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MAJOR ARTICLE

Incidence, Risk Factors and Outcome of Pre-engraftment Gram-Negative Bacteremia After Allogeneic and Autologous Hematopoietic Stem Cell Transplantation: An Italian Prospective Multicenter Survey

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Background. Gram-negative bacteremia (GNB) is a major cause of illness and death after hematopoietic stem cell transplantation (HSCT), and updated epidemiological investigation is advisable.

Methods. We prospectively evaluated the epidemiology of pre-engraftment GNB in 1118 allogeneic HSCTs (allo-HSCTs) and 1625 autologous HSCTs (auto-HSCTs) among 54 transplant centers during 2014 (SIGNB-GITMO-AMCLI study). Using logistic regression methods. we identified risk factors for GNB and evaluated the impact of GNB on the 4-month overall-survival after transplant.

Results. The cumulative incidence of pre-engraftment GNB was 17.3% in allo-HSCT and 9% in auto-HSCT. *Escherichia coli*, *Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* were the most common isolates. By multivariate analysis, variables associated with GNB were a diagnosis of acute leukemia, a transplant from a HLA-mismatched donor and from cord blood, older age, and duration of severe neutropenia in allo-HSCT, and a diagnosis of lymphoma, older age, and no antibacterial prophylaxis in auto-HSCT. A pre-transplant infection by a resistant pathogen was significantly associated with an increased risk of posttransplant infection by the same microorganism in allo-HSCT. Colonization by resistant gram-negative bacteria was significantly associated with an increased rate of infection by the same pathogen in both transplant procedures. GNB was independently associated with increased mortality at 4 months both in allo-HSCT (hazard ratio, 2.13; 95% confidence interval, 1.45–3.13; P <.001) and auto-HSCT (2.43; 1.22–4.84; P = .01).

Conclusions. Pre-engraftment GNB is an independent factor associated with increased mortality rate at 4 months after auto-HSCT and allo-HSCT. Previous infectious history and colonization monitoring represent major indicators of GNB.

Clinical Trials registration. NCT02088840.

Keywords. stem cell transplant; Gram negative bacteremia; multidrug resistance; epidemiology; survival.

Gram-negative bacteremia (GNB) is a leading cause of illness and death after hematopoietic stem cell transplantation (HSCT) [1–9]. Challenges include the changes in GNB incidence, susceptibility patterns to antibiotics and prognosis due to changes in transplant populations, the global epidemiology of infections, and antimicrobial strategies. Because of the poor outcomes associated with GNB in transplant

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recipients, there is much interest in the identification of risk and prognostic factors, which may help determine tailored infection-control strategies [4–10]. Therefore, updated epidemiological investigation in this population is advisable.

To assess the incidence, risk and prognostic factors of pre-engraftment GNB in HSCT recipients, data from patients undergoing allogeneic HSCT (allo-HSCT) and autologous HSCT (auto-HSCT) during 2014 were prospectively registered. These data provide the basis for promoting direct efforts in risk stratification, prevention, and management of gram-negative bacterial infections in the HSCT population.

METHODS

Study Design

The Severe Infections by Gram-Negative Bacteria (SIGNB) study was sponsored by the Italian Stem cell Transplantation Network (Gruppo Italiano Trapianto di Midollo Osseo [GITMO]) and the Italian Association of Clinical Microbiologists (Associazione Microbiologi Clinici Italiani [AMCLI]). The SIGNB-GITMO-AMCLI study was a prospective epidemiological survey performed in 54 transplant centers in Italy between 1 January and 31 December 2014. Study start times could differ among centers, but all consecutive transplants were enrolled. The results of this study were reported according to the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement [11]. The study was approved by the ethical committee of each center, and informed consent was obtained from the patients.

Data Collection

Variables included patients characteristics, diagnosis and phase of the underlying disease, prior auto-HSCT or allo-HSCT, neutropenia within 30 days before HSCT, GNB documented within 3 months before HSCT, stem cell donor, stem cell source, pretransplant conditioning regimen, the use of "in vivo" T-cell depletion with antithymocyte globulin or cell manipulation ex vivo, antibacterial prophylaxis during the neutropenia period, colonization by resistant gram-negative bacteria at the pretransplant screening and during pre-engraftment, development of grade II–IV mucositis, duration of pre-engraftment neutropenia, development of grade II–IV acute graft-vs-host disease (GVHD) before engraftment, microbiologically documented bacterial and fungal infections, viral diseases and clinically documented infections before engraftment, survival at 4 months after HSCT, and cause of death. Information pertaining to the GNB included timing after HSCT and in vitro susceptibility.

Definition of Infection and Colonization

All cases of GNB with microorganism isolation from ≥1 blood culture were considered. For each isolate in vitro susceptibility data included sensitivity or nonsensitivity to the third-generation cephalosporin ceftazidime (ceph-S or ceph-NS) and sensitivity or nonsensitivity to carbapenems (carba-S or carba-NS) for enterobacteria (defined as a minimum inhibitory concentration >1 mg/L for imipenem, meropenem, and/or ertapenem) and multidrug resistance (MDR) for gram-negative nonfermenters (defined as resistance to ≥3 antimicrobial groups among piperacillin-tazobactam, ceftazidime, fluoroquinolones, aminoglycosides, and carbapenems).

The investigators were also asked whether their center routinely performed pre- and posttransplant surveillance of colonization by ceph-NS enterobacteria, carba-NS enterobacteria, and MDR nonfermenters, using culture of rectal/perianal swab samples, and reported the cases of colonization. Therefore, for the colonization analysis, we excluded patients who did not undergo such screening.

Analyses

The analyses were performed separately for auto-HSCT and allo-HSCT. The cumulative incidence of pre-engraftment GNB was calculated, accounting for the competing risks of infection-free death. Cumulative incidence of GNB was calculated for any type and status of the underlying disease, stem cell donor, stem cell source, pretransplant conditioning, history of GNB before transplant, antibacterial prophylaxis, and acute GVHD. Considering the different times of engraftment for the 2 transplant procedures, we calculated the cumulative incidence of GNB 20 days after auto-HSCT and 30 days after allo-HSCT. All factors were evaluated in multivariate models to control potential confounders using logistic regression methods.

Survival analyses were performed according to the above variables. Deaths were attributed to GNB in patients who failed to respond to therapy (ie, who had unstable disease or disease progression, according to the responsible physician judge) and in patients with a partial response to therapy who died because of an acute event involving any of the sites of infection and in the absence of other causes thought to have primarily contributed to death. The probability of 4-month survival after HSCT was calculated using Kaplan-Meier estimates, log-rank tests were applied for univariate analysis, and 2-sided P values ≤.05 were considered to represent statistical significance. Multivariate analyses were performed using a Cox proportional hazards regression model. In this model, variables related to GNB and acute GVHD were considered as time-dependent covariates in order to evaluate their effect only in the period after their onset. All significant variables in the univariate analysis were included in the multivariate analysis; final models were also evaluated with backward and stepwise function. Statistical analyses were performed using SAS software, version 9.4. SIGNB-GITMO-AMCLI is registered with Clinicaltrials.gov (NCT02088840).

RESULTS

Patient Characteristics

Overall, 1118 allo-HSCTs from 44 centers (median per center, 20; range, 2–105) and 1625 auto-HSCTs from 52 centers (23; 4–101) were included in the study. Demographics and patient characteristics at HSCT are shown in Table 1. Most allo-HSCT and auto-HSCT recipients were affected by acute leukemia (65%) and multiple myeloma (52%), respectively. The vast majority of allo-HSCTs (74%) involved transplants from an HLA-mismatched related or unrelated donor.

Allo-Hematopoietic Stem Cell Transplantation

Pre-engraftment Infections and Details on Gram-Negative Bacteremia

The infections documented before engraftment are detailed in Table 2. Overall, 149 GNBs were documented in 140 of 1118 allo-HSCTs (12.5%). The rate of GNBs by transplant center ranged from 0% to 39.1% (median, 11.7%). The median rate of GNB accounted for 11.1% in centers with lower transplant activity (≤20 HSCTs) and 13.2% in those with higher activity (>20 HSCTs) (P = .82). *Escherichia coli* was the most common gram-negative pathogen (77 cases; 51.7%), followed by *Klebsiella pneumoniae* (28 cases; 18.8%) and *Pseudomonas aeruginosa* (21 cases; 14.1%). The susceptibility pattern of the isolates is detailed in Table 3.

Risk Factors for Gram-Negative Bacteremia in Allo-Hematopoietic Stem Cell Transplantation Recipients

The cumulative incidence of GNB 30 days after allo-HSCT was 17.3% (95% confidence interval [CI], 12.5%–22.7%) (Figure 1A). GNB-free pre-engraftment death occurred in 25 HSCT recipients (2.2%). The risk of GNB according to demographics, underlying disease, and transplant variables are detailed in Table 4. By multivariate analysis, variables associated with increased risk of pre-engraftment GNB were acute leukemia, a transplant from an HLA-mismatched donor (related or unrelated) and from cord blood, older recipient age, and duration of severe neutropenia (polymorphonuclear leukocyte count <100/μL), and ex vivo graft manipulation was protective against GNB.

Risk of Gram-Negative Bacteremia According to Pretransplant Infection and Colonization

A pretransplant bloodstream infection by ≥1 gram-negative pathogen (88 isolates) was reported in 84 patients (7.5%) (ceph-S *E. coli* in 17, ceph-NS/carba-S *E. coli* in 17, ceph-S *K. pneumoniae* in 4, ceph-NS/carba-S *K. pneumoniae* in 9, carba-NS *K. pneumoniae* in 6, non-MDR *P. aeruginosa* in 11, MDR *P. aeruginosa* in 4, *Enterobacter cloacae* complex in 6, and other pathogens in 14). An infection by the same species with the same susceptibility phenotype was documented in 16 of these 84 patients (19%) a median of 7 days (range, 1–25 days) after transplant (ceph-S

Table 1. Characteristics of Patients at Transplantation

Characteristic	Patients, No. (%)[a]	
	Allo-HSCT (n = 1118)	Auto-HSCT (n = 1625)
Age, median (range), y	44 (1–72)	56 (1–75)
Pediatric patients (age ≤18 y)	224 (20)	92 (5.7)
Male sex	652 (58.3)	958 (58.9)
Underlying disease		
Acute myeloid leukemia	420 (37.6)	47 (2.9)
Acute lymphoid leukemia	205 (18.3)	15 (0.9)
Other acute leukemias	6 (0.5)	0
Myelodysplastic syndromes	96 (8.6)	1 (<0.1)
Chronic myeloproliferative	64 (5.7)	2 (0.1)
Non-Hodgkin lymphoma	99 (8.8)	432 (26.6)
Hodgkin lymphoma	66 (5.9)	168 (10.3)
Chronic lymphoid leukemia	14 (1.2)	3 (0.2)
Multiple myeloma, plasmacellular leukemia, amyloidosis	59 (5.3)	846 (52.1)
Aplastic anemia	34 (3.0)	0
Hemoglobinopathy	28 (2.4)	0
Solid tumors	4 (0.4)	88 (5.4)
Other diseases	23 (2.1)	23 (1.4)
Phase of underlying disease at transplant		
Cancer in complete remission	617 (55.2)	668 (41.1)
Cancer not in complete remission/active	416 (37.2)	934 (57.5)
Nonmalignant stable/chronic diseases	85 (7.6)	23 (1.4)
Previous HSCT		
Auto-HSCT alone	204 (18.2)	343 (21.1)
Allo-HSCT alone	90 (8.0)	2 (0.1)
Auto- and allo-HSCT	15 (1.3)	1 (<0.1)
Donor type		
HLA matched, related	296 (26.5)	NA
HLA mismatched, related[b]	352 (31.5)	NA
HLA matched, unrelated volunteer	295 (26.4)	NA
HLA mismatched unrelated volunteer	145 (13.0)	NA
Unrelated cord blood	30 (2.7)	NA
Stem cell source		
Bone marrow	476 (42.6)	9 (0.5)
Peripheral blood	612 (54.7)	1616 (99.5)
Cord blood	30 (2.7)	0
Pretransplant conditioning		
Myeloablative	826 (73.9)	1472 (90.6)
Reduced intensity	251 (22.4)	32 (2.0)
Nonmyeloablative	41 (3.7)	121 (7.4)
T-cell depletion		
No	636 (56.9)	1625 (100)
Yes, in vivo (ATG or alemtuzumab)	386 (34.5)	0
Yes, ex vivo (graft manipulation)	96 (8.6)	0
Prolonged neutropenia during month before transplant (PML count <500/μL for ≥7 d)	219 (19.6)	82 (85.0)
Rituximab therapy before auto-HSCT	NA	367 (22.6)
Antibacterial prophylaxis during neutropenia[c]		
No	141 (12.6)	214 (13.2)
Yes	977 (87.4)	1411 (86.8)

Abbreviations: Allo-HSCT, allogeneic hematopoietic stem cell transplantation; ATG, antithymocyte globulin; auto-HSCT, autologous HSCT; HLA, human leukocyte antigen; NA, not applicable; PML, polymorphonuclear leukocyte.

[a]Data represent No. (%) of patients unless otherwise specified.

[b]The 352 transplants from HLA-mismatched related donors included 311 haploidentical transplants.

[c]A fluoroquinolone was used in 88% of allo-HSCT and 94% of auto-HSCT recipients who received antibacterial prophylaxis during neutropenia.

Table 2. Infections Documented Before Engraftment

Infection Findings	Allo-HSCT (n = 1118)	Auto-HSCT (n = 1625)
No documented infection, No. of patients (%)		
No fever or documented infection	329 (29.5)	755 (46.5)
Fever of unknown origin only	395 (35.3)	472 (29.0)
Clinically documented infections, No. of episodes/No. of patients (%)	68/67 (6.0)	87/85 (5.2)
Pneumonia	39/39 (3.5)	53/53 (3.3)
Skin infection	14/14 (1.2)	12/12 (0.7)
GI tract infection	6/6 (0.5)	20/18 (1.1)
Other	10/9 (0.8)	2/2 (0.1)
Microbiologically documented infections, No. of episodes/No. of patients (%)	412/331 (30.1)	355/320 (19.2)
Gram-negative bacterial infection	157/148 (13.2)[a]	162/157 (9.7)[b]
Gram-positive bacterial infection	209/193 (17.3)	182/172 (10.6)
Fungal infection	24/24 (2.1)	9/9 (0.5)
Viral infection	22/22 (2.0)	2/2 (0.1)

Abbreviations: Allo-HSCT, allogeneic hematopoietic stem cell transplantation; auto-HSCT, autologous HSCT; GI, gastrointestinal.

[a]Including 149 episodes of bacteremia in 140 patients plus 8 other site infections in 8 patients.

[b]Including 151 episodes of bacteremia in 146 patients plus 11 other site infections in 11 patients.

E. coli in 1 patient, ceph-NS *E. coli* in 5, ceph-NS *K. pneumoniae* in 2, carba-NS *K. pneumoniae* in 4, *E. cloacae* complex in 1, and non-MDR *P. aeruginosa* in 3). A significantly increased risk of pre-engraftment GNB caused by the same species with the same susceptibility phenotype was documented in patients with a pre-transplant GNB caused by ceph-NS/carba-S *E. coli*, carba-NS *K. pneumoniae,* or non-MDR *P. aeruginosa*. Pretransplant GNB caused by ceph-S *E. coli* did not represent a risk for a posttransplant infection by the same pathogen (Figure 2).

The rate of colonization by ceph-NS/carba-S *E. coli*, ceph-NS/carba-S *K. pneumoniae*, carba-NS *K. pneumoniae,* and MDR *P. aeruginosa* and the rate of pre-engraftment infection according to colonization are detailed in Table 5. Colonization by resistant gram-negative bacteria was always associated with a significantly increased risk of pre-engraftment infection by the same pathogen. In particular, a high probability of pre-engraftment infection by the same colonizing species 30 days after HSCT was observed for carba-NS *K. pneumoniae* (32.5% in colonized vs 0.1% in noncolonized; $P < .001$) and MDR *P. aeruginosa* (28.6% vs 0.6%; $P < .001$) (Figure 3A).

Survival

The overall survival 4 months after transplant was 86.3% (95% CI, 84.3%–88.4%). In multivariate analysis, acute leukemia, previous auto-HSCT, a disease not in complete remission at the time of HSCT, older age, prolonged pre-engraftment neutropenia, acute GVHD, and pre-engraftment GNB (hazard ratio, 2.13; 95% CI, 1.45–3.13; P <.001) were factors independently associated with increased mortality rate (Table 6).

Table 3. Distribution of Gram-Negative Species and Antimicrobial Susceptibility Patterns

Pathogen and Resistance Pattern[a]	Allo-HSCT (n = 149)	Auto-ASCT (n = 151)
Escherichia coli, total No. (%)	77 (51.7)	92 (60.9)
Ceph-S, carba-S, No. (% of *E. coli*)	46 (59.7)	63 (68.5)
Ceph-NS, carba-S, No. (% of *E. coli*)	30 (39.0)	29 (31.5)
Ceph-NS, carba-NS, No. (% of *E. coli*)	1 (1.3)	0
Klebsiella pneumoniae, total No. (%)	28 (18.8)	23 (15.2)
Ceph-S, carba-S, No. (% of *K. pneumoniae*)	6 (21.4)	7 (30.4)
Ceph-NS, carba-S, No. (% of *K. pneumoniae*)	6 (21.4)	10 (43.5)
Ceph-NS, carba-NS, No. (% of *K. pneumoniae*)	16 (57.1)	6 (26.1)
Other Enterobacteriaceae, total No. (%)	9 (6.0)[b]	10 (6.6)[c]
Ceph-S, carba-S, No. (% of other Enterobacteriaceae)	8 (88.9)	10 (100)
Ceph-NS, carba-S, No. (% of other Enterobacteriaceae)	0	0
Ceph-NS, carba-NS, No. (% of other Enterobacteriaceae)	1 (11.1)	0
Pseudomonas aeruginosa, total No. (%)	21 (14.1)	13 (8.6)
Non-MDR *P. aeruginosa*, No. (% of *P. aeruginosa*)	13 (61.9)	12 (92.3)
MDR *P. aeruginosa*, No. (% of *P. aeruginosa*)	8 (38.1)	1 (7.7)
Other gram-negative bacteria, total No. (%)	14 (9.4)[d]	13 (8.6)[e]
Non-MDR, No. (% of other gram–negative bacteria)	11 (78.6)	11 (84.6)
MDR, No. (% of other gram-negative bacteria)	3 (21.4)	2 (15.4)

Abbreviations: Allo-HSCT, allogeneic hematopoietic stem cell transplantation; auto-HSCT, autologous HSCT; carba-NS, nonsensitive to carbapenems; carba-S, sensitive to carbapenems; ceph-NS, nonsensitive to the third-generation cephalosporin ceftazidime; ceph-S, sensitive to ceftazidime; MDR, multidrug-resistant.

[a]Carba-S was defined as a minimum inhibitory concentration ≤1 mg/L for imipenem, meropenem, and ertapenem; MDR, as resistance to ≥3 of the following antibiotics: ciprofloxacin, amikacin, piperacillina-tazobactam, ceftazidime, meropenem, and imipenem.

[b]Including *Enterobacter* spp. (6 cases), *Klebsiella oxytoca* (2 cases), and *Serratia marcescens* (1 case).

[c]Including *Enterobacter* spp. (5 cases), *Morganella morganii* (2 cases), and *Proteus mirabilis*, *Serratia marcescens,* and *Yersinia enterocolitica* (1 case each).

[d]Including *Stenotrophomonas maltophilia* (3 cases), *Acinetobacter* spp. (3 cases), *Pseudomonas* spp. (4 cases), *Capnocytophaga* spp. (2 cases), *Rhizobium radiobacter* (1 case), and *Citrobacter* spp. (1 case).

[e]Including *Acinetobacter* spp. (6 cases), *Capnocytophaga* spp. (2 cases), and *Bacteroides fragilis*, *Citrobacter* sp, *Fusobacterium* spp., *Sphingomonas* spp., and *Pseudomonas* spp. (1 case each).

The mortality rate 30 days after the diagnosis of GNB was 17.9% (25 of 140 patients), and in 96% of patients (24 of 25) the infection was considered the primary cause of death. Of 46 patients who died before engraftment, the cause of death was a GNB in 18 (39.1%).

The probability of survival 4 months after allo-HSCT in 978 patients without any GNB was 88.3%, compared with 80.0% in 45 patients with ceph-S *E. coli* infection ($P = .09$), 86.7% in 30 with ceph-NS *E. coli* infection ($P = .73$), 40.0% in 15 with carba-NS *K. pneumoniae* infection ($P < .001$), 61.5% in 13 with non-MDR *P. aeruginosa* infection ($P = .001$) and 25% in 8 with MDR *P. aeruginosa* infection ($P < .001$) (Figure 4).

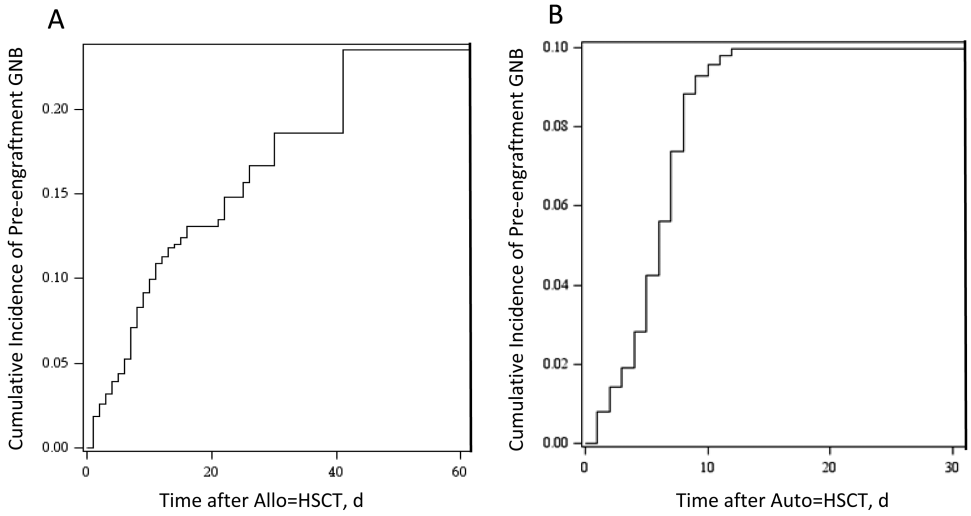

Figure 1. Cumulative incidence curve for gram-negative bacteremia (GNB) after allogeneic hematopoietic stem cell transplantation (allo-HSCT) (*A*) and auto-HSCT (*B*) in the SIGNB-GITMO-AMCLI epidemiological survey.

Auto-Hematopoietic Stem Cell Transplantation

Pre-engraftment Infections and Details on Gram-Negative Bacteremia

The infections documented before engraftment are detailed in Table 2. Overall, 151 GNBs were documented in 146 of 1625 auto-HSCTs (9.0%). The rate of GNB by transplant center ranged from 0% to 33.1% (median, 7.5%). The median rate of GNB accounted for 6.0% in centers with lower transplant activity (≤23 HSCTs) and 8.6% in those with higher activity (>23 HSCTs) (P = .93). *E. coli* was the most common gram-negative pathogen (92 cases; 60.9%), followed by *K. pneumoniae* (23 cases, 15.2%) and *P. aeruginosa* (13 cases; 8.6%). The susceptibility pattern of the isolates is detailed in Table 3.

Risk Factors for Gram-Negative Bacteremia in Auto-Hematopoietic Stem Cell Transplantation Recipients

The cumulative incidence of GNB 20 days after transplant was 9.0% (95% CI, 8%–11%) (Figure 1B). GNB free pre-engraftment death occurred in 6 patients (0.4%). The risk of GNB according to demographics, underlying disease, and transplant variables are detailed in Table 4. By multivariate analysis, variables associated with pre-engraftment GNB were a diagnosis of lymphoma, older recipient age, and no antibacterial prophylaxis.

Risk of Gram-Negative Bacteremia by Species According to Pretransplant Infection and Colonization

A pretransplant infection by a gram-negative pathogen was reported in 39 patients (2.4%) (ceph-S *E. coli* in 7, ceph-NS/carba-S *E. coli* in 5, ceph-S *K. pneumoniae* in 7, ceph-NS/carba-S *K. pneumoniae* in 2, carba-NS *K. pneumoniae* in 2, *E. cloacae* complex in 5, and other pathogens in 11). In only 3 patients was a posttransplant infection by the same pathogen documented (ceph-S *E. coli*, ceph-S *K. pneumoniae*, and carba-NS *K. pneumoniae* at 2, 7, and 7 days after transplant, respectively).

The rate of colonization by ceph-NS/carba-S *E. coli*, ceph-NS/carba-S *K. pneumoniae*, carba-NS *K. pneumoniae,* and MDR *P. aeruginosa* and the rate of pre-engraftment infection according to colonization are detailed in Table 5. A significant correlation between colonization and pre-engraftment infection by the same species 20 days after transplant was observed for ceph-NS/carba-S *E. coli* (10.5% in colonized vs 4.5% in non-colonized; P = .04), ceph-NS/carba-S *K. pneumoniae* (20.4% vs 0.3%; P < .001), and carba-NS *K. pneumoniae* (19.0% vs 0.01%; P < .001) (Figure 3B).

Survival

The overall survival 4 months after auto-HSCT was 97% (95% CI, 96.2%–97.9%). In multivariate analysis, a diagnosis of lymphoma, prolonged neutropenia during the month before auto-HSCT, a disease not in complete remission at the time of transplant, prolonged pre-engraftment neutropenia, and pre-engraftment GNB (hazard ratio, 2.43; 95% CI, 1.22–4.84; P = .01) were factors independently associated with increased mortality rates (Table 6). The mortality rate 30 days after GNB diagnosis was 4.1% (6 of 146 patients), and in all 6 patients GNB was considered the primary cause of death. Of 11 patients who died before engraftment, the cause of death was a GNB in 4 (36.4%).

The probability of survival at 4 months after transplant in 1479 patients without any GNB was 97.5%, compared with 98.4% in 63 patients with ceph-S *E. coli* infection (P = .66), 93.1% in 29 with ceph-NS/carba-S *E. coli* infection (P = .13), 85.7% in 7 with ceph-S *K. pneumoniae* infection (P = .04), 90% in 10 with ceph-NS/carba-S *K. pneumoniae* infection (P = .14), 66.7% in 6 with carba-NS *K. pneumoniae* infection (P < .001), and 83.3% in 12 with non-MDR *P. aeruginosa* infection (P = .001).

Table 4. Risk Factors of Gram Negative Bacteremia During the Pre-Engraftment Period According to Demographic, Underlying Disease, and Transplant Variables

	Allo-HSCT				Auto-HSCT			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variables	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Sex								
Male	1.00				1.00			
Female	1.066 (.76–1.49)	.71			0.95 (.68–1.33)	.78		
Age (increased by 10 y)	1.21 (1.10–1.33)	<.001	1.16 (1.06–1.27)	.001	1.09 (.99–1.22)	.10	1.20 (1.06–1.36)	.004
Underlying disease for allo-HSCT								
Acute leukemia	1.00				NA			
Other diseases	0.71 (.50–1.00)	.05	0.65 (.46–.92)	.01	NA			
Underlying disease for auto-HSCT								
Multiple myeloma	NA				1.00			
Lymphoma	NA				1.51 (1.07–2.13)	.03	1.86 (1.30–2.66)	<.001
Acute leukemia	NA				1.71 (.83–3.52)	.14	1.86 (.90–3.86)	.09
Other diseases	NA				1.18 (.60–2.29)	.63	2.36 (1.06–5.26)	.04
Phase of underlying disease at transplant								
Complete remission	1.00				1.00			
No complete remission	1.23 (.88–1.72)	.22			1.13 (.81–1.57)	.47		
Previous auto-HSCT								
No	1.00	.93			1.00			
Yes	0.98 (.64–1.50)				0.88 (.59–1.33)	.56		
Previous allo-HSCT								
No	1.00				NA			
Yes	1.04 (.60–1.80)	.89			NA			
Pretransplant neutropenia								
No	1.00				1.00			
Yes	1.11 (.74–1.65)	.62			1.08 (.53–2.20)	.84		
Pretransplant rituximab								
No	NA				1.00			
Yes	NA				1.58 (1.11–2.25)	.01		
Stem cell source								
Peripheral blood	1.00				NA			
Bone marrow	1.68 (1.19–2.36)	.003			NA			
Cord blood	2.46 (1.06–5.70)	.04			NA			
Donor type								
Matched related	1.00				NA			
Mismatched related	4.21 (2.37–7.49)	<.001	4.14 (2.31–7.42)	<.001	NA			
Matched unrelated volunteer	2.01 (1.05–3.82)	.03	1.68 (.87–3.25)	.12	NA			
Mismatched unrelated volunteer	3.53 (1.81–6.87)	<.001	2.92 (1.47–5.81)	.002	NA			
Cord blood	4.95 (1.89–12.94)	.001	3.50 (1.32–9.29)	.01	NA			
Conditioning regimen								
Myeloablative	1.00				NA			
Nonmyeloablative/reduced intensity	1.83 (1.31–2.56)	<.001			NA			
T-cell depletion								
No	1.00				NA			
Yes, ATG in vivo	1.03 (0.73–1.46)	.85			NA			
Yes, manipulation ex vivo	0.16 (.04–.67)	.01	0.13 (.03–.53)	.004	NA			
Antibacterial prophylaxis								
No	1.00				1.00			
Yes	0.71 (.45–1.12)	.14			0.52 (.35–.77)	.001	0.50 (.34–.75)	<.001
Acute GVHD during engraftment								
Grade 0–I	1.00				NA			
Grade II–IV	1.25 (0.32–4.81)	.75			NA			
Duration of pre-engraftment neutropenia								
PML count <500/μL	1.02 (1.01–1.03)	<.001			1.03 (1.008–1.052)	<.001		
PML count <100/μL	1.03 (1.02–1.04)	<.001	1.02 (1.01–1.03)	<.001	1.03 (1.01–1.06)	.003		
Mucositis								
CTC grade 0–I	1.00				1.00			
CTC grade II–IV	1.47 (.74–1.47)	.79			1.17 (.84–1.62)	.35		

Abbreviations: Allo-HSCT, allogeneic hematopoietic stem cell transplantation; ATG, antithymocyte globulin; auto-HSCT, autologous HSCT; CI, confidence interval; CTC, common toxicity criteria; GVHD, graft-vs-host disease; HR, hazard ratio; NA, not applicable; PML, polymorphonuclear leukocyte.

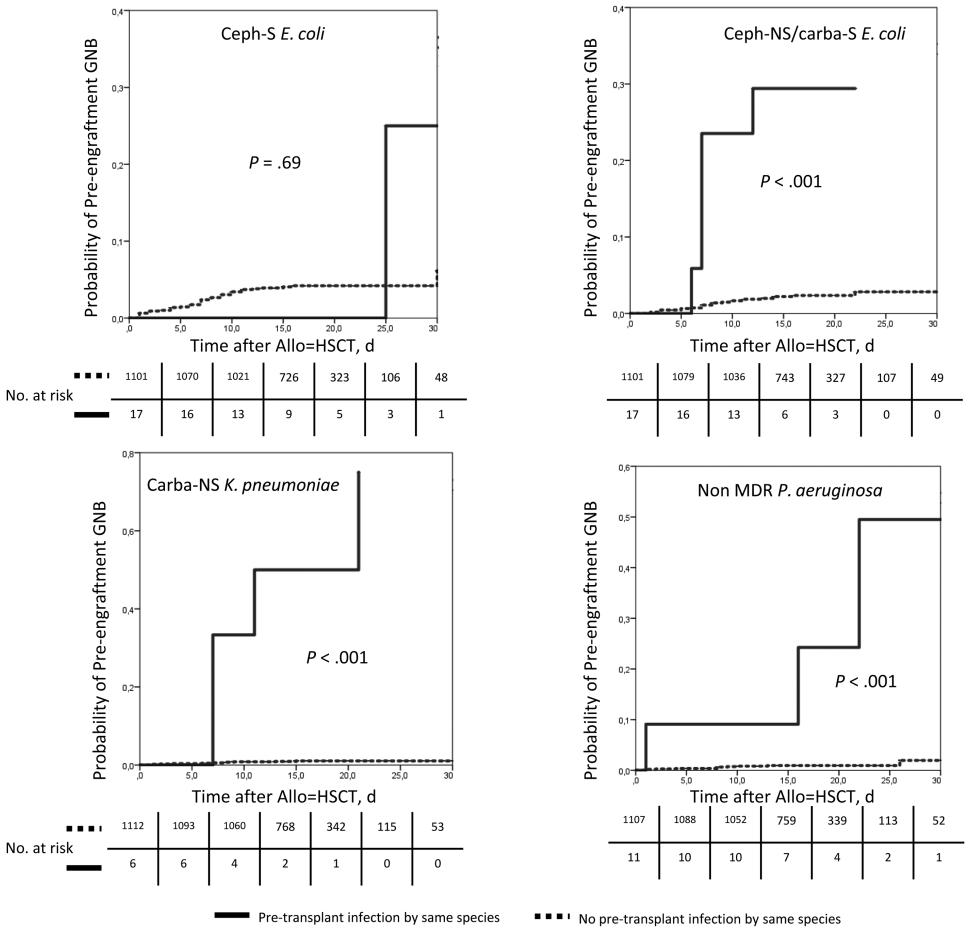

Figure 2. Risk of pre-engraftment gram-negative bacteremia (GNB) recurrence after allogeneic hematopoietic stem cell transplantation (allo-HSCT) according to pretransplant GNB caused by the same species with the same susceptibility phenotype. (The risk was not calculated for other pathogens, for which the rates of pretransplant GNB were very low.) Abbreviations: Carba-NS, nonsensitive to carbapenems; carba-S, sensitive to carbapenems; ceph-NS, nonsensitive to the third-generation cephalosporin ceftazidime; ceph-S, sensitive to ceftazidime; *E. coli*, *Escherichia coli*; *K. pneumoniae*, *Klebsiella pneumoniae*; MDR, multidrug-resistant; *P. aeruginosa*, *Pseudomonas aeruginosa*.

DISCUSSION

The emergence of infections by gram-negative bacteria resistant to antibiotics has become a public health problem of major concern worldwide [12–14]. However, in HSCT populations, information regarding the current incidence and prognostic factors of gram-negative infections and their antibiotic resistance patterns is mainly limited to retrospective, single-center experiences [7, 15–25]. The GITMO-AMCLI-SIGNB survey, which included 64% of allo-HSCTs and 51% of auto-HSCTs performed in Italy in 2014, is a prospective study designed to critically assess the incidence and risk factors of GNB during the pre-engraftment period, and their impact on

Table 5. Correlation Between Rectal Colonization by Resistant Gram-Negative Bacteria and Pre-Engraftment Gram Negative Bacteremia Caused by a Pathogen With the Same Susceptibility Phenotype

	Allo-HSCT		Auto-HSCT	
Microorganism	Colonized/Evaluable Patients, No. (%)	Pre-engraftment GNB Colonized/Not Colonized, % (P Value)	Colonized/Evaluable Patients, No. (%)	Pre-engraftment GNB Colonized/Not colonized, % (P Value)
Ceph-R/carba-S *Escherichia Coli*	69/909 (7.6)	8.7/1.3 (.001)	89/1307 (6.8)	9.0/4.3 (.06)
Ceph-R/carba-S *Klebsiella pneumoniae*	14/909 (1.5)	7.1/0.4 (.07)	21/1307 (1.6)	19.0/0.3 (<.001)
Carba-R *K. pneumoniae*	36/1058 (3.4)	27.8/0.4 (<.001)	21/1432 (1.5)	19.0/0.007 (<.001)
MDR *Pseudomonas aeruginosa*	7/897 (0.8)	28.6/0.6 (.001)	2/1307 (0.15)	50/0.007 (.003)

Abbreviations: Allo-HSCT and auto-HSCT, allogeneic and autologous hematopoietic stem cell transplantation; carba-R, resistant to carbapenems; carba-S, sensitive to carbapenems; ceph-R, resistant to the third-generation cephalosporin ceftazidime; GNB, gram-negative bacteremia; MDR, multidrug-resistant.

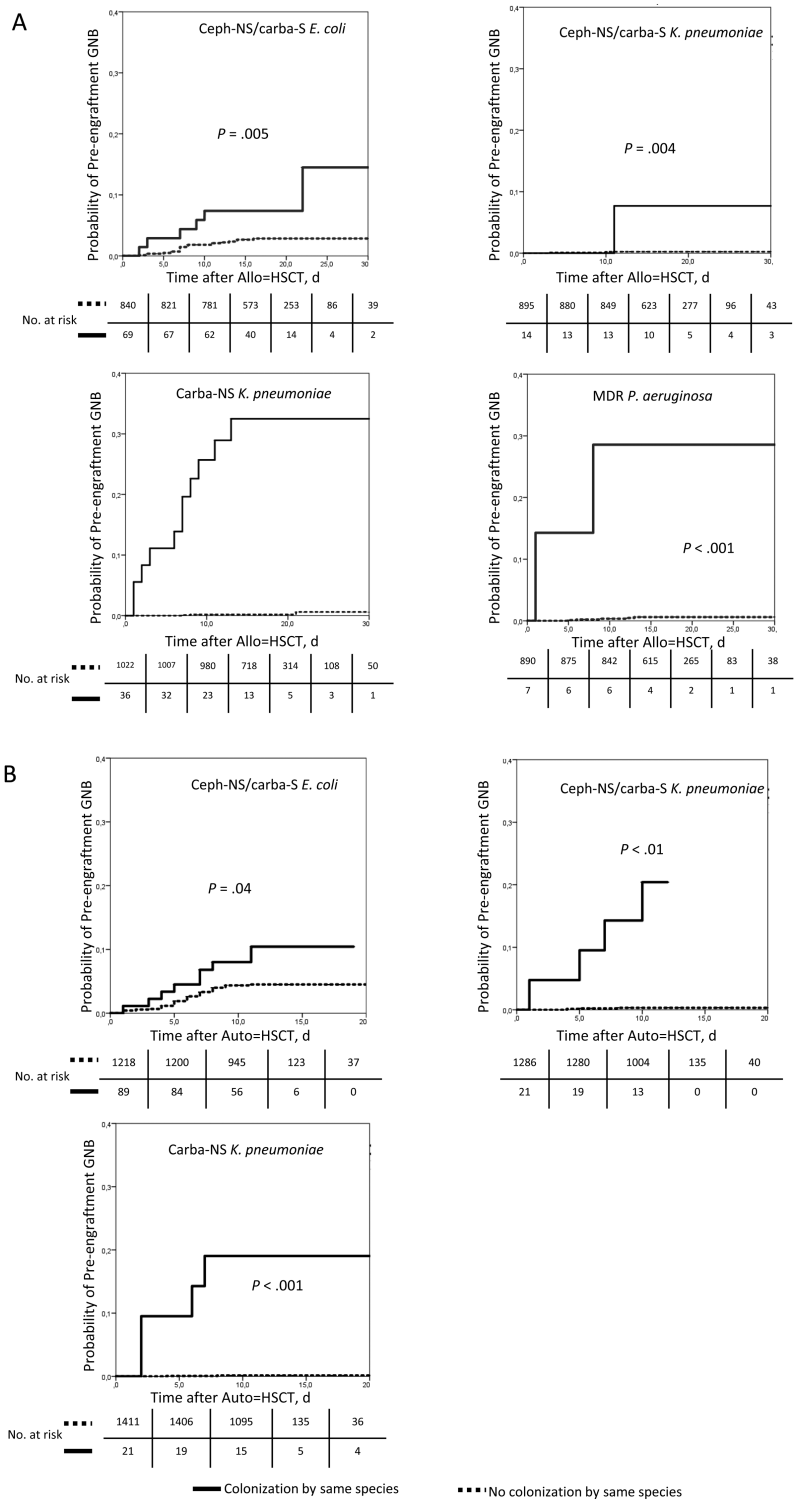

Figure 3. Risk of pre-engraftment gram-negative bacteremia (GNB) according to colonization by resistant GNB in allogeneic hematopoietic stem cell transplantation (allo-HSCT) (*A*) and autologous HSCT (auto-HSCT) (*B*) recipients. The risk was not calculated for other resistant pathogens, for which the rates of colonization were very low.) Abbreviations: Carba-NS, nonsensitive to carbapenems; carba-S, sensitive to carbapenems; ceph-NS, nonsensitive to the third-generation cephalosporin ceftazidime; *E. coli, Escherichia coli*; *K. pneumoniae, Klebsiella pneumoniae*; MDR, multidrug-resistant; *P. aeruginosa, Pseudomonas aeruginosa.*

patient outcome. A valuable characteristic of this study was the availability of complete prospectively collected denominator data.

The overall pre-engraftment cumulative incidence of GNB was 17.3% at 30 days after allo-HSCT and 9% at 20 days after auto-HSCT. *E. coli*, *K. pneumoniae*, and *P. aeruginosa* were the

Table 6. Probability of Death Within 4 Months After Transplant

	Allo-HSCT				Auto-HSCT			
	Univariate		Multivariate		Univariate		Multivariate	
Variables	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Female vs male sex	0.82 (.59–1.14)	.24			0.78 (.43–1.41)	.40		
Age (increased by 10 y)	1.15 (1.06–1.25)	.001	1.10 (1.01–1.20)	.03	0.99 (.83–1.18)	.90		
Underlying disease for allo-HSCT,					NA			
Acute leukemia	1.00							
No acute leukemia	0.81 (.59–1.12)	.21	0.42 (.28–.63)	<.001				
Underlying disease for auto-HSCT	NA							
Multiple myeloma					1.00			
Lymphoma					5.1 (2.44–10.7)	<.001	6.17 (2.78–13.6)	<.001
Acute leukemia					3.01 (.65–13.94)	.16		
Other diseases					4.1 (1.38–12.3)	.01	4.77 (1.24–18.3)	.02
Complete remission of underlying disease at transplant, no vs yes	1.82 (1.32–2.51)	<.001	2.16 (1.47–3.15)	<.001	3.55 (1.7–7.6)	.001	4.8 (2.19–10.34)	<.001
Prior auto-HSCT, yes vs no	1.43 (.10–2.06)	.051	1.76 (1.18–2.63)	<.001	0.86 (.41–1.77)	.68		
Prior allo-HSCT, yes vs no	1.60 (1.01–2.54)	.04			NA			
Pretransplant neutropenia, yes vs no	1.34 (.93–1.94)	.12			5.2 (2.6–10.5)	<.001	3.82 (1.80–8.12)	<.001
Pretransplant rituximab, yes vs no	NA				2.9 (1.7–5.2)	<.001		
Stem cell source					NA			
Bone marrow vs Peripheral	1.10 (.79–1.53)	.55						
Cord blood vs peripheral	1.93 (.89–4.19)	.09						
Donor type					NA			
Mismatched related vs matched related	1.93 (1.25–2.97)	.003						
Matched unrelated volunteer vs matched related	1.19 (.73–1.93)	.48						
Mismatched unrelated volunteer vs matched related donor	1.11 (.60–2.03)	.74						
Cord blood vs matched related	2.51 (1.10–5.71)	.03						
Nonmyeloablative/reduced intensity vs myeloablative conditioning	1.55 (1.11–2.16)	.01			NA			
T-cell depletion					NA			
In vivo ATG vs no T-cell depletion	1.04 (.74–1.46)	.82						
Ex vivo manipulation vs no T-cell depletion	1.0 (.26–1.79)	.99						
Antibacterial prophylaxis, yes vs no	0.76 (.49–1.17)	.21			1.31 (.52–3.31)	.57		
Mucositis, CTC grade II–IV vs CTC grade 0–I	0.94 (.68–1.31)	.73			1.36 (.76–2.44)	.30		
Duration of pre-engraftment neutropenia								
PML count <500/μL	1.02 (1.01–1.04)	<.001			1.09 (1.06–1.12)	<.001		
PML count <100/μL	1.03 (1.02–1.04)	<.001	1.03 (1.01–1.04)	<.001	1.09 (1.07–1.12)	<.001	1.07 (1.04–1.18)	<.001
Acute GVHD, grade II–IV vs grade 0–I	2.07 (1.17–3.65)	.01	2.15 (1.21–3.82)	.009	…			
Gram-negative bacterial infection, yes vs no	2.99 (2.08–4.31)	<.001	2.13 (1.45–3.13)	<.001	3.16 (1.61–6.19)	<.001	2.43 (1.22–4.84)	.01

Abbreviations: Allo-HSCT, allogeneic hematopoietic stem cell transplantation; ATG, antithymocyte globulin; auto-HSCT, autologous HSCT; CI, confidence interval; CTC, common toxicity criteria; GVHD, graft-vs-host disease; HR, hazard ratio; NA, not applicable; PML, polymorphonuclear leukocyte.

most common isolates in both transplant procedures. In auto-HSCT, the rates of ceph-NS and carba-NS isolates in *E. coli* and *K. pneumoniae* and the MDR rate in *P. aeruginosa* were similar to those reported in the general Italian hospitalized population [14]. Conversely, in allo-HSCT recipients the rates of resistance were significantly higher; ceph-NS isolates accounted for about 40% of *E. coli* and 78% of *K. pneumoniae* isolates and carba-NS isolates for 57% of *K. pneumoniae*, and MDR was detected in about 38% of *P. aeruginosa* isolates. The hospitalizations and exposition to multiple antibiotics courses during the pretransplant period presumably justify the greater selection of microorganisms with reduced susceptibility phenotypes in allo-HSCT.

We found that diagnosis of acute leukemia, a transplant from an HLA-mismatched donor (related or unrelated) and cord blood, older recipient age, and prolonged neutropenia were independent risk factors of for-engraftment GNB in allo-HSCT. Conversely, ex

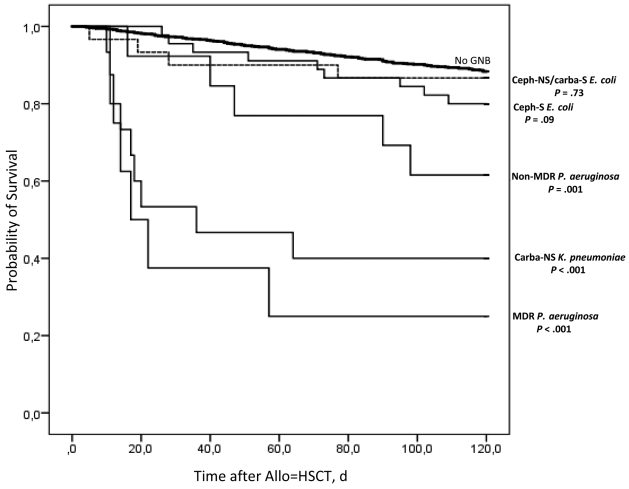

Figure 4. Probability of survival 4 months after allogeneic hematopoietic stem cell transplantation (allo-HSCT) according to the development of pre-engraftment gram-negative bacteremia caused by different species. (The probability of survival was not calculated for other pathogens, for which the number of episodes was very low.) Abbreviations: Carba-NS, nonsensitive to carbapenems; carba-S, sensitive to carbapenems; ceph-NS, nonsensitive to the third-generation cephalosporin ceftazidime; ceph-S, sensitive to ceftazidime; *E. coli*, *Escherichia coli*; *K. pneumoniae*, *Klebsiella pneumoniae*; MDR, multidrug-resistant; *P. aeruginosa*, *Pseudomonas aeruginosa*.

vivo T-cell depletion was protective, presumably related to the earlier engraftment and lower rate of early posttransplant complications (ie, GVHD), which characterize certain graft manipulations [26]. In the setting of auto-HSCT, a diagnosis of lymphoma, older age, and no antibacterial prophylaxis were predictive of GNB.

It is of interest that fluoroquinolone prophylaxis had different effects in the 2 transplant populations; it halved the rate of GNB after auto-HSCT but had no impact in allo-HSCT. Whether antibacterial prophylaxis is still indicated in neutropenic patients in an era of antibiotic resistance is a debated issue, and some centers no longer administer it given the high rate of fluoroquinolone resistance and the possible negative impact of prophylaxis in the selection of resistant intestinal flora [27–29]. Our data suggest that in high-risk patients with a history of antimicrobial pressure, like those undergoing allo-HSCT, fluoroquinolone prophylaxis is no longer protective, at least against GNB. However, low-risk patients not receiving antibiotic treatment—for example, patients with multiple myeloma who receive auto-HSCT immediately after nonintensive remission induction therapy—still seem to benefit from selective intestinal decontamination with fluoroquinolones during neutropenia. Our data are in agreement with those reported earlier in neutropenic patients with multiple myeloma undergoing auto-HSCT [30].

Pretransplant infection in allo-HSCT and colonization by resistant gram-negative bacteria in both allo- and auto-HSCT were highly predictive of a pre-engraftment infection by a pathogen with the same susceptibility phenotype [6]. Absent molecular characterization of the isolates, we could not demonstrate whether the same pathogen was responsible for both the pretransplant infection or colonization and the posttransplant GNB; however, this correlation seems highly reliable in the majority of cases. Indeed, the high rate of early infection relapses observed in allo-HSCT recipients with a pretransplant infection by a resistant pathogen may suggest the failure of previous antibiotic treatment to eradicate the infection, particularly by carba-NS pathogens. The predictive role of pretransplant infection and colonization in certain MDR infections may have relevance in the definition of the infection-control strategies and the selection of patients or conditions deserving tailored front-line treatments with old and new antibiotics [5, 8, 9, 31, 32].

Overall, the mortality rate 4 months after transplant was 13.7% for allo-HSCT and 3% for auto-HSCT. In addition to the well-known factors predicting poor outcome (in allo-HSCT: acute leukemia, previous auto-HSCT, disease not in complete remission at the time of transplant, older recipient age, prolonged pre-engraftment neutropenia, acute GVHD; in auto-HSCT: a lymphoma diagnosis, prolonged neutropenia during the month before transplant, disease not in complete remission at the time of transplant, and prolonged pre-engraftment neutropenia), GNB represented an independent prognostic factor in both populations and GNB was the cause of death in 39.1% of allo-HSCT recipients and 36.4% of auto-HSCT recipients who died before engraftment. The poor prognostic impact of GNB was related mainly to infections by carba-NS enterobacteria and by *P. aeruginosa*, regardless of the susceptibility pattern, whereas the outcome in patients infected by carba-S enterobacteria did not differ significantly from that in patients who did not experience any GNB [33]. This finding further underlines the importance of early tailored treatment strategies in patients at risk of infections by MDR pathogens [5, 6, 8, 9].

In conclusion, our study identifies incidence and risk factors for pre-engraftment GNB in a real-life HSCT scenario. It confirms that the phenomenon of antimicrobial resistance is relevant, particularly in allo-HSCT recipients, and dramatically affects overall outcome. Previous infectious history and colonization monitoring represent major indicators of the GNB risk. The results of the present study may be useful to identify HSCT subpopulations who might benefit from targeted antibiotic treatments, and they underline the crucial importance of continuous epidemiological monitoring in defining appropriate infection-control strategies.

Notes

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References

1. Blennow O, Ljungman P. The challenge of antibiotic resistance in haematology patients. Br J Haematol **2016**; 172:497–511.

2. Mikulska M, Del Bono V, Viscoli C. Bacterial infections in hematopoietic stem cell transplantation recipients. Curr Opin Hematol **2014**; 21:451–8.
3. Satlin MJ, Jenkins SG, Walsh TJ. The global challenge of carbapenem-resistant Enterobacteriaceae in transplant recipients and patients with hematologic malignancies. Clin Infect Dis **2014**; 58:1274–83.
4. Mikulska M, Viscoli C, Orasch C, et al; Fourth European Conference on Infections in Leukemia Group (ECIL-4), a joint venture of EBMT, EORTC, ICHS, ELN and ESGICH/ESCMID. Aetiology and resistance in bacteraemias among adult and paediatric haematology and cancer patients. J Infect **2014**; 68:321–31.
5. Girmenia C, Viscoli C, Piciocchi A, et al. Management of carbapenem resistant *Klebsiella pneumoniae* infections in stem cell transplant recipients: an Italian multidisciplinary consensus statement. Haematologica **2015**; 100:e373–6.
6. Girmenia C, Rossolini GM, Piciocchi A, et al; Gruppo Italiano Trapianto Midollo Osseo (GITMO); Gruppo Italiano Trapianto Midollo Osseo GITMO. Infections by carbapenem-resistant *Klebsiella pneumoniae* in SCT recipients: a nationwide retrospective survey from Italy. Bone Marrow Transplant **2015**; 50:282–8.
7. Trecarichi EM, Pagano L, Candoni A, et al; HeMABIS Registry–SEIFEM Group, Italy. Current epidemiology and antimicrobial resistance data for bacterial bloodstream infections in patients with hematologic malignancies: an Italian multicentre prospective survey. Clin Microbiol Infect **2015**; 21:337–43.
8. Averbuch D, Orasch C, Cordonnier C, et al. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia. Haematologica **2013**; 98:1826–35.
9. Averbuch D, Cordonnier C, Livermore DM, et al. Targeted therapy against multi-resistant bacteria in leukemic and hematopoietic stem cell transplant recipients: guidelines of the 4th European Conference on Infections in Leukemia (ECIL-4, 2011). Haematologica **2013**; 98:1836–47.
10. Stoma I, Karpov I, Milanovich N, Uss A, Iskrov I. Risk factors for mortality in patients with bloodstream infections during the pre-engraftment period after hematopoietic stem cell transplantation. Blood Res **2016**; 51:102–6.
11. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol **2008**; 61:344–9.
12. Vasoo S, Barreto JN, Tosh PK. Emerging issues in gram-negative bacterial resistance: an update for the practicing clinician. Mayo Clin Proc **2015**; 90:395–403.
13. Munoz-Price LS, Poirel L, Bonomo RA, et al. Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases. Lancet Infect Dis **2013**; 13:785–96.
14. Antimicrobial resistance surveillance in Europe 2015. Available at: http://ecdc.europa.eu/en/publications/_layouts/forms/Publication_DispForm.aspx?List=-4f55ad51-4aed-4d32-b960-af70113dbb90&ID=1637#sthash.G7ybpEOr.dpuf. Accessed 30 January 2017.
15. Cattaneo C, Zappasodi P, Mancini V, et al. Emerging resistant bacteria strains in bloodstream infections of acute leukaemia patients: results of a prospective study by the Rete Ematologica Lombarda (REL). Ann Hematol **2016**; 95:1955–63.
16. Mikulska M, Del Bono V, Raiola AM, et al. Blood stream infections in allogeneic hematopoietic stem cell transplant recipients: reemergence of gram-negative rods and increasing antibiotic resistance. Biol Blood Marrow Transplant **2009**; 15:47–53.
17. Busca A, Cavecchia I, Locatelli F, et al. Blood stream infections after allogeneic stem cell transplantation: a single-center experience with the use of levofloxacin prophylaxis. Transpl Infect Dis **2012**; 14:40–8.
18. Blennow O, Ljungman P, Sparrelid E, Mattsson J, Remberger M. Incidence, risk factors, and outcome of bloodstream infections during the pre-engraftment phase in 521 allogeneic hematopoietic stem cell transplantations. Transpl Infect Dis **2014**; 16:106–14.
19. Macesic N, Morrissey CO, Cheng AC, Spencer A, Peleg AY. Changing microbial epidemiology in hematopoietic stem cell transplant recipients: increasing resistance over a 9-year period. Transpl Infect Dis **2014**; 16:887–96.
20. Wang L, Wang Y, Fan X, Tang W, Hu J. Prevalence of resistant gram-negative bacilli in bloodstream infection in febrile neutropenia patients undergoing hematopoietic stem cell transplantation: a single center retrospective cohort study. Medicine (Baltimore) **2015**; 94:e1931.
21. Patriarca F, Cigana C, Massimo D, et al. Risk factors and outcomes of infections by multidrug-resistant gram-negative bacteria in patients undergoing hematopoietic stem cell transplantation. Biol Blood Marrow Transplant **2017**; 23:333–9.
22. Zając-Spychała O, Wachowiak J, Pieczonka A, et al. Bacterial infections in pediatric hematopoietic stem cell transplantation recipients: incidence, epidemiology, and spectrum of pathogens: report of the Polish Pediatric Group for Hematopoietic Stem Cell Transplantation. Transpl Infect Dis **2016**; 18:690–8.
23. Wang CH, Chang FY, Chao TY, et al. Characteristics comparisons of bacteremia in allogeneic and autologous hematopoietic stem cell-transplant recipients with levofloxacin prophylaxis and influence on resistant bacteria emergence. J Microbiol Immunol Infect **2016**. pii:S1684-1182(16)30003-2.
24. Stoma I, Karpov I, Milanovich N, Uss A, Iskrov I. Risk factors for mortality in patients with bloodstream infections during the pre-engraftment period after hematopoietic stem cell transplantation. Blood Res **2016**; 51:102–6.
25. Forcina A, Baldan R, Marasco V, et al. Control of infectious mortality due to carbapenemase-producing *Klebsiella pneumoniae* in hematopoietic stem cell transplantation. Bone Marrow Transplant **2017**; 52:114–9.
26. Aversa F, Prezioso L, Manfra I, Galaverna F, Spolzino A, Monti A. Immunity to infections after haploidentical hematopoietic stem cell transplantation. Mediterr J Hematol Infect Dis **2016**; 8:e2016057.
27. Gafter-Gvili A, Fraser A, Paul M, et al. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. Cochrane Database Syst Rev **2012**; 1:CD004386.
28. Bow EJ. Fluoroquinolones, antimicrobial resistance and neutropenic cancer patients. Curr Opin Infect Dis **2011**; 24:545–53.
29. Kimura S, Akahoshi Y, Nakano H, et al. Antibiotic prophylaxis in hematopoietic stem cell transplantation. A meta-analysis of randomized controlled trials. J Infect **2014**; 69:13–25.
30. Satlin MJ, Vardhana S, Soave R, et al. Impact of prophylactic levofloxacin on rates of bloodstream infection and fever in neutropenic patients with multiple myeloma undergoing autologous hematopoietic stem cell transplantation. Biol Blood Marrow Transplant **2015**; 21:1808–14.
31. Tamma PD, Rodriguez-Bano J. The use of noncarbapenem β-lactams for the treatment of extended-spectrum β-lactamase infections. Clin Infect Dis **2017**; 64:972–80.
32. Gentile I, Maraolo AE, Borgia G. What is the role of the new β-lactam/β-lactamase inhibitors ceftolozane/tazobactam and ceftazidime/avibactam? Expert Rev Anti Infect Ther **2016**; 14:875–8.
33. Mikulska M, Del Bono V, Bruzzi P, et al. Mortality after bloodstream infections in allogeneic haematopoietic stem cell transplant (HSCT) recipients. Infection **2012**; 40:271–8.

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