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TRANSPLANT INFECTIOUS DISEASE

ORIGINAL ARTICLE

Pre-engraftment bacteremia after allogeneic hematopoietic cell transplantation without primary fluoroquinolone antibacterial prophylaxis

Aude Nguyen[1,2] | Jordan Fender[3] | Johan Courjon[4] | Adrien Fischer[5] | Maria Mappoura[6] | Sarah Morin[6] | Federica Giannotti[6] | Anne-Claire Mamez[6] | Yves Chalandon[6] | Stavroula Masouridi-Levrat[6] | Dionysios Neofytos[1]

[1]Division of Infectious Diseases, Geneva University Hospitals, Geneva, Switzerland

[2]Infection Control Program and WHO Collaborating Centre, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

[3]Department of Internal Medicine, Rehabilitation and Geriatrics, Internal Medicine and Rehabilitation Unit, Geneva University Hospitals and University of Geneva, Geneva, Switzerland

[4]Infectious Diseases Unit, University Côte d'Azur, CHU Nice, Nice, France

[5]Bacteriology Laboratory, Department of Diagnostics, Geneva University Hospitals, Geneva, Switzerland

[6]Hematology Division, Department of Oncology, University Hospital of Geneva, and Faculty of Medicine, Geneva, Switzerland

Correspondence
Aude Nguyen, Division of Infectious Diseases and Infection control, Geneva University Hospitals, Rue Gabrielle-Perret-Gentil 4, 1211 Genève 14, Switzerland.
Email: aude.nguyen@hug.ch

Dionysios Neofytos, Division of Infectious Diseases, Geneva University Hospitals, Rue Gabrielle-Perret-Gentil 4, 1211 Genève 14, Switzerland.
Email: dionysios.neofytos@hug.ch

Abstract

Background: Bacteremia is a common complication in allogeneic hematopoietic cell transplant recipients (alloHCTr), especially during the pre-engraftment period. International guidelines recommend antibacterial prophylaxis (ABP), despite potential selection for multidrug-resistant organisms (MDRO). Limited contemporary data exist on the epidemiology of pre-engraftment bacteremia in alloHCTr, who do not receive ABP.

Methods: We performed a retrospective observational single-center cohort study including all consecutive adult alloHCTr (2015–2021), investigating the incidence, risk factors, and outcomes of bacteremia during the engraftment period. Primary fluoroquinolone (FQ) ABP is not routinely administered in our center.

Results: Among 421 patients identified, 124 bacteremia episodes were observed in 121/421 (29%) alloHCTr. The median time to the 1st bacteremia episode was 9 days

Abbrevations: ABP, antibacterial prophylaxis; aGvHD, acute graft versus host disease; allo-HCTr, allogeneic hematopoietic cell transplant recipients; ANC, absolute neutrophil count; AST, antimicrobial susceptibility testing; BM, bone marrow; BMT, bone marrow transplant; BSI, bloodstream infections; CDC, Centers for Disease Control and Prevention; CLABSI, central line associated bloodstream infection; CMV, cytomegalovirus; CoNS, coagulase-negative staphylococci; CPE, carbapenemase producing Enterobacterales; CRAB, carbapenem resistant *Acinetobacter baumannii*; CRPsA, carbapenem resistant *Pseudomonas aeruginosa*; D, donor; ECDC, European Centre for Disease Prevention and Control; ESBL, extended-spectrum-β-lactamase; ESBL-E, extended-spectrum-β-lactamase Enterobacterales; FQ, fluoroquinolones; GIT, gastrointestinal tract; GNB, Gram-negative bacteria; GvHD, graft versus host disease; HCT, hematopoietic cell transplantation; IQR, interquartile range; MAC, myeloablative conditioning; MDR, multidrug resistant; MDRO, multidrug-resistant organisms; MDS, myelodysplastic syndromes; MMUD, mismatched unrelated donor; MRSA, methicillin-resistant *Staphylococcus aureus*; NF, neutropenic fever; OR, odds ratio; PBSC, peripheral blood stem cells; R, recipient; RIC, reduced intensity conditioning; SD, standard deviation; VGS, viridans group streptococci; VRE, vancomycin-resistant *Enterococci*.

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(IQR 6–11). Most (105/124, 85%) episodes were monomicrobial, while >1 pathogens were identified in 19/124 (15%) episodes. Overall, 152 pathogens were isolated, with a predominance of Gram-positive (118/152, 78%), including coagulase-negative staphylococci (*n*:47), streptococci (*n*:46), and enterococci (*n*:15), followed by Gram-negative bacteria (GNB, 30/152, 20%), and anaerobes (4/152, 3%). There were 2/152 (1%) MDRO (extended-spectrum beta-lactamase producing) GNB. Multivariable analyses identified age >40-year-old (OR 2.4, $P = 0.02$), male gender (OR 1.8, $P = 0.02$), and a haploidentical/mismatched unrelated donor (OR 2.5, $P < 0.001$) as independent risk factors for bacteremia. All cause 30-day mortality among alloHCTr with bacteremia was 0.8% (1/121): one patient died due to an HCT-related complication.

Conclusion: Despite lack of primary FQ ABP, low rates of bacteremia were observed during the pre-engraftment period, with low MDRO prevalence and mortality. Our findings may allow to revisit the need for primary universal FQ ABP in high-risk neutropenic hematology patients.

KEYWORDS

allogeneic hematopoietic stem cell transplantation, bacteremia, bloodstream infection, antibiotics, engraftment period, antibacterial prophylaxis

1 | INTRODUCTION

Bloodstream infections (BSI) are a common complication after an allogeneic hematopoietic cell transplantation (HCT), especially during the pre-engraftment period, due to conditioning chemotherapy associated neutropenia and gastrointestinal tract (GIT) mucositis. The latter often results in GIT flora translocation presenting as BSI with enteric bacterial pathogens.[1] International guidelines recommend antibacterial prophylaxis (ABP) with a fluoroquinolone (FQ) for high-risk patients treated with chemotherapy and anticipated neutropenia for >7 days and allogeneic HCT recipients from conditioning to engraftment.[2–5] Although primary ABP is routinely used pre-engraftment in most transplant centers worldwide, bacterial BSI remain an important complication in patients with neutropenia, with a reported incidence between 13% and 55%.[3,6–9] Furthermore, concerns about the potential selection for multidrug-resistant organisms (MDRO) and other complications, such as *Clostridioides difficile* colitis, have been raised.[5,10,11] In fact, increasing rates of bacteremia due to bacterial MDRO in allogeneic HCT recipients have been reported, with potential associations with clinical outcomes.[1,12–16] Limited contemporary data exist on the epidemiology of bacteremia during the pre-engraftment period in patients, who do not routinely receive ABP.[8,15,17–21]

In our center, primary FQ ABP is not routinely administered during the pre-engraftment period in allogeneic HCT recipients. We hypothesized that in an era of close patient monitoring and prompt initiation of empirical antibacterial treatment, lack of primary FQ ABP is not associated with higher rates of pre-engraftment bacteremia or dismal clinical outcomes, including mortality, and may prevent selection of MDRO. We performed a retrospective study to describe the epidemiology, risk factors, and clinical outcomes of bacterial BSI during the pre-engraftment period after allogeneic HCT in a cohort without routine FQ ABP administration.

2 | METHODS

2.1 | Study design

We conducted a retrospective observational single-center cohort study on 421 consecutive adults, who underwent their first allogeneic HCT at Geneva University Hospitals between 2015 and 2021. Inclusion criteria consisted of patients ≥ 18 years of age, admitted at the Bone Marrow Transplant (BMT) unit for an allogeneic HCT from January 1, 2015 to December 31, 2021. All patients had signed an informed consent form for data utilization. We excluded patients <18 years of age and allogeneic HCT recipients who did not sign a consent form or removed their consent. The study was approved by the institutional Ethics Committee (2020-02120). The primary objective of this study was to describe the incidence of bacteremia between conditioning and engraftment. As secondary objectives we describe the pathogen distribution and epidemiology, risk factors for bacteremia, and clinical outcomes, including acute graft versus host disease (GvHD) and all-cause mortality at 30 days post-diagnosis of bacteremia and at 1-year post-transplant for the whole cohort.

2.2 | Data collection

The following data were collected from the institutional BMT unit database: demographics, underlying hematologic malignancy, and

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HCT-related variables (conditioning, donor type, stem cell source, CMV donor (D)/ recipient (R) serology status, GvHD prophylaxis and complications), and survival. The following additional data were retrieved from review of electronic medical records: neutropenic fever (NF) episodes with suspected causality, infections, empirical, and targeted antibiotic treatment received.

2.3 | Institutional screening, prophylactic, and empirical treatment strategies

The institutional prophylactic strategies remained unchanged during the study period. All patients benefit of MDRO screening at admission, consisting of rectal swab or stool culture for carbapenemase producing *Enterobacterales* (CPE), carbapenem resistant *Acinetobacter baumannii* (CRAB), carbapenem resistant *Pseudomonas aeruginosa* (CRPsA), extended-spectrum-β-lactamase (ESBL) Enterobacterales (ESBL-E), nasal and inguinal swab for methicillin-resistant *Staphylococcus aureus* (MRSA), and axillary swab for CRAB. Weekly surveillance blood cultures are performed from the central venous catheter on a fixed weekday, regardless of NF. All patients receive a central venous catheter or implantable chamber before transplantation. No primary FQ ABP during neutropenia is administered. Patients receive oral decontamination with neomycin/polymyxin B solution (non-absorbable) with conditioning until engraftment, co-trimoxazole for *Pneumocystis jirovecii* prophylaxis, and acyclovir as antiviral prophylaxis starting with conditioning, and antifungal primary prophylaxis with fluconazole and letermovir as anti-CMV prophylaxis starting May 2019 on transplant day, as previously described.[22–24] In case of NF, two sets of blood cultures (aerobic/anaerobic bottles) from central line and peripheral venipunctures are collected daily until fever resolution, and empirical antibiotic treatment is initiated, based on international guidelines and institutional protocol.[5,25] Briefly, a beta-lactam with antipseudomonal activity, predominantely cefepime, is administered as first line empirical therapy, except in patients colonized with ESBL-E, when a *P. aeruginosa*-acting carbapenem is used as primary empirical therapy. An agent with activity against coverage of resistant Gram-positive organisms (e.g., MRSA, or methicillin-resistant coagulase-negative *Staphylococcus* spp., CoNS), such as vancomycin, is added, if patients are at high risk (based on local signs of infections and high clinical-suspicion for a multi-drug resistant pathogen, such as MRSA) or when fever persists after 48 h of the empirical antibiotic therapy. Treatment is adjusted following the clinical evolution and microbiological results.

2.4 | Study definitions

Bacteremia was defined based on revised ECDC and CDC definitions.[26,27] More specifically, patients with relevant signs and symptoms and the isolation of any bacteria from 1 or more sets of blood cultures prompting initiation of targeted antimicrobial treatment by the clinical team were considered to have a bacteremia event. Patients with one single blood culture for CoNS with or without NF were not considered to have a true CoNS bacteremia and hence not included in the bacteremia group. Patients with a single blood culture with viridans group streptococci (VGS) were considered to have a true bacteremia event in the presence of relevant clinical presentation and treatment initiation. Positive surveillance blood cultures with commensal pathogens were considered as a true bacteremia event only if the same pathogen was retrieved in >1 blood cultures separately drawn and if targeted antibacterial treatment was administered. Patients could have a single or >1 bacteremia episodes. Patients were considered to have two separate bacteremia episodes in case similar or different organisms were identified after an interval of 7 days separating the episodes between negative blood cultures. When two or more pathogens were isolated simultaneously, bacteremia was defined as polymicrobial. Pathogen identification and susceptibility testing were interpreted according to the European Committee on Antimicrobial Susceptibility Testing (AST) (MALDI-TOF/MS, AST by disk diffusion; EUCAST v05-v11). Antibacterial resistance of MDRO was defined based on published consensus guidelines.[28] The pre-engraftment period was defined as the time from conditioning initiation (conventionally considered as 7 days prior to HCT) until the day of engraftment. According to consensus guidelines, neutropenia was defined as an absolute neutrophil count (ANC) < 500 cell/mm^3, while engraftment was defined as the first day of achieving a sustained over 3 consecutive days peripheral blood ANC > 500 cells/mm^3.[29–31] NF was defined as a single episode of fever ≥ 38.3°C or two episodes of ≥ 38°C during neutropenia.[29–31]

2.5 | Statistical analysis

The Chi-square and Student's *t*-test were used to compare categorical and continuous variables, respectively. Continuous variables were presented as a mean value, with standard deviation (SD) and range or median and interquartile range (IQR). Cumulative incidences for bacterial BSI were calculated in the overall study patient population. Considering the fact that a patient could develop >1 BSI, only the first BSI episode was considered for cumulative incidence calculations per patient. Patients were censored for death, a second HCT, or loss to follow-up, whichever occurred first. Cox regression was used to assess the risk factors for the development of bacteremia. All-cause 30-day mortality was analyzed using Kaplan–Meier survival curves. The log-rank test was used to compare survival distribution between different groups. A two-sided test was performed and a $P < 0.05$ was considered to be statistically significant. Statistical data analyses were conducted using STATA 16 statistical software.

3 | RESULTS

3.1 | Patient population

A total of 421 patients were included in the study (Table 1). The median age of patients at transplant was 56-year-old (IQR 46–63) and 66% patients were male. A total of 314 (75%) patients received a

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TABLE 1 Baseline patient characteristics.

	All patients n = 421 (%)	Patients with bacteremia n = 121 (%)	Patients without bacteremia n = 300 (%)	P-value
Demographics				
Age, median years (IQR)	56 (46, 63)	56 (48, 63)	56 (45, 58)	.15
Gender, male (%)	279 (66)	91 (75)	181 (63)	.02
Underlying disease				.24
Acute myeloid leukemia/MDS	276 (66)	79(65)	197 (66)	
Lymphoma	47 (11)	19 (16)	28 (9)	
Acute lymphocytic leukemia	35 (8)	6 (5)	29 (10)	
Chronic myeloid/lymphocytic leukemia	17 (4)	5(4)	12 (4)	
Other[a]	46 (11)	12 (10)	34 (11)	
CMV donor/recipient status				.15
D−R−	120 (29)	33 (27)	87 (29)	
D−R+	77 (18)	26 (21)	51 (17)	
D+R+	185 (44)	46 (38)	139 (46)	
D+R−	39 (9)	16 (13)	23 (8)	
Conditioning regimen				.62
Reduced intensity	314 (75)	88 (73)	226 (75)	
Myeloablative	107 (25)	33 (27)	74 (25)	
Donor				.001
Matched related	103 (24)	22(18)	81 (27)	
Matched unrelated	199 (47)	48(40)	151 (50)	
Haplo-identical	93 (22)	40 (33)	53 (18)	
Mismatched unrelated	26 (6)	11(9)	15 (5)	
Graft source				
Peripheral blood stem cells	371 (88)	103 (85)	268 (89)	.25
Bone marrow	50 (12)	18 (15)	32 (11)	
GvHD prophylaxis				
Post-HCT cyclophosphamide	115 (27)	50 (41)	65 (22)	<.001
Colonisation prior to HCT				.17
MRSA	1 (0.2)	1(1)	0	
VRE	4 (1)	0	4 (1)	
ESBL-*Enterobacterales*	53 (13)	20 (17)	33 (11)	
CPE	0	0	0	
MDR *Pseudomonas aeruginosa*	2 (0.5)	1 (1)	1 (0.3)	

Abbreviations: SD, Standard deviation; MDS, myelodysplastic syndrome; CMV, cytomegalovirus; D, donor; R, recipient; GvHD, graft vs. host disease; HCT, hematopoietic cell transplant; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*; ESBLE, extended-spectrum beta-lactamase; CPE, carbapenemase producing *Enterobacterales*; MDR, multidrug resistant.
[a]Other included: aplastic anemia, multiple myeloma, hemoglobinopathy, myeloproliferative syndromes, and X-linked adrenoleukodystrophy.

reduced-intensity conditioning regimen and graft source was peripheral blood stem cells (PBSCs) in 317 (88%) patients. The median time from HCT to engraftment was 18 days (IQR 15–20); two patients never achieved engraftment. Colonization with ESBL-E, vancomycin-resistant *Enterococcus* spp. (VRE), carbapenem resistant *P. aeruginosa*, and MRSA was documented pre-transplant in 53(13%), 4 (1%), 2 (0.5%), and 1 (0.2%) patient, respectively.

3.2 | Incidence and timing of bacteremia

Overall, 121 (29%) patients experienced at least one episode of bacteremia between conditioning and engraftment; 106/121 (88%) patients developed bacteremia from transplant to engraftment (Figure 1a), while 15/121 (12%) patients developed bacteremia between conditioning and HCT. There were 124 bacteremia episodes

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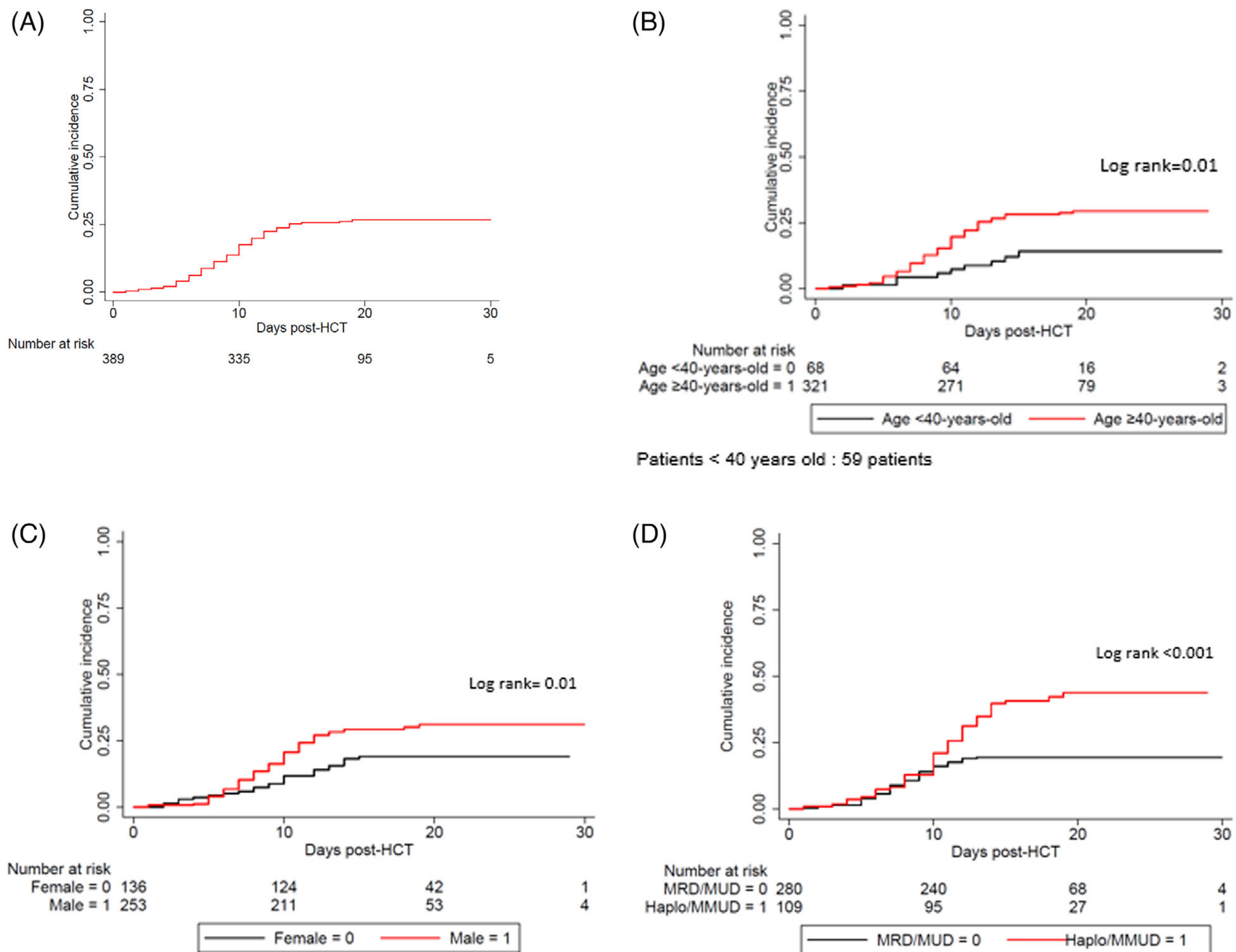

FIGURE 1 Cumulative incidence of bacteremia in 421 allogeneic hematopoietic transplant recipients between transplant and engraftment (a) overall, and based on (b) age, (c) gender, and (d) donor type: haploidentical and mismatched unrelated donors vs. other.

due to 152 pathogens among the 121 patients with bacteremia. Although most (118/121, 97.5%) patients had one bacteremia episode, there were 3/121 (2.5%) patients with two bacteremia episodes. Similarly, most (102/121, 84%) patients experienced a monomicrobial bacteremia, while 19 (16%) patients experienced polymicrobial bacteremia, caused by ≥2 pathogens. Median time from HCT to first bacteremia episode was 9 days (IQR 6–11). Median time from HCT to engraftment was similar between patients with (18 days, IQR 15–21) versus without bacteremia (days 17.5; IQR 15–20; $P = 0.11$). Median duration of bacteremia was 1 day (IQR 1–2).

3.3 Pathogen epidemiology

There were 152 pathogens isolated in 124 bacteremia episodes, with a predominance of Gram-positive pathogens (*N*:118/152, 78%), followed by Gram-negative bacteria (GNB; *N*:30/152, 20%), and anaerobes (*N*:4/152, 3%). Among Gram-positive pathogens, most infections were due to CoNS (*N*:47), followed by *Streptococcus mitis/oralis* (*N*:40; Table 2). CoNS was the only pathogen found in 40 episodes of monomicrobial bacteremia and concomitantly identified with another pathogen in 7 polymicrobial bacteremia episodes. Among GNB, Enterobacterales was the most commonly identified order (*N*:16), with *Escherichia coli* (*N*:8) and *Klebsiella* spp. (*N*:4) most frequently identified, while *P. aeruginosa* and *Stenotrophomonas maltophilia* were isolated in 7 and 1 episodes, respectively. Among 16 Enterobacterales tested for cefuroxime, cefepime, and FQ susceptibility, there were 3(19%), 1(6%), and 2(12.5%) resistant, respectively. Among the 46 streptococci, there were 8 (17%) isolates resistant to penicillin (not all isolates were tested against cephalosporins or FQ). There were only 2/135 (1.5%) bacteremia episodes due to ESBL-E (1 *K. pneumoniae*, 1 *Enterobacter cloacae*), one of those observed in a patient known to be colonized with this pathogen. There were no bacteremia episodes due to CPE, MRSA, or VRE observed. The distribution of bacteremia episodes overall and due to Gram-positive and Gram-negative pathogens during the 7-year study period is shown in Figure 2.

3.3 | Bacteremia without fever

Among 124 bacteremia episodes, 18(14.5%) episodes were detected by weekly blood culture surveillance in patients who were afebrile and

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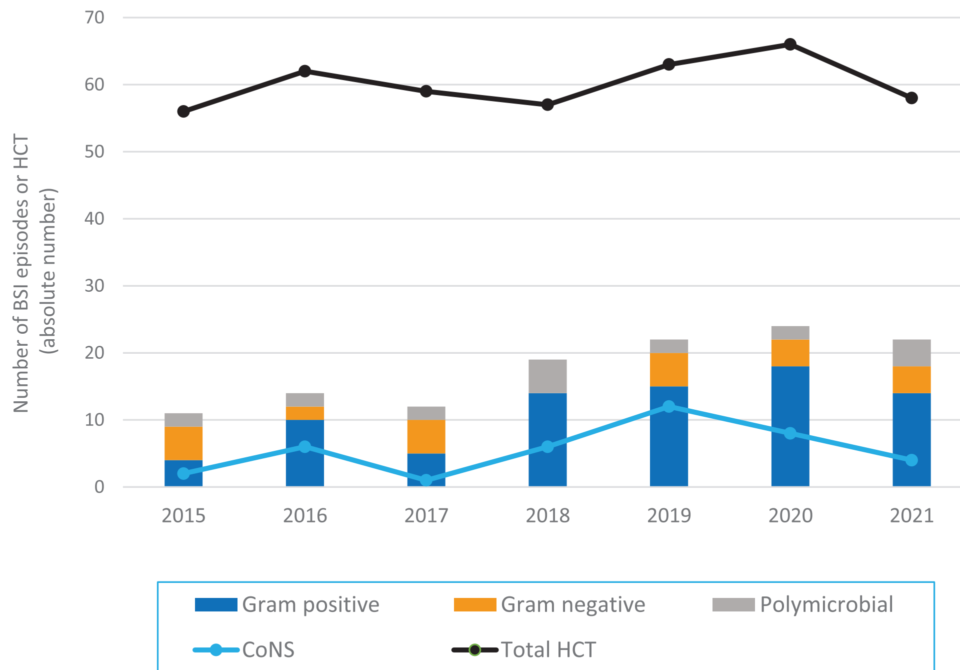

FIGURE 2 Yearly distribution of bacteremia and the proportions of bacteremia caused by Gram-positive and Gram-negative pathogens over time. Abbreviations: CoNS, Coagulase-negative staphylococci; HCT, hematopoietic cell transplant.

asymptomatic. Most (14/18, 78%) of those episodes were monomicrobial, caused predominately by Gram-positive cocci (11/18, 61 %), mainly due to CoNS (8/18; 44%). For the 8 episodes of CoNS bacteremia, the median number of positive bottles was 6.5 (IQR 4–9.5). Among the 2 monomicrobial Gram-negative bacteremias, *E. coli* and *P. aeruginosa* were identified. Polymicrobial bacteremias included various pathogens: *Bacteroides fragilis*, *E. avium*, *E. faecium*, *S. maltophilia*, *Granulicatella adiacens*, *Actinomyces oris*, and *Capnocytophaga sputigena*.

3.4 | Risk factors for pre-engraftment bacteremia

Risk factors for bacteremia during the pre-engraftment period were explored with univariable and multivariable regression analysis (Table 3). Clinically relevant independent variables and those with a *P*-value <.15 in univariable analyses were entered into a logistic regression model. In multivariable analysis, age >40-year-old (OR 2.4, *P* = 0.01), male gender (OR 1.8, *P* = 0.02), and a haploidentical/mismatched unrelated donor (MMUD) (OR 2.5, *P* < 0.001) were identified as independent predictors of bacteremia (Figure 1b–d). Considering the relatively large number of bacteremia episodes due to CoNS and to rule out potential associated biases, risk factor analyses were performed separately for patients with bacteremia due to only CoNS and those with non-CoNS bacteremia episodes. Multivariable analyses identified male gender and haploidentical/MMU donors as significant predictors of CoNS bacteremia (OR 2.5, *P* = 0.03 and OR 1.98, *P* = 0.05, respectively). Multivariable analyses identified haploidentical/MMU donors as significant predictors of non-CoNS bacteremia (OR 2.2, *P* = 0.003), while there was a trend for age > 40-year-old as significant predictor (OR: 2.0, *P* = 0.08).

3.5 | Mortality

All-cause 1-year mortality was 26% (109/421): 24% (29/121) and 27% (80/300) in patients with and without bacteremia, respectively (*P* = 0.62). No patient died at 7-days post-bacteremia diagnosis. All-cause 30-day mortality after bacteremia diagnosis was 0.8% (1/121 patients). This patient died due to an HCT-related complication unrelated to the bacteremia.

3.6 | Associations with GIT aGvHD ≥ grade 2

Among 421 patients, 183 (43.5%) patients were diagnosed with aGVHD grade ≥ 2 at a median of 34 (22–76) days post-HCT; 129 patients with aGVHD grade ≥2 had upper and/or lower GIT involvement. Patients with bacteremia during the pre-engraftment period were as likely to develop grade ≥2 aGVHD (59/121, 49%), as patients without (124/300, 41%; *P* = 0.19). Similarly, patients with bacteremia during the pre-engraftment period were as likely to develop grade ≥ 2 GIT aGVHD (43/121; 36%) versus patients without bacteremia (86/300; 29%; *P* = 0.20).

4 | DISCUSSION

This single-center retrospective cohort study provides contemporary data on the incidence, pathogen profiles, and risk factors of bacterial BSI during the pre-engraftment period in a center without FQ ABP over 7 years. Most published studies report data of patients receiving ABP during pre-engraftment or a small-sample size of patients not

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TABLE 2 Etiology of bacterial bloodstream infections.

Pathogen category	No. of isolates (%)
Total bloodstream isolates	152
Gram-positive pathogens	118 (78)
Gram-positive cocci	108 (71)
Staphylococci	47 (31)
S. aureus	0
S. epidermidis	44 (29))
Other coagulase-negative *Staphylococci*[a]	3 (2)
Streptococci	46 (30)
S. mitis/oralis	40 (26)
Other *Streptococci*	6 (4)
Enterococci	15 (10%)
E. faecalis	9 (6)
E. faecium	5 (3)
E. avium	1 (1)
Other Gram-positive pathogens[b]	10 (7)
Gram-negative bacteria	30 (20)
Enterobacterales	16 (11)
E. coli	8 (5)
***Klebsiella* spp.[c]**	4 (3)
***Proteus* spp.**	3 (2)
***E. cloacae*[c]**	1 (1)
Pseudomonas aeruginosa	7 (5)
Stenotrophomonas maltophilia	1 (1)
Other Gram-negative pathogens[d]	6 (4)
Anaerobic bacteria	4 (3)
***Bacteroides* spp.**	1 (1)
***Fusobacterium* spp.**	3 (2)

[a]*S. haemolyticus*, *S. ludgunensis*.
[b]Other included: *Granulicatella adiacens*, *Rothia* spp., *Actinomyces oris*, *Ruminococcus* spp.
[c]One *Klebsiella* spp. and one *E. cloacae* producing extended-spectrum beta lactamase (ESBL).
[d]Other included: *Capnocytophaga sputigena*, *Haemophilus* spp., *Moraxella* spp., *Neisseria* spp.

receiving ABP.[1,6,15,17–19,21,32,33] We report a BSI incidence of 29%, in accordance with earlier publications by other centers, albeit with a predominance of Gram-positive cocci.[1,6,33–35] This is in contrast to the current dominance of GNB bacteremias, as it has been reported by many centers.[15,20,36,37] Considering the high number of bacteremias due to CoNS in our cohort it is likely that a proportion of those infections did not always represent real bacteremia episodes, but rather detection of colonization of central lines. However, considering the fact that we followed strict formal definitions and all patients were deemed to be bacteremic by the clinical team and treated as such, we believe that our data represent true bacteremia episodes. Proportionally, CoNS was the most frequently identified single pathogen in bacteremias in our study, which may not necessarily reflect the epidemiology of bacteremias in other transplant centers.[1,6,15,33,37] In our institution, we do not use impregnated catheters neither antiseptic-impregnated dressings to decrease central line associated bloodstream infection (CLABSI). However, regular inspection of the insertion site and strict local care are performed consistently by the highly-qualified and trained nursing teams. The only change during the study period was the introduction of 70% isopropyl alcohol impregnated central venous catheter caps associated with temporary interruption of perfusion therapies between September 1, 2021 and August 31, 2022, which did not impact the overall CLABSI incidence.[38] We concluded that high rates of CoNS CLABSI remain an important problem in our BMT Unit and there is a need to investigate further practices to be implemented.

Almost 1 in 6 bacteremias were detected by weekly blood culture surveillance in patients who were afebrile and asymptomatic, half of them due to CoNS and the rest due to a large variety of Gram-positive and Gram-negative pathogens. Historically, routine weekly surveillance blood cultures have been introduced in our BMT Unit based on the hypothesis, that allo-HCT patients may have a blunted inflammatory response and thus remain asymptomatic, despite a serious infection, including bacteremia. It is likely, that some of those patients could develop signs and symptoms due to their bacteremia in the next hours/days after the surveillance positive blood culture was drawn. This is not possible to discern, as all those patients were promptly started on the antimicrobial therapy. However, the isolation of pathogens, such as *E. coli* or *P. aeruginosa*, suggests that those episodes represented real bacteremia events. The significance and cost-benefit ratio of routine, weekly, surveillance blood cultures in neutropenic patients, but also even in patients with GvHD on high-dose corticosteroid treatment, remains unclear and needs to be further investigated.[39–41]

Consistent with prior observations, sex, age, and haploidentical or mismatch unrelated donors were identified as significant predictors of pre-engraftment bacteremia. Male sex has been previously identified as a potential risk factor for bacteremia.[42] We hypothesized that considering the fact that central lines are placed at the jugular insertion site this may represent a higher risk for contamination, considering local hygiene in the setting of facial hair in male patients. Patients older than 40-year-old were also identified at higher risk for bacteremia during the pre-engraftment period, probably related to higher rate of translocation associated with conditioning-related mucositis in older patients. The importance of haplo-identical donors on the risk for bacteremia has already been reported.[6,15,33,43] It is likely that the type of immunosuppression and conditioning administered in those patients, frequently receiving cyclophosphamide post-transplant, may significantly increase their risk for potential complications, including bacteremias.[44,45]

Despite a relatively high number of bacteremias, including those due to GNB, mortality was very low in this cohort. Data from the Swiss Transplant Cohort Study (STCS) on allogeneic HCT recipients with bacteremias between 2009 and 2018 reported a 3-week mortality of 10%.[46] The lower mortality observed in our cohort. Could be, in part, attributed to improved clinical practices, such as to the presence of standard operating protocols in our institution for all hematology

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TABLE 3 Analysis of risk factors for pre-engraftment bacteremia.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
All patients with bacteremia vs. others						
Sex, male vs. female	1.8	1.1, 2.9	.01	1.8	1.2,4.7	.02
Age >40-year-old vs. ≤40-year-old	2.4	1.2, 4.8	.01	2.4	1.2,4.7	.02
Conditioning, MAC vs. RIC	0.9	0.5, 1.4	.58			
Donor type, MMUD/haploidentical vs. other	2.5	1.6, 3.9	<.001	2.5	1.6,3.9	<.001
BM source, PBSC vs. BM	0.7	0.4-1.3	.23			
Patients with CoNS bacteremia vs. others						
Sex, male vs. female	2.6	1.1,6.0	.03	2.5	1.1,5.9	.03
Age >40-year-old vs. ≤40-year-old	2.6	0.8,8.8	.12	2.6	0.8,9.0	.13
Conditioning, MAC vs. RIC	1.0	0.5,2.2	.95			
Donor type, MMUD/haploidentical vs. other	2.0	1.0,3.9	.04	1.98	1.0,3.9	.05
BM source, PBSC vs. BM	0.6	0.3–1.4	.25			
Patients with non-CoNS bacteremia vs. others						
Sex, male vs. female	1.5	0.9,2.6	.12	1.48	0.9,2.5	.16
Age >40-year-old vs. ≤40-year-old	2.1	0.9,4.6	.06	2.0	0.9,4.4	.08
Conditioning, MAC vs. RIC	0.9	0.5,1.5	.59			
Donor type, MMUD/haploidentical vs. other	2.2	1.3,3.6	<.001	2.2	1.3,3.6	<.001
BM source, PBSC vs. BM	0.7	0.4,1.5	.42			

Abbreviations: OR, Odds ratio; CI, confidence interval; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; MMUD, mismatched unrelated donor; BM, bone marrow; PBSC, peripheral blood stem cells; CoNS, coagulase negative staphylococci.

patients with neutropenia in case they become febrile, including immediate draw of two sets of blood cultures and initiation of prespecified empirical antibiotic treatment, based on the patient's pre-transplant MDRO screening. Indeed, timely initiation of the antibiotic therapy has been associated with improved clinical outcomes in patients with NF.[36,47] This might have contributed to the favorable clinical outcomes observed in our study, with none of the patients with bacteremia dying within 7 days post-diagnosis and only one patient dying within 30 days post-diagnosis, from a cause unrelated to the infection. Current progress and improved safety mechanisms in high-risk hematology neutropenic patients, based on standard operating procedures, including immediate initiation of appropriate antibiotic treatment based on national and international guidelines, allows for significantly improved clinical outcomes in patients with bacteremia, minimizing mortality and potentially decreasing unnecessary antibiotic exposure.[30,48]

The use of antibiotic prophylaxis remains controversial, particularly in view of the threat of antimicrobial resistance, where FQ constitutes a significant antibiotic pressure, associated with the selection of MDRO. In our center not providing prophylaxis, we did not observe higher rates of bacteremia or mortality, compared to rates reported from centers routinely administering ABP or other centers where ABP is not administered.[6,15,17–21,32,33,35] Lack of primary routine FQ ABP administration might have contributed to the very low rates of bacteremias due to MDRO, with only two patients presenting with an ESBL producing GNB bacteremia. The latter may also be attributed to the relatively low prevalence of MDRO in our country as previously reported.[49–51] Nevertheless, our data suggest that lack of routine use of primary FQ ABP in high-risk hematology patients may potentially decrease the selection for MDRO, without compromising clinical outcomes.[11,19]

Administration of broad-spectrum antibacterial agents has been associated with disrupted intestinal microbiome and higher risk for aGVHD.[17,52–60] However, our data suggest that patients with bacteremia pre-engraftment are neither at higher risk for aGVHD post-engraftment, nor for GIT aGVHD. Even after excluding CoNS bacteremias, we were not able to show any possible effect of bacteremias during the pre-graftment period on GvHD. It is likely that we were not able to discern a potential effect on GvHD due to the small number of patients included in our single-center cohort study, and even less patients with bacteremia. Nevertheless, more data are required to better describe the potential association between aGVHD and pre-engraftment bacteremia.

This study has many limitations, including its single center retrospective design. The particular practices on microbiological investigations and antibiotic use in our institution may not be generalizable to other centers. In addition, the spectrum of microorganisms isolated reflects our local epidemiology, with a low prevalence of MDRO, an epidemiology that could potentially vary in other centers.[61] Notably, the administration of non-absorbable antibiotics, namely neomycin-polymyxin B, until engraftment and co-trimoxazole (sulfamethoxazole 800 mg/trimethoprim 160 mg) as *P. jirovecii* prophylaxis three times weekly could have potentially impacted the epidemiology of

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bacteremia in our cohort. Data from the STCS have shown that *P. jirovecii* prophylaxis with co-trimoxazole have been associated with lower rates of bacteremias in solid organ transplant recipients [51]. Nevertheless, and while more data are required, we believe that such low dose of co-trimoxazole intermittently administered would have a minimal, if any, effect on the incidence of bacteremia in this cohort. Finally, empirical or targeted antibacterial treatment in the setting of NF or bacteremia continued until engraftment, in most cases, could have also led to lower rates of bacteremia.

In conclusion, we report relatively low rates of bacteremias in allogeneic HCT recipient between conditioning and engraftment despite lack of universal FQ ABP, albeit with lower numbers of GNB, low prevalence of MDRO, and favorable clinical outcomes. Our findings may allow for the discussion to be continued whether routine universal primary FQ ABP is still necessary or not in high-risk hematology patients with neutropenia in an era of close observation with immediate initiation of appropriate empirical antibiotic therapy in case of NF in those patients.

AUTHOR CONTRIBUTIONS

Aude Nguyen, Jordan Fender, and Dionysios Neofytos designed the study. Aude Nguyen, Jordan Fender, Johan Courjon, Anne-Claire Mamez, Maria Mappoura, Sarah Morin, Yves Chalandon, Stavroula Masouridi-Levrat, Adrien Fischer, and Dionysios Neofytos collected the data. Aude Nguyen and Dionysios Neofytos interpreted the data and wrote the manuscript.

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CONFLICT OF INTEREST STATEMENT

Y.C. has received honoraria for participation in symposia and advisory boards from MSD, Novartis, Incyte, BMS, Pfizer, Abbvie, Roche, Jazz, Gilead, Amgen, Astra-Zeneca, Servier; Travel support from MSD, Roche, Gilead, Amgen, Incyte, Abbvie, Janssen, Astra-Zeneca, Jazz, Sanofi all via the institution. D.N. has received research support from MSD and Pfizer and consulting fees from Roche Diagnostics, MSD, Pfizer, Basilea, and Gilead. All other authors report no potential conflicts.

PATIENT CONSENT STATEMENT

This study was approved by the Institutional review board of Geneva (2020-02120). All patients have signed an informed consent form for data utilization.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Aude Nguyen https://orcid.org/0000-0002-9640-5146

REFERENCES

1. Blennow O, Ljungman P, Sparrelid E, et al. 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(1):106-114.
2. 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(12):1826-1835.
3. Verlinden A, Mikulska M, Knelange NS, et al. Current antimicrobial practice in febrile neutropenia across Europe and Asia: the EBMT Infectious Disease Working Party survey. *Bone Marrow Transplant*. 2020;55(8):1588-1594.
4. Bucaneve G, Castagnola E, Viscoli C, et al. Quinolone prophylaxis for bacterial infections in afebrile high risk neutropenic patient. *Eur J Cancer Suppl*. 2007;5(2):5-12.
5. Mikulska M, Averbuch D, Tissot F, et al. Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines. *J Infect*. 2018;76(1):20-37.
6. Carreira AS, Salas MQ, Remberger M, et al. Bloodstream infections and outcomes following allogeneic hematopoietic cell transplantation: a single-center study. *Transplant Cell Ther*. 2022;28(1):50.e1-50.e8.
7. Averbuch D, Tridello G, Hoek J, et al. Intercontinental study on pre-engraftment and post-engraftment Gram-negative rods bacteremia in hematopoietic stem cell transplantation patients: risk factors and association with mortality. *J Infect*. 2020;81(6):882-894.
8. 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(1):11-17.
9. Barreto JN, Aitken S., Krantz EM, et al. Variation in clinical practice and attitudes on antibacterial management of fever and neutropenia in patients with hematologic malignancy: a survey of cancer centers across the United States. *Open Forum Infect Dis*. 2022;9(3):ofac005.
10. Satlin MJ. Chen L, Douglass C, et al. Colonization with fluoroquinolone-resistant enterobacterales decreases the effectiveness of fluoroquinolone prophylaxis in hematopoietic cell transplant recipients. *Clin Infect Dis*. 2021;73(7):1257-1265.
11. Averbuch D, Tridello G, Hoek J, et al. Antimicrobial resistance in gram-negative rods causing bacteremia in hematopoietic stem cell transplant recipients: intercontinental prospective study of the infectious diseases working party of the european bone marrow transplantation group. *Clin Infect Dis*. 2017;65(11):1819-1828.
12. Satlin MJ, Walsh TJ. Multidrug-resistant Enterobacteriaceae, *Pseudomonas aeruginosa*, and vancomycin-resistant Enterococcus: three major threats to hematopoietic stem cell transplant recipients. *Transpl Infect Dis*. 2017;19(6). https://doi.org/10.1111/tid.12762
13. Puerta-Alcalde P, Cardozo C, Marco F, et al. Changing epidemiology of bloodstream infection in a 25-years hematopoietic stem cell transplant program: current challenges and pitfalls on empiric antibiotic treatment impacting outcomes. *Bone Marrow Transplant*. 2020;55(3):603-612.
14. Chumbita M, Puerta-Alcalde P, Yanez L, et al. Resistance to empirical beta-lactams recommended in febrile neutropenia guidelines in Gram-negative bacilli bloodstream infections in Spain: a multicentre study. *J Antimicrob Chemother*. 2022;77(7):2017-2023.
15. Gill J, Busca A, Cinatti N, et al. Bacterial bloodstream infections after allogeneic hematopoietic stem cell transplantation: etiology, risk factors and outcome in a single-center study. *Microorganisms*. 2023;11(3);742.
16. Choi H, Ahn H, Lee R, et al. Bloodstream infections in patients with hematologic diseases: causative organisms and factors associated with resistance. *Infect Chemother*. 2022;54(2):340-352.

13993062, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/tid.14375 by Bibliotheque de l'Universite de Geneve, Division de l'information, Wiley Online Library on [03/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

17. Daoud-Asfour H, Henig I, Ghersin I, et al. Omitting ciprofloxacin prophylaxis in patients undergoing allogeneic hematopoietic stem cell transplantation and its impact on clinical outcomes and microbiome structure. *Transplant Cell Ther*. 2022;28(3):168.e1-168.e8.
18. Maurer AK, Li S, Hunter BD, et al. Ciprofloxacin prophylaxis is associated with a lower incidence of gram-negative bacteremia in patients undergoing allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. 2020;55(12):2319-2321.
19. Girmenia C, Bertaina A, Piciocchi A, et al. Incidence, risk factors and outcome of pre-engraftment gram-negative bacteremia after allogeneic and autologous hematopoietic stem cell transplantation: an Italian prospective multicenter survey. *Clin Infect Dis*. 2017;65(11):1884-1896.
20. Clerici D, Galli L, Greco R, et al. Levofloxacin prophylaxis vs. no prophylaxis in patients with neutropenia within an endemic country for carbapenem-resistant GNB. *Blood Adv*. 2023;7(9):1621-1634.
21. 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(6):824-830.
22. Roth RS, Masouridi-Levrat S, Chalandon Y, et al. Invasive mold infections in allogeneic hematopoietic cell transplant recipients in 2020: have we made enough progress? *Open Forum Infect Dis*. 2022;9(1):ofab596.
23. Royston L, Royston E, Masouridi-Levrat S, et al. Letermovir primary prophylaxis in high-risk hematopoietic cell transplant recipients: a matched cohort study. *Vaccines*. 2021;9(4):372
24. Chavaz L, Royston L, Masouridi-Levrat S, et al. CMV infection after letermovir primary prophylaxis discontinuation in allogeneic hematopoietic cell transplant recipients. *Open Forum Infect Dis*. 2023;10(4):ofad169.
25. Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline update. *J Clin Oncol*. 2018;36(14):1443-1453.
26. European Centre for Disease Prevention and Control. *Surveillance of Healthcare-Associated Infections and Prevention Indicators in European Intensive Care Units*. ECDC; 2017.
27. National Healthcare Safety Network. *Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and non-central Line Associated Bloodstream Infection)*. Centers for Disease Control and Prevention website. Updated January 2024. Accessed March 2024 (https://www.cdc.gov/nhsn/pdfs/pscmanual/4psc_clabscurrent.pdf)
28. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect*. 2012;18(3):268-281.
29. Taplitz RA, Kennedy EB, Bow EJ, et al. Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA Clinical Practice Guideline Update. *J Clin Oncol*. 2018;36(30):3043-3054.
30. Zimmer AJ, Freifeld AG. Optimal management of neutropenic fever in patients with cancer. *J Oncol Pract*. 2019;15(1):19-24.
31. Keck JM, Wingler MJB, Cretella DA, et al. Approach to fever in patients with neutropenia: a review of diagnosis and management. *Ther Adv Infect Dis*. 2022;9:20499361221138346.
32. Ogura S, Kimura M, Takagi S, et al. Characteristics of gram-negative bacteremia during febrile neutropenia among allogeneic hematopoietic stem cell transplant recipients on levofloxacin prophylaxis. *Eur J Clin Microbiol Infect Dis*. 2021;40(5):941-948.
33. Mikulska M, Raiola AM, Galaverna F, et al. Pre-engraftment bloodstream infections after allogeneic hematopoietic cell transplantation: impact of T cell-replete transplantation from a haploidentical donor. *Biol Blood Marrow Transplant*. 2018;24(1):109-118.
34. Ustun C, Young JH, Papanicolaou GA, et al. Bacterial blood stream infections (BSIs), particularly post-engraftment BSIs, are associated with increased mortality after allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. 2019;54(8):1254-1265.
35. 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(1):56-65.
36. Martinez-Nadal G, Puerta-Alcalde P, Gudiol C, et al. Inappropriate empirical antibiotic treatment in high-risk neutropenic patients with bacteremia in the era of multidrug resistance. *Clin Infect Dis*. 2020;70(6):1068-1074.
37. 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(1):47-53.
38. Camus V, Dalex E, Chalandon Y, et al. Investigating the impact of temporary interruption of perfusions on central line associated bloodstream infections in hematological patients: a before–after study. International Conference on Prevention and Infection Control 2023. Antimicrob Resist Infect Control. 2023;12(Suppl 1):81.
39. Chizuka A, Kami M, Kanda Y, et al. Value of surveillance blood culture for early diagnosis of occult bacteremia in patients on corticosteroid therapy following allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2005;35(6):577-582.
40. Nesher L, Chemaly RF, Shah DP, et al. Utility of routine surveillance blood cultures in asymptomatic allogeneic hematopoietic stem cell transplant recipients with indwelling central venous catheters at a comprehensive cancer center. *Am J Infect Control*. 2014;42(10):1084-1088.
41. Stohs E, Chow VA, Liu C, et al. Limited utility of outpatient surveillance blood cultures in hematopoietic cell transplant recipients on high-dose steroids for treatment of acute graft-versus-host-disease. *Biol Blood Marrow Transplant*. 2019;25(6):1247-1252.
42. Song W, Song X, Zhu Y, et al. Microbiology and clinical outcome of bloodstream infections in patients after hematopoietic stem cell transplantation. *Infect Drug Resist*. 2023;16: 5375-5386.
43. Yan CH, Wang Y, Mo XD, et al. Incidence, risk factors, microbiology and outcomes of pre-engraftment bloodstream infection after haploidentical hematopoietic stem cell transplantation and comparison with HLA-identical sibling transplantation. *Clin Infect Dis*. 2018;67(suppl 2):S162-S173.
44. Ustun C, Chen M, Kim S, et al. Post-transplantation cyclophosphamide is associated with increased bacterial infections. *Bone Marrow Transplant*. 2024; 59(1):76-84
45. Esquirol A, Pascual MJ, Kwon M, et al. Severe infections and infection-related mortality in a large series of haploidentical hematopoietic stem cell transplantation with post-transplant cyclophosphamide. *Bone Marrow Transplant*. 2021;56(10):2432-2444.
46. Sava M, Battig V, Gerull S, et al. Bloodstream infections in allogeneic haematopoietic cell recipients from the Swiss Transplant Cohort Study: trends of causative pathogens and resistance rates. *Bone Marrow Transplant*. 2023;58(1):115-118.
47. Rosa RG, Goldani LZ. Cohort study of the impact of time to antibiotic administration on mortality in patients with febrile neutropenia. *Antimicrob Agents Chemother*. 2014;58(7):3799-3803.
48. 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(4):e56-e93.
49. Buetti N, Marschall J, Timsit JF, et al. Distribution of pathogens and antimicrobial resistance in bacteraemia according to hospitalization duration: a nationwide surveillance study in Switzerland. *Clin Microbiol Infect*. 2021;27(12):1820-1825.

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50. Barnsteiner S, Baty F, Albrich WC, et al. Antimicrobial resistance and antibiotic consumption in intensive care units, Switzerland, 2009 to 2018. *Euro Surveill*. 2021;26(46):2001537.
51. Neofytos D, Stampf S, Hoessly LD, et al. Bacteremia during the first year after solid organ transplantation: an epidemiological update. *Open Forum Infect Dis*. 2023;10(6):ofad247.
52. Weber D, Hiergeist A, Weber M, et al. Detrimental effect of broad-spectrum antibiotics on intestinal microbiome diversity in patients after allogeneic stem cell transplantation: lack of commensal sparing antibiotics. *Clin Infect Dis*. 2019;68(8):1303-1310.
53. Rashidi A, Gao F, Fredricks DN, et al. Analysis of antibiotic exposure and development of acute graft-vs.-host disease following allogeneic hematopoietic cell transplantation. *JAMA Netw Open*. 2023;6(6):e2317188.
54. Lee SE, Lim JY, Ryu DB, et al. Alteration of the intestinal microbiota by broad-spectrum antibiotic use correlates with the occurrence of intestinal graft-versus-host disease. *Biol Blood Marrow Transplant*. 2019;25(10):1933-1943.
55. Shono Y, Docampo MD, Peled JU, et al. Increased GVHD-related mortality with broad-spectrum antibiotic use after allogeneic hematopoietic stem cell transplantation in human patients and mice. *Sci Transl Med*. 2016;8(339):339ra71.
56. Hidaka D, Hayase E, Shiratori S, et al. The association between the incidence of intestinal graft-vs.-host disease and antibiotic use after allogeneic hematopoietic stem cell transplantation. *Clin Transplant*. 2018;32(9):e13361.
57. Fuji S, Kapp M, Einsele H. Possible implication of bacterial infection in acute graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Front Oncol*. 2014;4:89.
58. Blennow O, Mattsson J, Remberger M., Pre-engraftment blood stream infection is a risk factor for acute GVHD grades II–IV. *Bone Marrow Transplant*. 2013;48(12):1583-1584.
59. Poutsiaka DD, Munson D, Price LL, et al. Blood stream infection (BSI) and acute GVHD after hematopoietic SCT (HSCT) are associated. *Bone Marrow Transplant*. 2011;46(2):300-307.
60. Inoue Y, Okinaka K, Fuji S, et al. Severe acute graft-versus-host disease increases the incidence of blood stream infection and mortality after allogeneic hematopoietic cell transplantation: Japanese transplant registry study. *Bone Marrow Transplant*. 2021;56(9):2125-2136.
61. Anresis A-V, IS ABV. *Swiss Antibiotic Resistance Report 2022*. The Federal Office of Public Health FOPH; 2022.

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