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Bacterial Bloodstream Infections in Patients Undergoing Allogeneic Hematopoietic Cell Transplantation With Post-Transplantation Cyclophosphamide

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A B S T R A C T

This study investigates the incidence and predictors for bacterial bloodstream infection (BSI) in 330 adults undergoing allo-HCT, and explores the effect of post-transplantation cyclophosphamide (PTCY) on the probability of presenting this complication. All patients received levofloxacin during the aplastic phase. Only the first episode of BSI was counted as an event. Patients were classified into 2 groups: PTCY-based (n = 200) versus other prophylaxis (n = 130). One hundred twenty-four patients were diagnosed with a first episode of BSI, most of them during the first 30 days (70.2%). Proportions of BSIs caused by Gram-positive bacteria were comparable to those caused by Gram-negative bacteria (48.3% versus 45.9%). The cumulative incidence of BSI was higher in patients receiving PTCY than in those receiving other prophylaxis (days 30 and 100: 35.0% and 37.0% versus 13.1% and 18.5%, $P < .001$). At day 30, the likelihood of BSI was 2.41 ($P = .012$) times higher in the PTCY group than in the non-PTCY group. The 30-day mortality rate in all patients with BSI was 8.0%, lower ($P = .002$) in the PTCY group (2.3%) than in the non-PTCY group (21.6%). Finally, the overall survival of patients receiving PTCY and diagnosed with BSI was similar to that of patients without presenting this complication.
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Bacterial bloodstream infections (BSI) are a prevalent post-transplantation complication and one of the primary causes of death in allogeneic hematopoietic cell transplantation (allo-HCT) recipients [1–3]. BSI are most frequently diagnosed during the pre-engraftment phase, with an incidence rate of 20% to 50%. The period of neutropenia and mucosal injury from transplant conditioning are predisposing factors for pre-engraftment BSI [4–7]. Moreover, the presence of an indwelling central venous catheter, graft-versus-host disease (GVHD), poor graft function, and delayed immune reconstitution increase the incidence of BSI during the post-transplantation period [8].

The use of post-transplantation cyclophosphamide (PTCY) for GVHD prevention has supposed a milestone in haploidentical HCT (haplo-HCT), with encouraging positive results [9–11]. PTCY action resides on the induction of apoptosis of rapidly proliferating alloreactive T-cells by sparing regulatory T-cells. Secondary to its efficacy, the use of PTCY is being extended to allo-HCT performed from HLA-mismatched and matched donors

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[12–15]. Despite the reduction of GVHD and the fast quantitative immune reconstitution attributed to PTCY, few studies have been published exploring risk factors for BSI among patients receiving PTCY [16–21]. Moreover, the ranges of incidences of BSIs reported in these studies went from 30% to 50%.

Although the use of PTCY is becoming prevalent, the reported evidence on the incidence of BSI in this setting, as well as the potential influence in transplantation outcomes, remains limited. PTCY-based prophylaxis has been progressively implemented at our HCT Program since 2014 [22,23]. This study investigates the incidence, etiology, and risk factors for BSI in adults undergoing allo-HCT at our Institution between 2014 and 2021, with particular attention to risk factors for BSI attributed to PTCY prophylaxis, and transplantation outcomes.

METHODS

Patient Selection

A total of 330 consecutive adults with malignant hematological disorders who underwent allo-HCT at Hospital Clinic de Barcelona, Spain, between January 2014 and March 2021, were included in the study. Two hundred (60.6%) patients received PTCY-based prophylaxis. Data were collected retrospectively and updated in January 2022. The study was approved by the Ethics Committee of the Hospital Clinic de Barcelona and conducted following standards set forth by the Declaration of Helsinki.

Conditioning Regimen, GVHD Prophylaxis, and Infectious Prophylaxis

Myeloablative regimens (MAC) contained high-dose busulfan (3.2 mg/kg/d intravenously [IV] × 4 days) or 12 Gy of total body irradiation combined with fludarabine (30 mg/m^2/d IV × 4 days). Reduced-intensity regimens combined standard doses of fludarabine with lower doses of busulfan (3.2 mg/kg/d IV × 3 days) or 8 Gy of total body irradiation. Unmanipulated T-cell replete peripheral blood stem cell grafts were the predominant stem cell source. Granulocyte colony-stimulating factor was not administered during the study period.

PTCY-based prophylaxis consisted of 50 mg/kg/d of PTCY IV on days 3, and 4 followed by tacrolimus (TK) initiated at a dose of 0.03/kg/24 h IV on day 5. TK was titrated to a level of 5 to 15 ng/L. In addition, when haploidentical donors were selected for allo-HCT mycophenolate mofetil was administered from day 5 to day 35. Other GVHD prophylaxis combined the use of calcineurin inhibitors (cyclosporine or TK) with standard doses of methotrexate, mycophenolate mofetil, or sirolimus. Immunosuppressant medication was maintained therapeutic until day 90 and tapered down progressively up to day 180 in the absence of GVHD. No patient received anti-thymocyte globulin (ATG).

The institutional anti-microbial prophylaxis was as follows: levofloxacin 500 mg daily from day 1 until neutrophil engraftment, fluconazole 400 mg daily from day 1 until day 60, acyclovir 800 mg twice daily from day 1 until 1 year after the allo-HCT, and either trimethoprim-sulfamethoxazole 160/800 mg three times per week, or inhaled pentamidine 300 mg monthly until the achievement of peripheral blood CD4+ cell count> 200 cells/mL. No patient received letermovir for cytomegalovirus prevention.

Main Definitions and Supportive Care

BSI was defined as the isolation of a bacterial pathogen from at least one set of blood cultures (one aerobic and one anaerobic) drawn from a transplant recipient either from the day of starting PTCY or from the day of the stem cell infusion for patients receiving other prophylaxis, to long-term follow-up. All BSI episodes were confirmed after reviewing clinical charts. To define a BSI as that caused by a common skin colonizer such as coagulase-negative staphylococci or *Corynebacterium*, we required a suggestive clinical presentation and (i) ≥2 blood cultures drawn from different sites, (ii) ≥1 positive blood culture obtained from the peripheral vein blood and a positive catheter culture. Those patients with any positive culture that was considered a contaminant were included in the group of not-infected patients. Polymicrobial infection was defined when the BSI was caused by 2 or more different microorganisms.

A nontunneled jugular central line was placed in all cases on admission and maintained until neutrophil engraftment and until patients achieved transfusion independence. Dressings and site care with antiseptic were routinely performed every 7 days or immediately when the dressing was soiled, loose, or damp. In the event of fever, blood cultures were drawn using an aerobic and an anaerobic bottle and processed by the Clinical Microbiology Laboratory at HCB. Catheter-related BSI was defined according to the guidelines from the Infectious Disease Society of America and was generally managed by replacing the infected central line and with systemic intravenous antibiotics.

Statistical Analysis

The diagnosis of at least 1 episode of BSI was considered the first main dependent variable. Among those patients with more than one BSI during the post-transplantation follow-up period, the only episode of BSI considered was the first one. Risk factors and the cumulative incidence of BSI were analyzed using Fine-Gray proportional hazard regression models for competing risk analyses, and accounting for death and relapse as competing events. The risk factors for BSI were investigated separately in 3 three time periods: from day 0 to day 30; from day 0 to day 100; and from day 100 to 2 years.

The second main topic of interest was BSI-related mortality and the impact of BSI in post-transplantation overall survival (OS). For this analysis, patients diagnosed with a first BSI episode after presenting disease relapse were censored (n = 10); the effect of the relapse and its treatment in OS would potentially be more important than the effect of the BSI itself. OS was estimated using Kaplan-Meier product-limit method, and post-transplantation follow-up was censored at 2 years. The impact of the explanatory variable (BSI) and other risk factors on OS was analyzed using univariate and multivariate regression models. The variable BSI infection was always analyzed as a time-dependent variable.

The explanatory variables in the multivariate analysis were those considered clinically relevant, and those found statistically significant as explanatory variables in the univariate analysis. All P values were 2-sided, and only estimated coefficients with $P < .05$ of being different from zero were considered statistically significant. Statistical analysis was performed using R Software [24].

RESULTS

Baseline Characteristics and Main Post-Transplantation Information

The study cohort was divided into 2 groups of patients according to the GVHD prophylaxis (PTCY-based versus other prophylaxis). As shown in Table 1, the baseline characteristics were balanced, except for the variables donor type and transplantation period. At our Institution, PTCY-based prophylaxis was first limited to haplo-HCT. This prophylaxis was consecutively expanded to allo-HCT performed from HLA-mismatched unrelated donor (MMUD) and matched unrelated donor (MUD), and recently to matched sibling donor (MSD) allo-HCT. This explains why the proportion of transplantations performed from alternative donors was higher in the PTCY group (57.0% versus 5.4%, $P = .001$), and use of PTCY was more prevalent between 2018 and 2021 [65.0% versus 25.4%], $P<0.001$).

As reported in Table 2, the median days for neutrophil and platelet engraftments was longer in the PTCY group (19 versus 16 days [$P < .001$] and 17 versus 11 days [$P < .001$]). The cumulative incidence functions (CIF) of grade II-IV and III-VI acute GVHD at day 100 and moderate/severe cGVHD at 2 years were 24.0%, 6.5%, and 9.8% for patients receiving PTCY and 35.4% ($P = .013$), 13.1% ($P = .038$), and 41.1% ($P < .001$) for those who did not. Post-transplantation outcomes were comparable between the 2 cohorts.

Incidence and Timing of Bloodstream Infections after Allo-HCT

Table 2 shows that 124 (37.6%) patients were diagnosed with at least one BSI after allo-HCT. Overall, most BSI were diagnosed during the first 30 days (n = 87, 70.2%); 13 (10.5%) episodes occurred between day 30 and day 100; and 24 (19.3%) after day 100. Moreover, the cumulative incidences of BSI at days 30, 100, and 2 years were 26.4%, 29.7%, and 34.7%, respectively.

The incidence of BSI was higher in patients receiving PTCY (43.5% versus 28.5%, $P = .001$) (Table 2). Eighty-seven (43.5%) out of 200 patients receiving PTCY were diagnosed with BSI at a median time of 13 days (interquartile range [IQR]: 10-20), and 80.5% of the episodes occurred during the first 30 days (CIF at 30, 100 days and 2 years: 35.0%, 37.0%, and 42.1%). Among patients receiving other prophylaxis, 37 (28.5%) were diagnosed with at least one episode of BSI at a median time of

Table 1
Baseline Patient Characteristics and Allo-HCT Information

	Overall (N = 330)	PTCY-Based Prophylaxis (N = 200 [60.6%])	Other GVHD Prophylaxis (N = 130 [39.4%])	*P* Value
Age Median (range)	53 (18-70)	52 (18-70)	54 (18-70)	.219
Older than 60 years	103 (31.2)	63 (31.5)	40 (30.8)	.889
Female sex	149 (45.2)	85 (42.5)	64 (49.2)	.230
Baseline Diagnosis				—
AML	134 (40.7)	82 (41.0)	52 (40.0)	
ALL	43 (13.0)	29 (14.5)	14 (10.8)	
MDS	65 (19.7)	38 (19.0)	27 (20.8)	
MPN	21 (6.4)	12 (6.0)	9 (6.9)	
CML	11 (3.3)	5 (2.5)	6 (4.6)	
Lymphoproliferative disorders	49 (14.8)	31 (15.5)	18 (13.8)	
Other	7 (2.1)	3 (1.5)	4 (3.1)	
HCT-CI >3	75 (22.7)	46 (23.0)	29 (22.3)	.883
Karnofsky performance status 70%-80%	79 (23.9)	44 (22.0)	35 (26.9)	.270
Donor type				<.001
10/10 MSD	86 (26.1)	13 (6.5)	73 (56.1)	
10/10 MUD	123 (37.3)	73 (36.5)	50 (38.5)	
9/10 MMUD	80 (24.2)	73 (36.5)	7 (5.4)	
Haploidentical	41 (12.4)	41 (20.5)	0	
Intensity				.736
MAC	146 (44.2)	87 (43.5)	59 (45.4)	
RIC	184 (55.8)	113 (56.5)	71 (54.6)	
High dose TBI (12 Gy)	48 (14.5)	33 (16.5)	15 (11.5)	.212
GVHD prophylaxis (extended)				—
PTCY-MMF-TK	47 (14.2)	47 (23.5)	—	
PTCY-TK	153 (46.4)	153 (76.5)	—	
MTX-CNI	54 (16.4)	—	54 (41.6)	
MMF-CNI	74 (22.4)	—	74 (56.9)	
SIR-TK	2 (0.60)	—	2 (1.5)	
Stem cell source: peripheral blood	320 (97.0)	193 (96.5)	127 (97.7)	.745
Transplantation date				<.001
2014–2017	167 (50.6)	70 (35.0)	97 (74.6)	
2018–2021	163 (49.4)	130 (65.0)	33 (25.4)	

AML indicates acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasms; CML, chronic myeloid leukemia; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; RIC, reduced-intensity conditioning; MMF, mycophenolate mofetil; MTX, methotrexate; CNI, calcineurin inhibitors; SIR, sirolimus.

55 days (IQR: 6-118), and 45.9% of these occurred during the first 30 days (CIF at 30, 100 days and 2 years: 13.1%, 18.5%, and 23.8%) (Figure 1). Therefore the median time of BSI diagnosis was shorter in patients with PTCY than in patients in the other group.

Notably, 75 (60.4%) out of 124 patients were diagnosed with the first BSI during the neutropenic and peri-engraftment phase (early post-transplantation phase). Based on this result, additional landmark analysis was conducted comparing the incidences of BSI according to GVHD prophylaxis during the early post-transplantation phase and after engraftment. For this analysis, the median of days for neutrophil engraftment (19 days in patients receiving PTCY and 16 days in those receiving other prophylaxis) was used to divide the post-transplantation follow-up period into 2 early and late post-transplantation phases. As reported in Figure 1, those patients receiving PTCY had a higher incidence of BSI diagnosed during the early post-transplantation phase (Global CIF: 30.5% versus 10.8%, $P < .001$), and a comparable probability of being diagnosed with a BSI achieving engraftment and during the first 2 years after allo-HCT (2-year CIF: 16.7% versus 14.7%, $P = .727$) than patients with other prophylaxis

Etiology of BSI

Table 3 details the etiology of the most prevalent BSIs. Overall, the proportions of BSIs caused by Gram-positive bacteria (GPB) were similar to those caused by Gram-negative bacteria (GNB) (48.4% versus 46.0%). *Staphylococcus* bacteria (n = 38) and *Escherichia coli* (n = 17) were the most prevalent isolated GPB and GNB during the first 30 days after allo-HCT. Beyond day 30, GNB BSIs were most frequent than GPB BSIs (n = 13 versus 21), with *E. coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* being the most prevalent ones.

Among patients receiving PTCY, the proportion of isolated GPB and GNB were similar (17% versus 16%) during the entire post-transplant period. The most frequent isolated bacteria during the first 30 days were *Staphylococcus epidermidis* (n = 21) and *E. coli* (n = 17). After day 30, the most frequent ones were both *Staphylococcus* and *Streptococcus* GPB and *E. coli* and *K. pneumoniae* GNB.

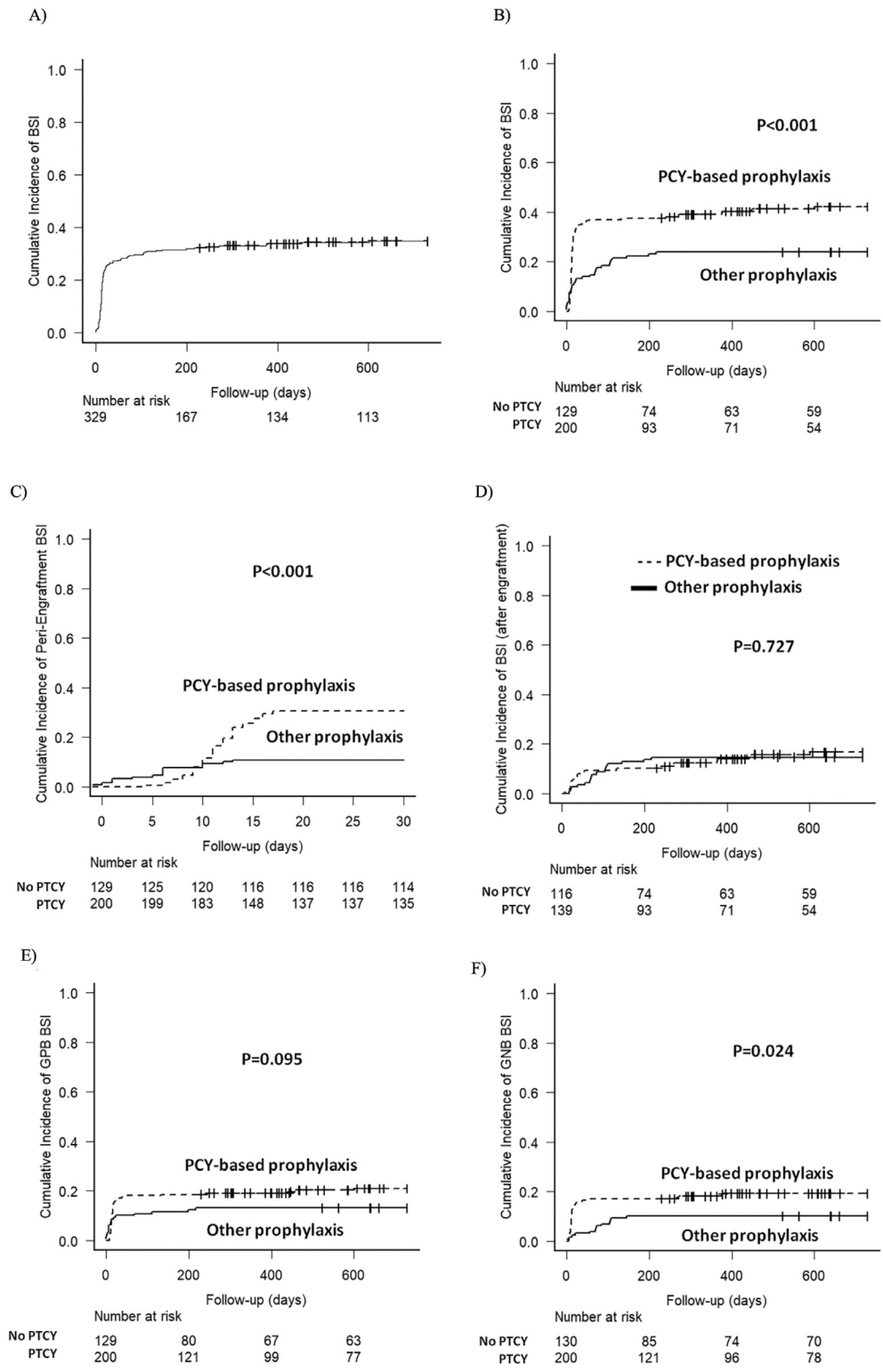
Risk Factors for BSI

Risk factors for BSI are summarized in Supplementary Table S1 (univariate) and Table 4 (multivariate). The multivariate analysis confirmed that using PTCY increases the likelihood of

Table 2
Main Post-Transplantation Information and Outcomes

	Overall(N = 330)	PTCY-Based (N = 200 [60.6%])	Other Prophylaxis (N = 130 [39.4%])	*P* Value
Post-transplantation information and outcomes				
Engraftment information				
Median days neutrophil engraftment (IQR)	18 (15-21)	19 (17-23)	16 (14-18)	.005
Median days platelet engraftment (IQR)	14 (11-22)	17 (12-27)	11 (10-14)	<.001
Primary graft failure	4 (1.2)	4 (2.0)	0	.105
Nadir neutropenia (median ≥ 19 days)	147 (44.5)	116 (58.0)	31 (23.8)	.001
Mucositis				
Grade 3-4	103 (31.2)	65 (32.5)	38 (29.2)	.512
Requirement of total parenteral nutrition	57 (17.3)	38 (19.0)	19 (14.6)	.303
Cumulative incidence of GVHD, % (95% CI)				
Grade 2-4 acute GVHD at day 100	28.5 (23.7-33.4)	24.0 (18.3-30.1)	35.4 (27.2-43.6)	.013
Grade 3-4 acute GVHD at day 100	9.1 (6.3-12.5)	6.5 (3.6-10.5)	13.1 (8.0-19.5)	.038
Moderate/Severe chronic GVHD at 2 years	22.6 (18.0-27.6)	9.8 (5.9-14.8)	41.1 (32.2-49.7)	<.001
Median follow-up, mo (IQR)	25.9 (8.7-51.8)	19.8 (9.4-45.7)	37.0 (7.9-60.5)	.020
Main outcome information at 2 years				
Relapse	82 (24.8)	43 (21.5)	39 (30.0)	—
Death	105 (31.8)	59 (29.5)	46 (35.3)	—
Causes of death				
Relapse	54 (16.3)	27 (13.5)	27 (20.7)	
Infection	19 (5.7)	13 (5.9)	6 (4.6)	
GVHD	14 (4.2)	6 (3.0)	8 (6.1)	
GF	5 (1.5)	4 (1.8)	1 (0.7)	
Other	13 (3.9)	9 (4.0)	4 (3.0)	
Main post-transplantation outcomes, % (95% CI) *				
2-year overall survival	67.1 (61.6-72.0)	68.4 (61.1-74.7)	64.4 (55.5-72.0)	.353
2-year relapse-free survival	58.5 (52.9-63.7)	60.0 (52.6-66.6)	56.1 (47.1.64.1)	.485
2-year non-relapse mortality	15.7 (12.0-19.9)	16.5 (11.6-22.1)	14.6 (9.2-21.3)	.649
2-year cumulative incidence of relapse	25.7 (21.1-30.6)	23.5 (17.7-29.8)	29.3 (21.7-37.3)	.223
Rates and incidence of BSI				
Rates of BSI, no. (%)	124 (37.6)	87 (43.5)	37 (28.5)	.001
Timing of first BSI				
Median of days to diagnosis (IQR)	13 (10-54)	13 (10-20)	55 (6-118)	.001
BSI diagnosed before and during engraftment	75 (60.4)	61 (73.5)	14 (37.8)	.001
BSI diagnosed during first 30 days	87 (70.2)	70 (80.5)	17 (45.9)	0.001
BSI diagnosed between day 31 and 100	13 (10.5)	6 (6.9)	7 (18.9)	.119
BSI diagnosed after day 100	24 (19.3)	11 (12.6)	13 (35.2)	.738
Overall cumulative incidence of BSI, % (95% CI)				
Before and during engraftment	22.7 (28.427.4)	30.5 (24.2-37.0)	10.8 (6.2-16.8)	<.001
After stem cell engraftment and until 2 years	15.5 (11.4-20.3)	16.7 (10.8-23.7)	14.7 (8.9-21.7)	.727
Cumulative incidence of BSI, % (95% CI)				
Day 30	26.4 (21.7-31.2)	35.0 (28.4-41.6)	13.1 (8.0-19.5)	<.001
Day 100	29.7 (24.8-34.7)	37.0 (30.3-43.7)	18.5 (12.3-25.6)	<.001
2 years	34.7 (29.6-39.9)	42.1 (35.1-49.0)	23.8 (16.9-31.5)	<.001
Cumulative incidence of GPB BSI*				
Day 30	14.2 (10.7-18.2)	17.0 (12.2-22.5)	10.0 (5.6-15.9)	.099
Day 100	15.2 (11.5-19.2)	18.0 (13.0-23.6)	10.8 (6.2-16.8)	.095
2 years	17.7 (13.8-22.0)	20.9 (15.5-26.8)	13.1 (8.0-19.5)	.095
Cumulative Incidence of GNB BSI				
Day 30	10.9 (7.8-14.6)	16.0 (11.3-21.4)	3.1 (1.0-7.2)	.006
Day 100	13.0 (9.7-16.9)	17.0 (12.2-22.5)	6.9 (3.4-12.2)	.020
2 years	15.5 (11.8-19.6)	19.1 (14.0-24.9)	10.0 (5.6-15.9)	.024
30-Day mortality rate among all patients with BSI, no. (%)	10 (8.0)†	2 (2.3)‡	8 (21.6)§	0.002

GF indicates graft failure; IQR, interquartile range; CI, confidence interval.
The cumulative incidence of BSI has been calculated accounting for dead and relapse as competing events.
* Secondary to the misbalance in the median follow-up between the two study groups, the post-transplantation follow-up has been censored at 2 years.
† N = 126
‡ N = 87
§ N = 37



Legend: A-B) Cumulative incidences of BSI (entire cohort and according to the GVHD prophylaxis). C-D) Cumulative incidences of BSI during the pre- and peri-engraftment period and after stem cell engraftment according to the GVHD prophylaxis E-F) Cumulative incidences of BSI caused by *Gram-positive* or *Gram-negative bacteria* and according to the GVHD prophylaxis.

Figure 1. Cumulative Incidence of BSI. (A, B) Cumulative incidences of BSI (entire cohort and according to the GVHD prophylaxis). (C,D) Cumulative incidences of BSI during the pre- and peri-engraftment period and after stem cell engraftment according to the GVHD prophylaxis. (E, F) Cumulative incidences of BSI caused by Gram-positive or Gram-negative bacteria and according to the GVHD prophylaxis.

Table 3
Incidences of BSI According to Transplantation Period

Etiology of the Most Prevalent BSIs, n (%)	Entire Post-Transplantation Period(N = 330)	BSI Diagnosed During the First 30 Days			BSI Diagnosed After Day 30 and Up to Day 100			BSI Diagnosed After Day 100 and Up to 2 Years*		
		Overall BSI (N = 330)	PTCY(N = 200 [60.6%])	No PTCY (N = 130 [39.4%])	*P* Value	Overall BSI (N = 325)	PTCY (N = 196 [60.3%])	No PTCY (N = 129 [39.7%])	*P* Value	Overall BSI (N = 306%)	PTCY(N = 184 [60.1%])	No PTCY (N = 122 [39.9%])	*P* Value
Total	124 (37.6)	87 (26.3)	70 (35.0)	17 (13.0)	<.001	13 (4.0)	6 (3.0)	7 (5.4)	.287	24 (7.8)	11 (6.0)	13 (10.6)	.192
Gram-positive bacteria	60 (48.4)	47 (14.2)	34 (17.0)	13 (10.0)		4 (1.2)	3 (1.5)	1 (0.7)		9 (2.9)	6 (3.2)	3 (2.5)	
Streptococcus	7	2	2	0		0	0	0		5	4	1	
Staphylococcus	43	38	26	12		3	2	1		2	2	1	
Enterococcus	7	5	4	1		1	1	0		1	0	1	
Other Gram-positive bacteria	3	2	2	0		0	0	0		1	0	0	
Gram-negative bacteria	57 (46.0)	36 (10.9)	32 (16.0)	4 (3.0)		7 (2.2)	2 (1.0)	5 (3.9)		14 (4.6)	4 (2.2)	10 (8.1)	
E. coli	25	17	16	1		3	1	2		5	2	3	
Klebsiella	15	8	7	1		1	0	1		6	2	4	
Pseudomonas	8	4	4	0		3	1	2		1	0	1	
Other Gram-negative bacteria	9	7	5	2		0	0	0		2	0	2	
Polymicrobial infection	7 (5.6)	4 (1.2)	4 (2.0)	0		2 (0.6)	1 (0.5)	1 (0.7)		1 (0.3)	1 (0.6)	0	

* Any second episode of BSI has not been accounted for in this study, so the incidence of late BSIs can eventually be underestimated

BSI diagnosis during the first 30 (hazard ratio [HR] 2.41, $P = .012$) and 100 days (HR 1.98, $P = .027$) after allo-HCT, compared with the likelihood of BSI diagnosis in non-PTCY patients.

Older patients (HR 1.02, $P = .044$), patients with a Karnofsky performance status ≤80% (HR 1.63, $P = .029$), and patients who engrafted after day 18 (HR 1.60, $P = .036$) were at higher risk for being diagnosed a BSI episode during the first 100 days after stem cell infusion. The diagnosis of grade III-IV aGVHD substantially increased the risk of a BSI episode during the first 100 days after allo-HCT (HR 7.71, $P < .001$). The selection of alternative donor sources (MMUD and haploidentical donors) had no significant effect in the risk of BSI (HR 0.81, $P = .419$).

From Table 3, 24 (7.8%) first episodes of BSIs were diagnosed between day 100 and up to 2 years after allo-HCT. The multivariate results from Table 4 indicated that in the period between day 100 and up to 2 years, the likelihood of a BSI episode was not statistically different in the 2 groups of patients (HR 1.17, $P = .846$). The table also shows that patients with grade III-IV aGVHD had a higher risk of being diagnosed with a BSI after day 100 than patients without this complication (HR 3.93, $P < .001$).

BSI among Patients Receiving PTCY-Based Prophylaxis

The donor types and other possible risk factors for BSI were explored separately in the 200 patients receiving PTCY. The day 30 CIF of BSI in patients receiving grafts from MSD, MUD, MMUD, and haploidentical donors were 46.2%, 42.5%, 32.9%, and 22.0%, respectively ($P = .088$) (Supplementary Figure S1). As reported in Table 5, in the univariate regression model, the selection of haploidentical donors was associated with a lower risk of BSI during the first 30 days after allo-HCT (HR 0.50, $P = .046$). However, this association was not confirmed in the multivariate analysis (HR 0.75, $P = .240$).

Older age (HR 1.03, $P = .007$), receiving MAC regimens (HR 1.81, $P = .042$), and engraftment 18 days after stem cell infusion (HR 1.88, $P = .017$) were statistically significant predictors for being diagnosed with BSI during the first 30 days after allo-HCT. In addition, patients with grade III-IV aGVHD (HR 7.68, $P = .020$) had a higher risk for diagnosis of BSI between days 30 and 2 years after allo-HCT than otherwise.

BSI: Clinical-Related Information and Mortality

Patients with BSI diagnosed during the 30 days after allo-HCT had a more prolonged hospitalization time (median 32 days versus 29, $P = .007$) and a higher rate of readmissions (74.3% versus 55.9%, $P = .01$), compared with those that did not. Eleven (8.8%) of the 124 patients with BSI were transferred to the intensive care unit. Three (2.4%) patients died as a result of the first episode of BSI, all caused by an *E. Coli*, and in a median of 2 days. Moreover, the 30-day mortality rate in the 124 patients with BSI was 8.0% (2.3% in patients receiving PTCY, compared with 21.6% in patients receiving other prophylaxis, $P = .002$).

Table 6 shows the effect of BSI in OS. Results are reported for all patients, as well as for the sample of patients receiving PTCY versus other prophylaxis. The 10 patients who were diagnosed with a first BSI after presenting disease relapse were excluded from the sample. Overall, patients with BSI had lower OS than patients without a history of BSI (2-year: 59.7% versus 71.1%, $P = .050$); the estimated HRs were 1.76 ($P = .004$) in the univariate analysis and 1.62 ($P = .006$) in the multivariate. When the analysis was restricted to patients with PTCY and patients without PTCY, the univariate analysis confirmed the negative effect of BSI in OS only in patients receiving other

Table 4
Risk Factors for BSI Diagnosed During the Early and Post-Transplantation Period

Multivariate Analysis	Risk Factors for BSI Diagnosed During the Early Post-Transplantation Follow-Up				Risk Factors for BSI Diagnosed After Day 100	
	BSI Diagnosed During First 30 Days HR (95% CI)	*P* Value	BSI Diagnosed During First 100 Days HR (95% CI)	*P* Value	BSI Diagnosed From Day 100 to 2 Years HR (95% CI)	*P* Value
GVHD Prophylaxis, PTCY-based (versus Others)	2.41 (1.27-4.78)	.012	1.98 (1.07-3.65)	.027	1.17 (0.22-6.25)	.846
Age at transplantation, continuous	1.02 (0.99-1.06)	.056	1.02 (1.01-1.03)	.044	1.03 (0.98-1.07)	.204
KPS ≤ 80% (versus 90%-100%)	1.89 (1.20-2.99)	.006	1.63 (1.04-2.55)	.029	N/A	—
Stem Cell Source, BM (versus PB)	2.29 (0.88-5.93)	.087	1.63 (1.04-2.55)	.195	N/A	—
Conditioning intensity, RIC (versus MAC)	0.74 (0.44-1.27)	.280	0.81 (0.50-1.32)	.605	0.65 (0.22-1.90)	.437
MMUD donor type, haplo (versus MSD, MUD)	0.78 (0.48-1.28)	.340	0.81 (0.50-1.32)	.410	1.60 (0.35-7.26)	.538
Nadir Neutropenia ≥ 19 days (versus < 19 days)	1.73 (1.07-2.79)	.024	1.60 (1.02-2.51)	.036	N/A	—
Transplant Time Period 2018 –2021 (versus 2014–2017)	1.40 (0.82-2.39)	.220	1.29 (0.79-2.11)	.295	0.70 (0.22-2.24)	.553
Time-dependent variable						
Grade 3-4 acute GVHD	N/A	—	7.71 (2.57-23.13)	<.001	3.93 (1.24-12.47)	<.001
Grade mod/severe chronic GVHD	N/A	—	N/A	—	0.43 (0.07-2.64)	.366

KPS indicates Karnofsky performance status; BM, bone marrow; PB, peripheral blood.
Post-transplantation follow-up was censored at day 30, day 100, and 2 years, respectively. Any second episode of BSI has not been accounted for in this study, so the incidence of late BSIs can eventually be underestimated. The variable transplantation time period was included as a control variable to provide robustness to the present study. Results provided by the univariate analysis are reported in Supplementary Table S1.

prophylaxis (HR 2.55 [*P* = .002]) (Supplementary Figure S2). These results were confirmed in the multivariate analysis after controlling for other risk factors for OS. As reported in Table 6, in the sample of patients receiving PTCY the association between BSI and risk for mortality was not statistically significant (HR 1.16, *P* = .597).

DISCUSSION

This study reports a 2-year incidence of 37.5% BSIs in a cohort of 330 adults undergoing allo-HCT from a single Institution. All patients received levofloxacin as anti-bacterial prophylaxis. Two hundred patients received PTCY-based prophylaxis. The risk for BSI diagnosed during the first 30 days after allo-HCT was 2.41 times higher among patients who received PTCY prophylaxis than among patients receiving other prophylaxis.

The 2-year 37.5% BSI incidence documented in our study was diagnosed mainly during the first 30 days after allo-HCT (70.2%). This incidence is in line with that reported by different investigators, ranging from 16% to 40% [7,25-27]. The new and most relevant result provided from this study was that PTCY-based prophylaxis significantly increased by a factor of 2.41 (HR) the risk for being diagnosed with a BSI during the early post-transplant phase. The use of PTCY for GVHD prevention is being expanded to allo-HCT performed from unrelated donors and MSD [28]. Carreira et al. [19] reported results on BSIs in a cohort of 657 adults undergoing allo-HCT, where 447 patients received PTCY-based prophylaxis (97% combined with ATG and CsA). Main conclusions were that using PTCY increased 1.78 times the risk for BSI diagnosed during the first 100 days after allo-HCT. Our results are in line with those of Carreira et al. [19], although none of the patients in our sample received ATG-based prophylaxis, so we cannot compare the risk for BSI among patients receiving PTCY and among those receiving ATG.

The global incidence of BSI in patients receiving PTCY was 42.1% (2-year CIF GPB and GNB BSI of 20.9% and 19.1%, respectively). Consistently with findings in previous studies [16,18], the majority of BSI episodes occurred during the first 30 days after the transplant (day 30 CIF of BSI 35.0%). Oltolini et al. [16] analyzed the incidence of pre-engraftment BSI in a cohort of 235 adults all of them undergoing PTCY-based allo-HCT. The incidence of BSI reported at 28 days was 32%, without differences among donor types (P=0.988). Similarly, García-Cadenas et al. reported a pre-engraftment incidence of BSI of 42% in a cohort of 117 adults undergoing allo-HCT all receiving PTCY. Once again no differences were found between donor types [17].

In our analysis, patients undergoing haplo-HCT had fewer BSIs than those undergoing allo-HCT from MSD and unrelated donors (CIF day 30: 22.0% versus 38.4%). The risk for BSI episodes in our sample of haplo-HCT was lower than the reported in previous studies, all of them in the range between 35% and 62% [18,20,21]. This difference could be attributed to the lower proportion of older patients and of patients receiving MAC regimens (15 [36.6%] of 41) among the patients undergoing haplo-HCT in our sample, since age and MAC regimes were identified as risk factors for BSI in the multivariate estimation. In line with findings from previous research [16,17] in our study the donor type did not significantly impact on the probability of being diagnosed with BSI, and the selection of mismatched or haploidentical donors were not predictors of BSI in patients receiving PTCY-based prophylaxis. The expansion in the use of PTCY-base prophylaxis has made the immunosuppressive combinations more homogeneous between donor

Table 5
Risk Factors for BSI Among Patients Receiving PTCY-Based Prophylaxis.

	BSI Diagnosed During First 30 Days HR (95% CI)	*P* Value	BSI Diagnosed From Day 30 to 2 Years HR (95% CI)*	*P* Value
Univariate analysis				
Age				
Continuous	1.02 (1.01-1.04)	.013	1.01 (0.97-1.05)	.57
Older than 60 years (versus younger)	1.87 (1.18-2.96)	.007	1.20 (0.26-5.48)	.81
KPS ≤ 80% (versus 90%-100%)	1.42 (0.84-2.39)	.18	1.51 (0.34-6.98)	.57
Donor type, Haplo (versus others)†	0.50 (0.25-0.98)	.046	0.34 (0.04-2.64)	.31
Stem cell source, bone marrow (versus peripheral blood)	1.82 (0.74-4.50)	.19	3.87 (0.66-22.5)	.13
Conditioning intensity, RIC (versus MAC)	0.98 (0.61-1.59)	.96	0.74 (0.20-2.68)	.64
High-Dose TBI (≥ 8 Gy), Yes (versus No)	0.86 (0.43-1.71)	.67	1.06 (0.21-5.31)	.94
Grade 3-4 mucositis, Yes (versus No)	0.77 (0.47-1.25)	.30	0.87 (0.24-3.16)	.84
TPN requirement, Yes (versus No)	0.90 (0.53-1.74)	.91	1.40 (0.31-6.31)	.66
Nadir neutropenia ≥ 19 days (versus <19 days)	1.86 (1.12-3.07)	.015	0.94 (0.25-3.48)	.93
Time-dependent variable				
Grade 3-4 acute GVHD	N/A	—	5.95 (1.36-26.03)	.017
Grade mod/severe chronic GVHD	N/A	—	1.83 (0.27-12.38)	.53
Multivariate analysis				
Age at transplantation, continuous variable	1.03 (1.01-1.05)	.007	—	—
Donor type, Haplo (versus others)	0.65 (0.33-1.29)	.220	0.41 (0.07-2.37)	.325
Conditioning intensity, RIC (versus MAC)	0.55 (0.31-0.97)	.042	0.95 (0.25-3.76)	.952
Nadir neutropenia ≥ 19 days (versus < 19 days)	1.88 (1.07-3.09)	.019	—	—
Time-dependent variable				
Grade 3-4 acute GVHD	—	—	7.68 (1.36-43.28)	.020
Grade mod/severe chronic GVHD	—	—	2.39 (0.37-15.15)	.352

Haplo indicates haploidentical; TPN, total parenteral nutrition.

* Only 6 patients receiving PTCY-based prophylaxis were diagnosed with a BSI between day 30 to day 100 after stem cell infusion. Because no patient with a BSI diagnosed during this time period had grade 2-4 aGVHD or disease relapse before the diagnosis of the BSI, these patients were analyzed together with patients with a first BSI diagnosed between day 100 to 2 years.

† Patients undergoing allo-HCT from haploidentical donors receive PTCY-TK-MMF for GVHD prevention and those patients undergoing allo-HCT from MSD, MUD and MMUD receive PTCY-TK. Because patients receiving grafts from haploidentical donors receive higher doses of immunosuppression, for the present analysis the variable donor type has been grouped as reported in Table 6.

types, and the rates of GVHD have decreased. These factors could potentially explain the independence between donor type and risk for BSI.

The etiology of the BSI is a determinant of the BSI-attributable mortality. Puerta-Alcalde et al. [25,29] investigated the epidemiological changes during the BSI episodes in patients undergoing HCT at our Institution between 1993 and 2017. A decrease in the GPC bacteria and a progressively increase in Gram-Negative bacilli BSI, especially *E. coli, P. aeruginosa, and K. pneumoniae*, were evidenced. The present study includes a more contemporaneous cohort of patients, but the rates of BSI caused by GNB were comparable (48.4%) to those reported in previous studies at our institution [25,29].

A high incidence of first BSI was documented in our analysis, but the 30-day mortality rate observed in all patients with BSI was only 8.0%. This relatively low mortality rate could be endorsed to the effective patient health education and nursing care provided during the post-transplant period. Moreover, the 30-day BSI related mortality rate was lower in the sample of patients receiving PTCY (2.3%) than in the sample of patients receiving other prophylaxis (21.6%). Based on this result, the effects of BSI on the probability of mortality was evaluated in two separate samples of patients, grouped according to the GVHD prophylaxis. The association between BSI and higher risk mortality was found only in patients receiving other prophylaxis (Table 6 and Supplementary Figure S2). Other investigators have reported similar results in cohorts of patients that did not receive PTCY [1,8,30,31]. The collateral effect has been attributed to the increased toxicity derived from the BSI episode itself, to the requirement of intensive care unit admission and/or a more prolonged hospitalization time, and to additional risk factors that may also coexist in a post-allo-HCT patient with a BSI: gut dysbiosis, poor graft function, prolonged immunosuppression, or GVHD.

In our study, patients receiving PTCY had a higher incidence of BSI diagnosed during the early post-transplantation phase. However, and similarly to the finding reported by other investigators [17], lethal BSI infections in these patients were uncommon. In addition, once patients recovered from the infection, the probability of mortality among them was not different from that of not-infected ones. This result suggests that the morbidity derived from BSIs is lower in patients receiving PTCY than in the non-PTCY group; the lower morbidity could be explained by the lower exposition to other risk factors that may also coexist in a post-allo-HCT patient diagnosed with BSI, such as a prolonged immunosuppression or GVHD.

The retrospective design and the lack of patients receiving ATG are considered 2 limitations for this comparative analysis. Additionally, routine colonization testing with rectal smears was implemented at our Institution during 2018. Because the majority of patients receiving other prophylaxis different from PTCY did not go through this test, the variable was not included in the study.

PTCY-based prophylaxis is becoming prevalent in the allo-HCT community because of its efficacy on preventing GVHD. This study shows that PTCY increased the risk for BSI during the early post-transplant phase. However, among patients

Table 6
Impact of the First Episode Of BSI in Post-Transplantation Outcomes

	Risk Factors for Overall Survival Entire Cohort		Risk Factors for Overall Survival Patients Receiving PTCY		Risk Factors for Overall Survival Patients Receiving Other Prophylaxis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Univariate analysis						
BSI infection* time-dependent variable	1.76 (1.19-2.60)	.004	1.53 (0.91-2.57)	.101	2.55 (1.38-4.70)	.002
Multivariate analysis						
BSI infection, time-dependent variable	1.62 (1.06-2.49)	.006	1.16 (0.65-2.06)	.597	2.12 (1.09-4.12)	.025
GVHD prophylaxis, PTCY-based (versus others)	0.57 (0.34-0.95)	.003	N/A		N/A	
Age at allo-HCT, >60 years (versus ≤60)	1.17 (0.77-1.77)	.451	1.43 (0.81-2.52)	.206	0.88 (0.45-1.71)	.713
KPS ≤80% (versus 90%-100%)	1.95 (1.27-2.99)	.002	2.46 (1.40-4.32)	.001	1.30 (0.65-2.61)	.452
HCT-CI score ≥3 (versus < 3)	1.66 (1.07-2.58)	.0211	2.26 (1.24-4.10)	.007	0.88 (0.43-1.81)	.745
Donor Selection, Haplo and MMUD (versus others)	2.28 (1.35-3.84)	.001	2.15 (1.19-3.86)	.010	2.90 (0.92-9.14)	.686
Time-dependent variable						
History of grade 3-4 aGVHD	3.32 (1.99-5.54)	<.001	3.12 (1.37-7.10)	.006	3.76 (1.85-7.62)	<.001
History of disease relapse	11.14 (1.35-3.84)	<.001	10.21 (5.76-18.08)	<.001	13.13 (6.75-25.53)	<.001

Post-transplantation follow-up has been censored at 2 years. First BSI infections diagnosed after disease relapse have been censored (n = 10). Results provided by the univariate analysis are reported in Supplementary Table S2. Explanatory variables found to be statistically significant in the univariate analysis or those considered clinically relevant were included in the multivariate model.

* The impact of BSI in OS in patients receiving PTCY and other prophylaxis is additionally showed in Supplementary Figure S2 (Mantel Byar Plot).

receiving PTCY prophylaxis, the event of BSI was not associated with higher mortality, as was the case among patients with other prophylaxis. In the PTCY group, BSI-related mortality was low, and, once the patients recovered from this complication, the probability of mortality after allo-HCT was comparable to that of patients without a history of BSI. These findings contribute to the limited published evidence about the incidence and effects of BSI in patients receiving PTCY and grafts from related and unrelated donors.

Conflict of interest statement: P.P-A. has received honoraria for talks on behalf of Merck Sharp and Dohme, Gilead, Lilly, ViiV Healthcare and Gilead Science. C.G-V. has received honoraria for talks on behalf of Gilead Science, MSD, Novartis, Pfizer, Janssen, Lilly, as well as a grant from Gilead Science and MSD.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2022.09.001.

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