27 (1.8–60)	0.009
< 14 years	30	8	0.002
≥ 14 years	46	47	
Sex			0.344
Male	53	34	
Female	23	21	
Primary disease			0.085
AML	29	23	
MDS-sAML	11	1	
ALL	23	14	
Advanced MDS	3	2	
CML-BC	5	4	
HL	2	0	
NHL	1	4	
AA	2	7	
Pre-HSCT status			
Previous bacteremia			0.656
Non-MDR isolates	6	3	
Other MDR isolates	4	6	
Carbapenem-resistant MDR	1	0	
Previous chemotherapy			
≥ 2 cycles	61	42	0.153
≥ 5 cycles	28	19	0.826
> 5 cycles	19	10	0.538
Disease status			0.026
In CR	28	28	
Not in CR	46	20	
Serum ferritin			0.057
< 1000 ng/mL	50	30	
≥ 1000 ng/mL	14	7	
Not checked	12	18	
Immunosuppression			
Late-CSA + lose-dose ATG	0	48	
Early-CSA + high-dose ATG	74	0	
Late-CSA + high-dose ATG	2	7	
Infusion dose CD34+, 10^6/kg			
Median (range)	4.39 (2.87–17.37)	5.16 (2.66–24.62)	0.290
< 4×10^6/kg	37	17	0.041
≥ 4×10^6/kg	39	38	
Duration of neutropenia			
Median (range)	13 (10–35)	12 (8–35)	0.003
< 14 days	38	38	0.021
≥ 14 days	36	15	
Engraftment			
Neutrophils, median (range)	13 (10–35)	12 (8–35)	0.003
Thrombocytes, median (range)	13.5 (7–43)	12 (8–37)	0.001

molecular typing methods. Haplo-ID donors were family members who shared one HLA haplotype with the recipient, but differed to various degrees for the HLA-A, B, and DR antigens of the unshared HLA haplotype, while HLA-ID sibling donors shared both HLA haplotypes.

All donors received granulocyte colony-stimulating factor (G-CSF) at a dose of 5 μg/kg of body weight per day for 5 days before harvest. Patients in the Haplo-ID group received both G-CSF-primed BM and peripheral blood (PB) as the source of stem cells as described by Huang et al. [22] while patients in the HLA-ID group, except those with SAA, received only PB progenitor cells. For patients with SAA, PB plus BM stem cells were the preferred source in both Haplo-ID and HLA-ID groups. The target total mononuclear cell counts were > 2×10^8/kg of recipient weight.

European group for blood and marrow transplantation risk score

To assess the risks of HSCT, the European Group for Blood and Marrow Transplantation (EBMT) risk score [23] was calculated for each individual patient before transplantation based on five pre-transplantation variables: age, disease stage, time from diagnosis to transplantation, donor type, and donor–recipient sex combination.

Conditioning regimens, transplantation, and GvHD prophylaxis

The FA5-BUCY regimen, registered on http://ClinicalTrials.gov (NCT02328950) [24] and consisting of fludarabine 30 mg/m^2/day and 2 g/m^2/day Ara-C/cytarabine from day − 13 to day − 9, followed by 3.2 mg/kg/day busulfan (BU) from day − 7 to day − 5 and 1.8 g/m^2/day cyclophosphamide (CY) from day − 4 to day − 3, was used in all leukemic and advanced MDS patients (71/76 patients in the Haplo-ID group: 28 with high-risk and 43 with relapsed/refractory hematological malignancies). Patients with AA received fludarabine-based conditioning [25, 26], consisting of 30 mg/m^2/day fludarabine and 30 mg/kg/day CY from day − 6 to day − 3, followed by ATG-Fresenius®, 10 mg/kg/day from day − 5 to day − 3. Patients with lymphoma received the FBM regimen [27], consisting of 30 mg/m^2/day fludarabine from day − 9 to day − 5, 150 mg/m^2/day carmustine (BCNU) from day − 7 to day − 6, and 110 mg/m^2 melphalan on day 4.

For patients with leukemia, advanced MDS and lymphoma undergoing Haplo-ID, GvHD prophylaxis consisted of rabbit anti-thymocyte globulin (35 cases with Thymoglobulin, Genzyme, 10 mg/kg, and 36 cases with ATG-Fresenius®, 40 mg/kg) from day − 4 to day − 1, cyclosporine A (plasma level target at 100–250 ng/ml, starting from day −10, and tapered from the second or third month if no signs of GvHD), mycophenolate mofetil (5 mg/kg bid, starting from day + 7 and tapered after engraftment), and short-term methotrexate (MTX, 15 mg/m^2 at day + 1, and 10 mg/m^2 at day + 3 and + 6). Patients in the HLA-ID subgroup received Thymoglobulin (Genzyme, 5 mg/kg) from day − 2 to day − 1 and intravenous cyclosporine A starting from day − 1 (plasma level target at 100–250 ng/ml and tapered from the second or third month if no signs of GvHD).

Acute GvHD was graded according to the Glucksberg criteria [28]. Chronic GvHD was graded according to the revised Seattle classification [29].

Supportive care measures

All patients were treated according to our institutional transplant guidelines for antiviral and antifungal prophylaxis. Patients received also antibacterial prophylaxis with trimethoprim–sulfamethoxazole (TMP–SMX, trimethoprim 160 mg and sulfamethoxazole 800 mg twice biweekly) that was started from the initiation of the conditioning.

All patients received central venous catheters, which were generally removed after engraftment. Routine catheter care was identical for all patients and conformed to our institutional Medical Center Infection Control standards.

Engraftment

Patients were evaluated for hematopoietic recovery and chimerism [30] to document donor engraftment.

Definition and management of PE-BSI

The pre-engraftment phase was defined as the time from the initiation of the conditioning regimen until resolution of the neutropenia (ANC > 0.5 × 10^9/L).

The definition of BSI was adapted from the 2004 Center for Disease Control and Preventions definitions for nosocomial infections [31]. BSI was defined as the isolation of bacteria not normally known to colonize the skin, such as Gram-negative bacilli or pathogens, such as *Staphylococcus aureus* or fungi, from at least one blood culture [32]. For bacteria that typically colonize the skin, such as coagulase-negative *Staphylococcus*, *Propionibacterium*, viridans group of *Streptococcus*, and non-JK strains of *Corynebacterium*, BSI was defined as either two consecutive positive blood cultures, two positive blood cultures within 72 h, or one positive blood culture or one positive intravascular catheter tip culture within 72 h. Blood cultures were obtained in response to an indication of infection, usually fever (oral temperature ≥ 38 °C). All suspected infected catheters were aseptically removed, and the catheter tips were sent for culture to confirm the catheter-related BSI.

All febrile neutropenic patients were treated promptly with empiric intravenous broad-spectrum antibiotics on an individual basis and in accordance with the current guidelines [33–36] until the results of the blood cultures and/or catheter tip cultures were known. Briefly, antibiotic monotherapy in patients non-allergic to cephalosporin included cefoperazone/sulbactam, piperacillin/tazobactam or carbapenem, whereas multiple therapies included the combination of an aminoglycoside with cefoperazone/sulbactam, piperacillin/tazobactam or carbapenem. A glycopeptide such as teicoplanin or vancomycin was added when deemed necessary. Antibiotics were modified according to the susceptibility of all organisms isolated.

Statistics

Data were analyzed with the SPSS 13 statistical package (Chicago, IL, USA). A *P* value of 0.05 (two-tailed) was considered statistically significant. Cox proportional hazards regression reporting hazard ratios (HR) and 95% confidence intervals (CI) were used in univariate analyses. Variables analyzed included demographics (age, gender), underlying disease necessitating HSCT, number of chemotherapy cycles prior to HSCT, previous bacteremia, disease status, serum ferritin prior to HSCT and type of HSCT. We performed the w2 test for comparisons of categorical data, and the Mann–Whitney *U* test for comparisons of non-categorical variables.

Results

Engraftment and donor chimerism

A total of 131 consecutive patients underwent allogeneic HSCT during the study period. Patients' epidemiological characteristics were comparable between the Haplo-ID and HLA-ID groups (Table 1). Patients in the Haplo-ID group received fresh grafts from BM and PB containing a median total of 4.39×10^6 $CD34^+$ cells/kg (range 2.87–17.37×10^6/kg), while those in the HLA-ID group received a median of 5.16×10^6 PB-derived $CD34^+$ cells/kg (range 2.66–24.62×10^6/kg). The median time to neutrophil and platelet engraftment was 13 days (range 10–35) and 13.5 days (range 7–43), respectively, in the Haplo-ID group, and 12 days (range 8–35) and 12 days (range 8–37), respectively, in the HLA-ID group. However, more patients experienced neutropenia lasting longer than 14 days in the Haplo-ID group (36/76) than in the HLA-ID group (15/55) ($P = 0.021$).

Donor chimerism was studied in both groups. Two Haplo-ID patients were not evaluable as they died before engraftment due to severe BSI with either pan-resistant *Pseudomonas aeruginosa* and *Candida tropicalis* or *Klebsiella pneumoniae*. For the other 74 patients in the Haplo-ID group, 95.9% had complete donor chimerism and 4.1% had mixed donor/recipient chimerism, which eventually converted to full donor chimerism during the 6 months follow-up. All patients had complete donor chimerism after engraftment in the HLA-ID group.

Bloodstream infection

Prior to initiation of HSCT, a total of 11 episodes of bacteremia were recorded in the Haplo-ID group. These were caused by non-multidrug resistance (MDR) strains in 6 out of 11 patients, MDR strains in 4 (4/11), and carbapenem-resistant MDR in one case. In the case of the HLA-ID group, bacteremia occurred in nine episodes, three being due to non-MDR and six to MDR strains (Table 1).

During the HSCT, bloodstream infections were detected in 24/131 HSCT patients (17 in Haplo-ID and 7 in HLA-ID) after 28 febrile neutropenic episodes (Table 2). The patients' age ranged from 1.11 to 49 years, with a median age of 20 years. There were 15 (15/24) males and 9 (9/24) females. These patients' diagnoses were AML, sAML, ALL, MDS, and AA in 8 (24.4%), 2 (8.33%), 8 (24.4%), 1 (4.2%), and 5 (20.8%) patients, respectively. The sources of PE-BSI were central venous line infection, gastroenteritis, lower respiratory tract infection (LRTI), perianal skin infection, and unknown origin in 7 (29.2%), 6 (25%), 5 (20.8%), 4 (16.7%), and 2 (8.3%) episodes, respectively.

As shown in Table 2, the potential risk factors for PE-BSI such as EBMT score, previous broad-spectrum antibiotics, severity of neutropenia, and intestinal mucositis were comparable in both Haplo-identical and HLA-identical groups. The most common clinical presentation of PE-BSI in both groups was high fever (over 39 °C). Shock and circulatory compromise were seldom observed following effective antibiotic therapy. The response to antibiotic therapy in the two groups was 88.2% and 85.71%, and the mortality attributable to PE-BSI was 11.76% and 14.3%, respectively. However, the overall mortality in patients with pre-engraftment BSI was 62.5% (15/24), which is significantly higher than that in patients without BSI [25.2% (27/107), $P = 0.0001$].

Univariate analysis of risk factors for pre-engraftment BSI

The duration of neutropenia was significantly associated with the incidence of PE-BSI by univariate analysis ($P = 0.046$; Table 3). There was a trend towards significance between PE-BSI and previous bacteremia, especially Gram-negative (Gram −ve) PE-BSI was significantly related to the incidence of previous Gram −ve bacteremia ($P = 0.037$). There was no effect of the type of HSCT, disease status, age, previous cycles of chemotherapy, EBMT score including time from diagnosis to transplantation, and donor–recipient sex combination or infusion dose of CD34+ cells. Contrary to previous reports [19, 20], our analysis did not show the predictive value for pre-HSCT serum ferritin level, previous therapy with broad-spectrum antibiotics including with carbapenems, severity of neutropenia, or intestinal mucositis.

Microorganisms isolated in blood cultures and resistance profile

Among the 28 isolates retrieved from the blood of the 24 patients with BSI, 21 isolates (75%) were Gram-negative bacteria (GNB), 6 (21.4%) were Gram-positive bacteria (GPB), and 1 (3.6%) was fungi. There were no significant differences between the Haplo-ID and HLA-ID groups with respect to GNB or GPB pathogens (Tables 4 and 5). Moreover, GNB TMP–SMX-resistant strains were predominant in both groups and most GNB and GPB isolates remained sensitive to quinolones (Fig. 1, Tables 4 and 5).

When further examining the antibiotic susceptibility of the GNB pathogens, it showed that 92.3% (12/13) GNB that were resistant to third-generation cephalosporins were still sensitive to carbapenems (Fig. 1, Table 4). GPB pathogens were rarely resistant to methicillin or vancomycin (Table 5).

Discussion

Despite significant advances in the management of the complications of HSCT, PE-BSI remains one of the

Table 2 Patient characteristics, risk factors, epidemiological characteristics, and clinic outcome of PE-BSI compared by transplantation types

	Haplo-ID (17 cases)	HLA-ID (7 cases)	*P* value
Median age, years (range)	20.0 (1.1–49)	18 (9–40)	
Sex			0.117
Male	13	2	
Female	4	5	
Primary disease			0.026
AML	5	3	
MDS-sAML	2	0	
ALL	8	0	
Advanced MDS	1	0	
CML-BC	0	0	
HL	0	0	
NHL	0	0	
AA	1	4	
Pre-HSCT status			
Previous bacteremia			1.000
Non-MDR isolates	3/17	0	
Other MDR isolates	2/17	1/7	
Carbapenem-resistant MDR	1/17	0	
Previous chemotherapy			
≥ 2 cycles	14/16	3/3	0.134
≥ 5 cycles	4/16	1/3	1.000
> 5 cycles	4/16	1/3	1.000
Disease status			0.100
In CR	5/16	2/3	
Not in CR	11/16	1/3	
Risk factors			
EBMT score			1.000
≤ 2	8	4	
> 2	9	3	
Time from diagnosis to transplantation			0.307
< 12 m	14/17	4/7	
≥ 12 m	3/17	3/7	
Donor–recipient sex combination			0.669
F → M	7/17	2/7	
Non-F → M	10/17	5/7	
Previous treatment with broad-spectrum antibiotics	16/17	4/7	0.059
Severe neutropenia	15/17	4/7	0.126
Intestinal mucositis	10/17	3/7	1.000
Shock at presentation	11.76% (2/17)	0	
Body temperature	39.2 (38.5–40)	39 (38.9–40.2)	
Microorganism of pre-engrafted BSI			
Monomicrobial	11.76% (2/17)	14.29% (1/7)	1.000
Gram +ve cocci	23.53% (4/17)	0/7	0.238
Gram −ve organisms			
Polymicrobial	5.88% (1/17)		
Fusarium and Gram −ve bacilli	5.88% (1/17)	14.29% (1/7)	
Mix of Gram −ve organisms	5.88% (1/17)		
Gram +ve cocci and −ve organisms			
Source of bacteremia			
Catheter related	5	2	
Gastrointestinal tract	5	1	
Respiratory tract	4	1	
Perianal skin	3	1	
Unknown source	1	1	
Response to antibiotic therapy	88.2% (15/17)	85.71% (6/7)	1.000
Early case-fatality rate (48 h)	0	0	
Overall case-fatality rate (30 days)	11.76% (2/17)	0	
Attributable mortality	11.76% (2/17)	14.3% (1/7)	1.000

major causes of overall mortality both in the current study and in previous reports [4, 6, 10, 11, 37], even with effective antimicrobial treatment. The frequently reported risk factors of PE-BSI are the status of the underlying disease, prolonged and profound neutropenia, disruption of protective barriers such as mucosal

Table 3 Risk factors for PE-BSI by univariate analysis

Variable	Incidence (%)	HR	95% CI	*P* value
Type of transplantation				0.159
HLA-ID	12.7			
Haplo-ID	22.4	0.778	0.572–1.060	
Disease status				0.388
In CR	12.5			
Not in CR	18.2	0.830	0.562–1.226	
Age				0.605
< 14 years	21.1	0.841	0.443–1.598	
≥ 14 years	17.2			
Previous chemotherapy				0.527
< 2 cycles	25.0	0.607	0.067–5.507	
≥ 2 cycles	16.5			
< 5 cycles	18.3	0.901	0.596–1.362	0.637
≥ 5 cycles	14.9			
Serum ferritin				0.217
< 1000 ng/mL	16.2			
≥ 1000 ng/mL	18.6	0.579	0.259–1.295	
EBMT score				0.709
≤ 2	17.1	0.701	1.677	
> 2	19.7	0.584	1.463	
Time from diagnosis to transplantation				0.696
< 12 m	19.1	0.730	1.229	
≥ 12 m	16.2	0.545	2.463	
Donor–recipient sex combination				0.589
F → M	20.9			
Non-F → M	17.0	0.471	1.523	
Previous bacteremia				0.024
No	15.2			
Yes	36.8	0.385	0.169–0.873	
Previous therapy with broad-spectrum antibiotics	20	0.727	1.707	0.438
Previous treatment with carbapenems	19.8	0.679	1.220	0.554
Infusion dose CD34+, 10^6/kg				0.682
< 4×10^6/kg	16.7			
≥ 4×10^6/kg	19.5	0.927	0.654–1.315	
Duration of neutropenia				0.046
< 14 days	11.8			
≥ 14 days	25.5	0.612	0.398–0.942	
Severe neutropenia	20.2	0.697	1.125	0.372
Intestinal mucositis	25%	0.383	1.181	0.190
Gram −ve bacteremia				0.037
With previous Gram −ve BSI	50.0	0.224	0.060–0.834	
Without previous Gram −ve BSI	16.3			
Gram +ve bacteremia				0.422
With previous Gram +ve BSI	27.3	0.598	0.171–2.090	
Without previous Gram +ve BSI	17.5			

surfaces, and immunosuppressive medications. Some have also suggested that patients older than 18 years of age and/or peripheral blood stem cell grafts probably confer high risk for BSI [4]. In particular, the type of allo-HSCT and the degree of HLA mismatch between donor and recipient are considered as independent risk factors for the development of BSI, which may correlate with the intensity of immunosuppression [7–12, 37].

However, our results did not suggest that G-CSF-primed Haplo-ID transplantation increased the risk of pre-engraftment BSI or related mortality compared to HLA-identical transplantation. Here, PE-BSI was observed in 23.7% of Haplo-ID HSCT recipients, with an attributable mortality rate of 2.6%, which was not higher than that in HLA-ID HSCT recipients reported in this study or in previous studies [2, 4, 5]. Although the duration of neutropenia could be an independent risk factor of pre-engraftment BSI as shown in the current study, our conditioning regimens (including FA5-BUCY) and protocol for Haplo-ID transplant that included combined G-CSF-primed bone barrow (G-BM) and peripheral blood stem cells (PBSC) appeared to have facilitated prompt engraftment at a median of 13 days (range 10–35) for granulocytes and 13.5 days (range 7–43) for platelets, with full donor chimerism after 4 weeks in most patients, which was in agreement with the results by Huang's group [22, 38]. In addition, the incidence of pre-engraftment BSI depended mainly on the extent of oral and intestinal mucositis, a common complication post-HSCT that is related to high-intensity conditioning

Table 4 Distribution of Gram-negative pathogens and drug resistance compared by transplantation types

Gram-negative bacteria	Haplo-ID (76 cases)					HLA-ID (55 cases)				
	No. of isolates (*n*)	Carbapenem sensitive (*n*)	CRE (*n*)	Quinolone resistant (*n*)	TMP–SMX resistant (*n*)	No. of isolates (*n*)	Carbapenem sensitive (*n*)	CRE (*n*)	Quinolone resistant (*n*)	TMP–Smx resistant (*n*)
Any	16/76	15/16	1/16	3/16	7/16	5/55	5/5	0	0	3/5
Pseudomonas aeruginosa	5/76	5/5	0/5	0/5	0/5	1/55	1/1	0	0	0/1
Escherichia coli	3/76	3/3	0/3	2/3	2/3	2/55	2/2	0	1/2	2/2
Klebsiella pneumoniae	5/76	4/5	1/5	4/5	4/5	1/55	1/1	0	0	0/1
Enterobacter cloacae	1/76	1/1	0/1	1/1	1/1	0	0	0	0	0
Maltophilia Aeromonas	1/76	1/1	0/1	0/1	0/1	0	0	0	0	0
Acid-producing bacterium	1/76	1/1	0/1	0/1	1/1	1/55	1/1	0	0	1/1
Fatal BSI	2/76	1/2	1/2	1/2	2/2	0	0	0	0	0

[4, 5, 39–41]. In this study, intestinal mucositis was generally mild and manageable in both groups who had received the recently developed FA5-BUCY conditioning regimen [24], which resulted in better quality of life and treatment adherence, decreased risk of mucosal barrier injury associated with BSI, and ultimately improved outcome in these patients. Contrary to other published studies mentioned above, we did not find a strong association between the incidence of pre-engraftment BSI and age, disease status, serum ferritin, previous cycles of chemotherapy, previous therapy with broad-spectrum antibiotics, EBMT score, infusion dose of $CD34^+$ cells, or severity of neutropenia.

As clear guidelines have been put forward, it is important to promptly treat patients with empiric broad-spectrum intravenous antibiotics [33–36]. As the incidence and susceptibility of pathogenic bacteria may vary greatly between transplant centers, a thorough evaluation of the local epidemiology of pathogens is granted in order to decide on the choice of the best regimen for empirical treatment of febrile neutropenia during allo-HSCT. According to our multicenter study, GNB was the preponderant organism in blood isolates after HSCT, and there was significantly more GNB resistant to third-generation cephalosporins, although only rare cases had exhibited resistance to carbapenem and vancomycin so far. Thus, the combination of carbapenem and vancomycin could be recommended as the initial empirical therapy before the causative pathogen has been identified.

In this era of increasing antimicrobial resistance, the usefulness of antibiotic prophylaxis for bacterial BSI during the HSCT procedure has been questioned. Recent data indicated a shift in pathogen from GPB to GNB and that the increased risk of antimicrobial resistance during HSCT might be a consequence of the widespread use or early introduction of antibiotic prophylaxis such as quinolones, penicillin, or doxycycline

Table 5 Distribution of Gram-positive pathogens and drug resistance compared by transplantation types

Gram-positive bacteria	Haplo-ID (76 cases)					HLA-ID (55 cases)				
	No. of isolates (*n*)	Methicillin resistant (*n*)	Vancomycin resistant (*n*)	Quinolone resistant (*n*)	TMP–SMX resistant (*n*)	No. of isolates (*n*)	Methicillin resistant (*n*)	Vancomycin resistant (*n*)	Quinolone resistant (*n*)	TMP–SMX resistant (*n*)
Any	3/76	1/3	0	0	0	3/55	0	0	0	0
Streptococcus viridans	2/76	0	0	0	0	2/55	0	0	0	0
Coagulase-neg. staphylococci	1/76	1/1	0	0	0	0	0	0	0	0
Staphylococcus aureus	0	0	0	0	0	1/55	0	0	0	0
Fatal BSI	0	0	0	0	0	0	0	0	0	0

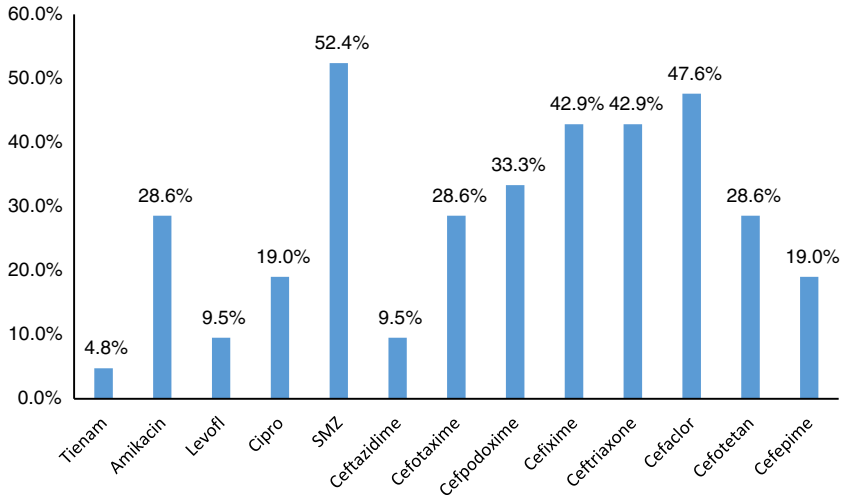

Fig. 1 Antibiotic resistance profile of Gram-negative organisms (GNR) isolated from positive blood cultures of recipients with PE-BSI

[8, 42–46]. Our data also showed the predominance of TMP–SMX resistance in both groups after routine administration of prophylactic TMP–SMX starting from the conditioning, while most isolates remained sensitive to quinolones. Therefore, it is necessary to carefully consider the benefits of antibiotic prophylaxis and the best time for its administration. Despite the emergence of antibiotic resistance, our results suggested that TMP–SMX prophylaxis is still deemed appropriate. We assumed that antibiotic resistance may be attenuated if TMP–SMX were administered at the time of neutropenia instead of conditioning to shorten the course of prophylactic antibiotic treatment. It might be better to provide only preemptive antibiotic treatment based on the susceptibility of previous BSI before stem cell infusion, as previous GNB occurring during chemotherapy was a high risk factor for pre-engraftment BSI. On the other hand, early transplant with less prior chemotherapy combined with intensive supportive care may reduce the risk of BSI during chemotherapy [24], particularly in the refractory patients, might result in less PE-BSI as well.

In summary, our multicenter study show that G-CSF-primed Haplo-ID HSCT did not increase the risk of PE-BSI, strongly suggesting that G-CSF-primed Haplo-ID HSCT, in combination with the FA5-BUCY regimen [24], is a promising alternative for advanced hematological disorders. Our report revealed a prevalence of GNB in pre-engraftment BSI at our centers, and that TMP–SMX prophylaxis starting from the conditioning may contribute to resistant GNB infections in allogeneic HSCT recipients over time. Therefore, new strategies for antibiotic prophylaxis administration to prevent the incidence of pre-engraftment bacteremia need to be evaluated.

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Authors' contributions Prof. Jianda Hu and Prof. Ting Yang designed and performed the research. Dr. Jinhua Ren and Dr. Qiaoxian Ling collected the data. Dr. Qiaoxian Ling performed the statistical analyses. Prof. Ting Yang interpreted the data and wrote the manuscript. All authors participated in the management of patient care. All authors critically reviewed and approved the manuscript.

Compliance with ethical standards

This study was conducted in accordance with the ethical standards of the local institutional review board (the Medical Ethics Committee of Fujian Medical University Union Hospital and the Helsinki Declaration). Informed consent was obtained from all patients and donors before they were included in the study.

Conflict of interest The authors declare that they have no competing interests.

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