Journal of Infection 81 (2020) 882–894

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Intercontinental study on pre-engraftment and post-engraftment Gram-negative rods bacteremia in hematopoietic stem cell transplantation patients: Risk factors and association with mortality

Diana Averbuch[a,*], Gloria Tridello[b], Jennifer Hoek[c], Malgorzata Mikulska[d], Thomas Pabst[e], Lucrecia Yañez San Segundo[f], Hamdi Akan[g], Tülay Özçelik[h], Irene Donnini[i], Galina Klyasova[j], Aida Botelho de Sousa[k], Tsila Zuckerman[l], Cristina Tecchio[m], Rafael de la Camara[n], Sahika Zeynep Aki[o], Per Ljungman[p], Zafer Gülbas[q], Emmanuelle Nicolas-Virelizier[r], Elisabetta Calore[s], Katia Perruccio[t], Ron Ram[u], Claudio Annaloro[v], Rodrigo Martino[w], Batia Avni[a], Peter J. Shaw[x], Alexandra Jungova[y], Katia Codeluppi[z], Tracey O'Brien[β], Anna Waszczuk-Gajda[γ], Montserrat Batlle[δ], Anastasia Pouli[ε], Catherina Lueck[λ], Lidia Gil[θ], Simona Iacobelli[μ], Jan Styczynski[π], Dan Engelhard[a,1], Simone Cesaro[b,1]

[a] Hadassah University Hospital, Jerusalem, Israel
[b] Pediatric Hematology Oncology, Mother and Child Hospital, Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy
[c] EBMT Data Office, Leiden, the Netherlands
[d] Division of Infectious Diseases, University of Genoa and Ospedale Policlinico San Martino, Genova, Italy
[e] Department of Medical Oncology, University Hospital Bern, Bern, Switzerland
[f] Hospital U. Marqués de Valdecilla, Santander, Spain
[g] Ankara University Faculty of Medicine, Ankara, Turkey
[h] Bilim University, Florence Nightingale Hospital, Istanbul, Turkey
[i] Azienda Ospedaliera Universitaria Careggi, Firenze, Italy
[j] National Research Center for Hematology, Moscow, Russian Federation
[k] Hospital dos Capuchos, Lisboa, Portugal
[l] Rambam Medical Center, Haifa, Israel
[m] Department of Medicine, Hematology and Bone Marrow Transplant Unit, University of Verona, Verona, Italy
[n] Hospital de la Princesa, Madrid, Spain
[o] Gazi University Faculty of Medicine, Ankara, Turkey
[p] Karolinska University Hospital, Stockholm, Sweden
[q] Anadolu Medical Center Hospital, Kocaeli, Turkey
[r] Centre Leon Berard, Lyon, France
[s] Clinica di Oncoematologia Pediatrica, Padova, Italy
[t] Ospedale Santa Maria della Misericordia, Università di Perugia, Perugia, Italy
[u] Tel Aviv Sourasky Medical Center, Sourasky Medical School, Tel Aviv University, Tel Aviv, Israel
[v] Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano, Italy
[w] Hospital Santa Creu I Sant Pau, Barcelona, Spain
[x] The Children's Hospital at Westmead, Sydney, Australia
[y] Charles University Hospital, Pilsen, Czech Republic
[z] Hematology, Azienda Unità Sanitaria Locale –IRCCS di Reggio Emilia, Italy
[β] Sydney Children's Hospital, Randwick Sydney, Australia

* Correspondence to: Pediatric Infectious Diseases, Hadassah-Hebrew University Medical Center, Jerusalem, Israel.

E-mail addresses: dina8282@walla.co.il, adiana@hadassah.org.il (D. Averbuch), gloria.tridello@aovr.veneto.it (G. Tridello), idwp.ebmt@lumc.nl (J. Hoek), m.mikulska@unige.it (M. Mikulska), thomas.pabst@insel.ch (T. Pabst), lucrecia@humv.es (L. Yañez San Segundo), hamdiakan@gmail.com (H. Akan), tulay.ozcelik@hotmail.com (T. Özçelik), irdonni@tin.it (I. Donnini), klyasova.g@blood.ru (G. Klyasova), aida.botelho@chlc.min-saude.pt (A. Botelho de Sousa), t_zuckerman@rambam.health.gov.il (T. Zuckerman), cristina.tecchio@univr.it (C. Tecchio), jrcamara@telefonica.net (R. de la Camara), sahikazeynep@gmail.com (S.Z. Aki), per.ljungman@ki.se (P. Ljungman), zafer.gulbas@anadolusaglik.org (Z. Gülbas), emmanuelle.nicolas@lyon.unicancer.fr (E. Nicolas-Virelizier), elisabetta.calore@unipd.it (E. Calore), katia.perruccio@ospedale.perugia.it (K. Perruccio), ronr@tlvmc.gov.il (R. Ram), cannaloro@gmail.com (C. Annaloro), rmartino@santpau.cat (R. Martino), batiaa@hadassah.org.il (B. Avni), peter.shaw@health.nsw.gov.au (P.J. Shaw), jungovaa@fnplzen.cz (A. Jungova), codeluppi.katia@asmn.re.it (K. Codeluppi), t.obrien@unsw.edu.au (T. O'Brien), annawaszczukgajda@gmail.com (A. Waszczuk-Gajda), mbatle@iconcologia.net (M. Batlle), a.pouli@hotmail.gr (A. Pouli), Lueck.Catherina@mh-hannover.de (C. Lueck), lidia.gil@skpp.edu.pl (L. Gil), simona.iacobelli@ebmt.org (S. Iacobelli), jstyczynski@cm.umk.pl (J. Styczynski), engelhard@hadassah.org.il (D. Engelhard), simone.cesaro@aovr.veneto.it (S. Cesaro).

[1] Contributed equally to this manuscript.

https://doi.org/10.1016/j.jinf.2020.11.002

[γ] The Medical University of Warsaw, Warsaw, Poland
[δ] ICO-Hospital Universitari Germans Trias I Pujol, Badalona, Spain
[ε] St. Savvas Oncology Hospital, Athens, Greece
[λ] Hannover Medical School, Hannover, Germany
[θ] University of Medical Sciences, Poznan, Poland
[μ] Tor Vergata University, Rome, Italy
[π] Collegium Medicum, Nicolaus Copernicus University Torun, Bydgoszcz, Poland

ARTICLE INFO

Article history:
Accepted 5 November 2020
Available online 10 November 2020

Keywords:
Bacteremia
Stem cell transplantation
Risk factors
Gram-negative
Mortality
Fluoroquinolone prophylaxis
Pre-engraftment
Post-engraftment

SUMMARY

Objectives: We present here data on Gram-negative rods bacteremia (GNRB) rates, risk factors and associated mortality.
Methods: Data on GNRB episodes were prospectively collected in 65 allo-/67 auto-HSCT centers in 24 countries (Europe, Asia, Australia). In patients with and without GNRB, we compared: demography, underlying disease, HSCT-related data, center' fluoroquinolone prophylaxis (FQP) policy and accreditation status, and involvement of infection control team (ICT).
Results: The GNRB cumulative incidence among 2818 allo-HSCT was: pre-engraftment (pre-eng-allo-HSCT), 8.4 (95% CI 7–9%), post-engraftment (post-eng-allo-HSCT), 5.8% (95%CI: 5–7%); among 3152 auto-HSCT, pre-eng-auto-HSCT, 6.6% (95%CI: 6–7%), post-eng-auto-HSCT, 0.7% (95%CI: 0.4–1.1%). GNRB, especially MDR, was associated with increased mortality.
Multivariate analysis revealed the following GNRB risk factors:
(a) pre-eng-allo-HSCT: south-eastern Europe center location, underlying diseases not at complete remission, and cord blood source;
(b) post-eng-allo-HSCT: center location not in northwestern Europe; underlying non-malignant disease, not providing FQP and never accredited.
(c) pre-eng-auto-HSCT: older age, autoimmune and malignant (vs. plasma cell) disease, and ICT absence.
Conclusions: Benefit of FQP should be explored in prospective studies. Increased GNRB risk in auto-HSCT patients transplanted for autoimmune diseases is worrying. Infection control and being accredited are possibly protective against bacteremia. GNRB are associated with increased mortality.

Introduction

Bacteremia develops in 11–65% of allogeneic[1–4] and 7–20% autologous hematopoietic stem cell transplantation (HSCT) patients,[5,6] it is reportedly associated with adverse outcomes, including prolonged hospitalization, engraftment delay, increased graft-versus-host disease (GVHD) risk and mortality.[7–9] Between 15 and 74% of bacteremia episodes are due to Gram-negative rods (GNR),[10] and their incidence and proportion is increasing in some centers and countries,[11,12] with GNR bacteremia (GNRB) an independent predictor of post-HSCT mortality in several studies.[2,7,13] The GNRB rate varies between centers, influenced by patients' age, underlying disease, transplant-related factors, fluoroquinolone prophylaxis policy, infection control measures and more. Several studies (mainly single-center retrospectives) focus on assessing GNRB risk factors in allo-HSCT patients during the past decade.[2,14] We have previously prospectively analyzed rates and risk factors for GNRs' antimicrobial resistance in HSCT patients in a large intercontinental cohort of the European Bone Marrow Transplantation society (EBMT) transplant centers.[15] In the present study, we examined rates and risk factors for GNRB during the pre- and post-engraftment periods in allogeneic and autologous HSCT recipients within the same cohort.

Materials and methods

Study design and data collection

A questionnaire was distributed among the EBMT centers asking about their willingness to participate in this study. Participating centers were requested to provide information regarding their general policy, including routine fluoroquinolone prophylaxis (FQP) in HSCT patients and active involvement of the infection control team (ICT) in their department during the study period.

Patients in whom allogeneic or autologous HSCT was performed during February 2014-May 2015 in the participating centers were prospectively followed. Their background demographic and HSCT-related data were obtained using the EBMT database (ProMise). Data on GNRB episodes that occurred from the beginning of conditioning regimen until six months after HSCT were reported using special case reporting form, including pathogen and presence of certain factors at the time of bacteremia, such as neutropenia duration and GVHD.[15]

The primary endpoint was to determine the GNRB incidence and risk factors before and after engraftment either in allo-HSCT or in auto-HSCT patients.

This study was performed in accordance with the appropriate regulations in the participating countries including approval by the ethical committees as required; and registered at Clinicaltrials.gov: NTC02257931.

Definitions

Myeloablative and non-myeloablative conditioning and engraftment were defined according to the EBMT guidelines.[16] Geographic regions included[15]:

1) North-western Europe: Austria, Belgium, Denmark, Finland, France, Germany, Netherlands, Sweden, Switzerland, UK;
2) South-eastern Europe: Croatia, Cyprus, Czech Republic, Greece, Israel, Italy, Lithuania, Poland, Portugal, Russia, Slovakia, Spain, Turkey;
3) Other countries: Australia, China.

Centers that had obtained accreditation by the Joint Accreditation Committee International Society Cell Therapy (ISCT-Europe) and EBMT (JACIE) or The Foundation for the Accreditation of Cellular Therapy (FACT) at or before the study period were defined as JACIE/FACT accredited.

Multidrug-resistant (MDR) GNR was defined as bacteria resistant to ≥1 agent in ≥3 of the following categories: a) broad-spectrum cephalosporin (ceftazidime or cefepime); b) anti-*Pseudomonas* beta-lactam beta-lactamase inhibitor; c) carbapenems; d) aminoglycosides; e) fluoroquinolones. All *Stenotrophomonas maltophilia* strains were considered MDR.[15]

Statistical analysis

The main characteristics of patients were reported by descriptive statistics on the total of the available information. The cumulative incidence of bacteremia was calculated by the cumulative incidence method, considering the relapse, secondary malignancy, death and a subsequent transplant as competing events. Due to the limited sample size in some countries, it was not possible to estimate the cumulative incidence of bacteremia per country. To report results per country homogenously way, the rates were reported. For incidence and risk factors analysis of pre-engraftment GNRB bacteremia, the period since conditioning onset and during the pre-engraftment neutropenia was taken into account; engraftment was considered as a competing event. For post-engraftment GNRB bacteremia analysis, the period since documented neutrophil engraftment and during six months after HSCT was considered; relapse of the underlying disease was considered as a competing event. For risk factors analysis of total GNRB, the period since conditioning onset and during six months after HSCT was considered; relapse of the underlying disease was considered as a competing event.

The following baseline parameters were compared in patients who developed vs. those who did not develop at least one GNRB: demography, underlying disease, Karnofsky/Lansky score, HSCT type and conditioning, CMV donor and recipient status, center FQP policy and ICT involvement. Based on center‘ responses to the pre-study questionnaire, we divided patients to those who were transplanted in centers that provide or not provide FQP routinely; and in centers where ICT was or was not routinely involved in the department during the study period. Data on FQP and ICT involvement in each patient is not available in the EBMT registry. In the analysis of the post-engraftment bacteremia, we included two additional factors: whether engraftment occurred within two weeks after HSCT or later; and the presence of the pre-engraftment GNRB.

Differences between groups were tested using linear or logistic regression models, using the generalized estimating equation methods to take into account the dependence of observations nested by patient and center.[17] Variables that were found significant in the univariate model were included in the multivariate analysis. Pre- and post-engraftment bacteremia were analyzed separately.

For a subgroup of patients, with the date of GVHD available, the impact of GVHD on the post-engraftment bacteremia was assessed, as a time-dependent covariate, by the Cox model. We performed a separate subanalysis of risk factors for the MDR and non-MDR GNRB. The results obtained from these analyses are considered as exploratory and hypothesis-generating.

The impact of pre- and post-engraftment bacteremia on mortality was assessed by using the cause-specific Cox regression model. Mortality before and after engraftment was analyzed separately, considering the engraftment as a competing event for the pre-engraftment period; and the cause-specific hazard ratios were estimated. The models have been adjusted by the main confounders taken into account.

A p-value <0.05 was considered statistically significant. All p-values are two-sided. All the analyses were performed using the statistical software SAS v. 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Allogeneic HSCT

Participating centers and bacteremia rates

Sixty-five centers from 24 countries performed allo-HSCT; of them, 38 centers performed it in adults, 17 in children and 10 centers in both. Three centers from two middle-outcome countries participated in our study; others were from high-outcome countries. Three centers from middle-outcome countries; and 23/62 allo-HSCT centers from high-outcome countries were never JACIE/FACT accredited. Among centers where involvement of ICT was reported, it was involved in 45/62 allo-HSCT centers in high-outcome countries; and in all three centers in middle-outcome countries.

1965/2258 (87.0%) of patients were transplanted in centers providing FQP; 2229/2509 (88.8%) of patients were transplanted in centers with ICT operating. Among 2040 patients transplanted in 35 centers where information on both FQP policy and ICT involvement was available, 1714 (84%) were from 28 centers where ICT operated and FQP was provided; and 7.9% - in two centers where ICT was not involved and FQP was not provided.

Background information on 2818 allo-HSCTs performed during the study period is presented in Table 1. The incidence of GNRB was 13.7% (95% CI 12.2–15.2) for adults and 14.2% (95% CI 11.4–17.3) for children; rates per country are presented in Supplementary Table 1. The incidence was 5.3 (95% CI 3.8–7.1) in the north-western vs. 17.6% (95% CI 15.8–19.5) in south-eastern Europe and 16.8% (95% CI 10.0–25.2) in the other countries.

The cumulative incidence of pre-engraftment GNRB was 8.4% (95% CI 7–9%) and post- engraftment GNRB 5.8% (95% CI: 5–7%).

Microbiological results

A total of 392 GNRs were isolated, including 277 (70.7%) *Enterobacteriaceae*; 107 (27.3%) non-fermentative GNRs and 8 (2.0%) other GNRs.

The cumulative incidence of *Enterobacteriaceae* bacteremia in allo-HSCT patients was 9.6% (95% CI: 8.5–10.9) and of non-fermentative rods was 3.6% (95% CI: 2.9–4.4).

Distribution of pathogens in the pre- and post-engraftment period in allogeneic HSCT is presented in Supplementary Table 2. The median time to GNRB was 18 (range 3–191) days since conditioning, it was 17 (range 5–188) days for monomicrobial *Enterobacteriaceae* and 26 (range 3–191) days for monomicrobial non-fermentative rods (p=0.003). The incidence of episodes in allogeneic transplants is presented in Supplementary Fig. 1.

Risk factors for Gram-negative bacteremia (Table 1)

Pre-engraftment bacteremia

In the univariate analysis, south-eastern Europe center location, underlying diseases not at complete remission at the time of HSCT, mismatched donor, CMV-seropositive recipient status, cord blood stem cell source, lower Karnofsky/Lansky score, HSCT in center providing FQP, and GVHD prophylaxis including steroids, were associated with increased risk of GNRB.

In the multivariate analysis, south-eastern Europe center location, underlying diseases not at complete remission at the time of HSCT, and cord blood source were associated with increased GNRB risk. We assessed an association between the pre-engraftment bacteremia and the duration of pre-engraftment neutropenia. The rate of pre-engraftment bacteremia was 5.6% when neutropenia lasted

Table 1
Background characteristics and factors associated with Gram-negative rods bacteremia (GNRB) in allogeneic-HSCT (total, pre- and post-engraftment).

	All HSCTs n=2818 (%)	Pre-engraftment GNRB					Post-engraftment					Total GNRB				
		Number with bacteremia	Univariate		Multivariate		Number with bacteremia	Univariate		Multivariate		Number with bacteremia	Univariate		Multivariate	
		236	HR (95% C.I.)	p	HR (95% C.I.)	p	129	HR (95% C.I.)	p	HR (95% C.I.)	p	365	HR (95% C.I.)	p	HR (95% C.I.)	p
Center location																
Northwest	753 (26.7)	25	1.00	<0.0001*	1.00	<0.0001*	14	1.00	<0.0001*		0.002*	39	1.00	<0.0001*	1.00	<0.0001*
Southeast	1755 (62.3)	198	3.50 (2.24–5.46)	<0.0001	3.85 (2.26–6.57)	<0.0001	101	3.48 (1.90–6.39)	<0.0001	5.90 (2.05–16.98)	0.001	299	3.57 (2.48–5.15)	<0.0001	4.28 (2.82–6.50)	<0.0001
Other	310 (11.0)	13	1.38 (0.70–2.75)	0.36	1.77 (0.23–13.62)	0.58	14	7.48 (3.26–17.17)	<0.0001	11.34 (2.71–47.48)	0.001	27	2.42 (1.42–4.13)	0.001	3.00 (1.31–6.86)	0.009
Sex					NS					NS					NS	
Male	1705 (60.5)	133	1.00				84	1.00				217	1.00			
Female	1113 (39.5)	103	1.20 (0.92–1.58)	0.18			45	0.83 (0.54–1.29)	0.41			148	1.06 (0.84–1.33)	0.65		
Age at HSCT (years)	Median 41.5 (range 0.1–74.9)				NS					NS					NS	
10-year increase			1.04 (0.98–1.11)	0.21				0.93 (0.85–1.03)	0.18				1.00 (0.94–1.05)	0.91		
Underlying disease					NS										NS	
Acute leukemia	1582 (56.1)	142	1.00	0.31*			68	1.00	0.022*	1.00	0.03*	210	1.00	0.07*		
Other malignancies	956 (33.9)	70	0.79 (0.59–1.07)	0.13			37	0.87 (0.56–1.35)	0.55	1.37 (0.80–2.36)	0.25	107	0.82 (0.64–1.06)	0.12		
Nonmalignant disease	280 (9.9)	24	0.88 (0.55–1.42)	0.60			24	2.10 (1.14–3.88)	0.018	2.95 (1.30–6.72)	0.01	48	1.29 (0.88–1.89)	0.19		
Missing data	0	0					0					0				
Status of the disease at transplant										NS					NS	
Complete remission	1553 (64.1)	109	1.00		1.00		74	1.00				183	1.00			
Other status	868 (35.9)	94	1.52 (1.14–2.03)	0.0045	1.48 (1.02–2.13)	0.037	28	0.71 (0.45–1.12)	0.14			122	1.23 (0.96–1.58)	0.098		
Missing data	397	33					27					60				
Donor type					NS					NS					NS	
Matched relative	886 (31.5)	55	1.00	0.017*			46	1.00	0.65*			101	1.00	0.074*		
Matched unrelated	1410 (50.1)	121	1.37 (0.99–1.91)	0.06			63	0.81 (0.52–1.27)	0.35			184	1.13 (0.86–1.48)	0.39		
Mismatched	519 (18.4)	59	1.74 (1.19-2.54)	0.004			20	0.90 (0.47–1.71)	0.74			79	1.45 (1.05–2.01)	0.02		
Missing data	3	1					0					1				
Donor sex					NS					NS					NS	
Male	1649 (59.4)	131	1.00				83	1.00				214	1.00			
Female	1126 (40.6)	97	1.11 (0.84–1.46)	0.46			45	0.80 (0.53–1.20)	0.28			142	0.99 (0.78–1.25)	0.90		
Missing data	43	8					1					9				
CMV serology in patient and donor					NS					NS					NS	

(*continued on next page*)

Table 1 (*continued*)

	All HSCTs n=2818 (%)	Pre-engraftment GNRB					Post-engraftment					Total GNRB				
		Number with bacteremia	Univariate		Multivariate		Number with bacteremia	Univariate		Multivariate		Number with bacteremia	Univariate		Multivariate	
		236	HR (95% C.I.)	*p*	HR (95% C.I.)	*p*	129	HR (95% C.I.)	*p*	HR (95% C.I.)	*p*	365	HR (95% C.I.)	*p*	HR (95% C.I.)	*p*
-/-	665 (26.2)	33	1.00	0.018*			27	1.00	0.93*			60	1.00	0.14*		
-/+	215 (8.5)	16	1.48 (0.80–2.75)	0.21			9	0.76 (0.29–1.99)	0.57			25	1.15 (0.67–1.97)	0.62		
+/-	563 (22.2)	54	1.90 (1.20–3.00)	0.0061			26	0.84 (0.44–1.63)	0.61			80	1.43 (0.98–2.08)	0.066		
+/+	1095 (43.1)	107	1.89 (1.25–2.84)	0.0025			51	0.88 (0.50–1.54)	0.66			158	1.46 (1.04–2.04)	0.027		
Missing data	280	26					16					42				
Stem cell source										NS						
Bone marrow+/-Peripheral blood	866 (30.7)	82	1.00	0.01*	1.00	0.013*	36	1.00	0.74*			118	1.00	0.004*	1.00	0.001*
Peripheral blood	1792 (63.6)	129	0.84 (0.63–1.12)	0.22	0.72 (0.49–1.07)	0.10	85	1.04 (0.65–1.66)	0.88			214	0.84 (0.66–1.09)	0.18	0.90 (0.67–1.20)	0.46
Cord blood	160 (5.7)	25	1.68 (1.04–2.73)	0.034	2.25 (0.98–5.20)	0.057	8	1.41 (0.59–3.36)	0.44			33	1.66 (1.08–2.55)	0.02	2.51 (1.44–4.39)	0.001
Missing data	0	0					0					0				
HSCT number					NS					NS					NS	
First	2421 (86.0)	204	1.00				114	1.00				318	1.00			
Second or more	395 (14.0)	32	1.01 (0.69–1.47)	0.97			15	0.80 (0.45–1.42)	0.45			47	0.91 (0.66–1.25)	0.55		
Missing data	2	0					0					0				
Ex-vivo manipulation of the cells					NS					NS					NS	
None	2597 (93.7)	212	1.00				120	1.00				332	1.00			
Yes	175 (6.3)	20	1.52 (0.95–2.45)	0.08			8	0.97 (0.41–2.27)	0.94			28	1.28 (0.84–1.95)	0.25		
Missing data	46	4					1					5				
Total body irradiation given					NS					NS					NS	
No	2160 (77.6)	181	1.00				106	1.00				287	1.00			
Yes	623 (22.4)	53	1.03 (0.75–1.41)	0.87			23	0.67 (0.39–1.15)	0.15			76	0.88 (0.67–1.16)	0.38		
Missing data	35	2					0					2				
Karnofsky or Lansky status	Median 90 (range 0–100)				NS					NS						
10-point increase			0.82 (0.74–0.91)	0.0002				0.96 (0.67–1.36)	0.81				0.84 (0.76–0.94)	0.001	0.84 (0.75–0.94)	0.003
Missing data	420	23					19					42				
Center provides fluoroquinolone prophylaxis					NS										NS	
No	293 (13.0)	10	1.00				25	1.00		1.00		35	1.00			
Yes	1965 (87.0)	167	2.58 (1.29–5.13)	0.007			69	0.47 (0.26–0.83)	0.01	0.23 (0.10–0.51)	0.0004	236	1.11 (0.72–1.71)	0.64		

(*continued on next page*)

Table 1 (*continued*)

	All HSCTs n=2818 (%)	Pre-engraftment GNRB					Post-engraftment					Total GNRB				
		Number with bacteremia	Univariate		Multivariate		Number with bacteremia	Univariate		Multivariate		Number with bacteremia	Univariate		Multivariate	
		236	HR (95% C.I.)	*p*	HR (95% C.I.)	*p*	129	HR (95% C.I.)	*p*	HR (95% C.I.)	*p*	365	HR (95% C.I.)	*p*	HR (95% C.I.)	*p*
Missing data	560	59					35					94				
Infection control team					NS					NS					NS	
No	280 (11.2)	22	1.00				13	1.00				35	1.00			
Yes	2229 (88.8)	189	1.07 (0.69–1.65)	0.78			107	1.30 (0.66–2.58)	0.45			296	1.16 (0.78–1.74)	0.46		
Missing data	309	25					9					34				
Conditioning regimen					NS					NS					NS	
Total body irradiation myeloablative	439 (15.9)	39	1.00	0.84*			16	1.00	0.20*			55	1.00	0.36*		
Busulfan based myeloablative	1164 (42.1)	102	0.99 (0.68–1.45)	0.97			58	1.66 (0.82–3.36)	0.16			160	1.17 (0.83–1.64)	0.37		
Other myeloablative	288 (10.4)	21	0.82 (0.47–1.42)	0.48			7	0.78 (0.29–2.07)	0.62			28	0.81 (0.49–1.32)	0.40		
Non myeloablative	877 (31.7)	70	0.91 (0.61–1.35)	0.63			47	1.43 (0.70–2.93)	0.33			117	1.03 (0.73–1.47)	0.86		
Missing data	50	4					1					5				
Steroids given as GVHD prophylaxis					NS					NS					NS	
No	2621 (96.3)	211	1.00				117	1.00				328	1.00			
Yes	100 (3.7)	16	1.97 (1.14–3.40)	0.0145			8	1.82 (0.82–4.06)	0.14			24	1.94 (1.23–3.08)	0.005		

(*continued on next page*)

Table 1 (*continued*)

	All HSCTs n=2818 (%)	Pre-engraftment GNRB					Post-engraftment					Total GNRB				
		Number with bacteremia	Univariate		Multivariate		Number with bacteremia	Univariate		Multivariate		Number with bacteremia	Univariate		Multivariate	
		236	HR (95% C.I.)	p	HR (95% C.I.)	p	129	HR (95% C.I.)	p	HR (95% C.I.)	p	365	HR (95% C.I.)	p	HR (95% C.I.)	p
Missing data	97	9					4					13				
Graft-vs-host disease prophylaxis regimen					NS					NS					NS	
Cyclosporin A or Tacrolimus	1164 (42.8)	108	1.00	0.22*			62	1.00	0.34*			170	1.00	0.085*		
Cyclosporin A or Tacrolimus + methotrexate	1466 (53.9)	109	0.80 (0.61–1.06)	0.12			57	0.82 (0.53–1.26)	0.36			166	0.81 (0.64–1.03)	0.09		
Other	91 (3.3)	10	1.16 (0.60–2.25)	0.66			6	1.49 (0.65–3.43)	0.35			16	1.33 (0.77–2.28)	0.31		
Missing data	97	9					4					13				
Jacie/FACT accreditation 2016					NS										NS	
Accredited	1478 (52.5)	128	1.00				58	1.00		1.00		186	1.00			
Not accredited	1340 (47.6)	108	0.96 (0.74–1.26)	0.77			71	1.69 (1.12–2.56)	0.01	2.00 (1.12–3.55)	0.02	179	1.16 (0.92–1.47)	0.20		
Missing data	0	0					0					0				
Time to engraftment				Not relevant									not performed			
> 14 days	1734						71	1.00		NS						
≤ 14 days	900						51	1.66 (1.08–2.56)	0.02							
Missing data	184						7									
Pre-engraftment Gram-negative bacteremia				Not relevant						NS			not performed			
No	2557						118	1.00								
Yes	223						11	1.09 (0.52–2.26)	0.82							
Missing data	38						0									
Acute GVHD				Not relevant						NS			not performed			
No	1898							1.00								
Yes	237							3.96 (0.55–28.8)	0.17							
Missing data	683						55									

HSCT - hematopoietic stem cell transplantation; GVHD - graft versus host disease; NS – not significant
* overall comparison

Table 2
Factors associated with mortality in allogeneic HSCT (multivariate analysis).

Parameter	Number (%)	Pre-engraftment mortality		Post-engraftment mortality	
		HR (95% C.I.)	*P* value	HR (95% C.I.)	*P* value
Pre-engraftment GNR bacteremia					
No	2563 (93.1)	1.00		1.00	
Yes, MDR	88 (3.2)	1.97 (1.34–2.88)	0.0005	2.05 (1.21–3.48)	0.008
Yes, non-MDR	101 (3.7)	1.37 (0.93–2.04)	0.11	1.33 (0.74–2.38)	0.34
Missing data	45				
Post-engraftment GNR bacteremia			Not relevant		
No	2561 (96.1)			1.00	
Yes, MDR	45 (1.7)			7.48 (4.14–13.51)	<0.0001
Yes, non-MDR	59 (2.2)			2.73 (1.19–6.23)	0.017
Missing data	132				
Center location				NS	
Northwest	748 (26.7)	1.00	0.03*		
Southeast vs Northwest	1740 (62.2)	1.32 (1.08–1.62)	0.0074		
Other (China, Australia) vs Northwest	309 (11.1)	1.35 (0.66–2.76)	0.41		
Stem cell source				NS	
Bone marrow+/- Peripheral blood	858 (30.7)	1.00	0.0001*		
Peripheral blood	1779 (63.6)	1.19 (0.95–1.49)	0.14		
Cord blood	160 (5.7)	2.43 (1.61–3.67)	<0.0001		
HSCT number					
First	2401 (85.9)	1.00		1.00	
Second or more	394 (14.1)	1.37 (1.10–1.71)	0.005	1.51 (1.16–1.97)	0.003
Missing data	2				
Age at HSCT					
10-year increase	2797	1.17 (1.11–1.23)	<0.0001	1.12 (1.05–1.20)	0.0005
Karnofsky or Lansky status					
10-point increase	2475	0.76 (0.70–0.83)	<0.0001	0.78 (0.70–0.86)	<0.0001
Missing data	322				

HSCT - hematopoietic stem cell transplantation; GNR - Gram-negative rod; MDR – multidrug resistant; NS – not significant
* overall comparison

14 days or less; and it was 8.5% when neutropenia lasted over 14 days (p=0.1).

Following the finding that centers' FQP was not associated with a decreased rate of pre-engraftment bacteremia, we investigated the possible interaction between the FQP policy and bacteremia rates in centers located in: (a) the north-western vs. south-eastern Europe; (b) the countries with high (>20%) and low (≤20%) rates of FQ resistance in the community,[18] based on the reported community-acquired *E. coli* fluoroquinolones-resistance rates.[19,20] The interactions did not result significant, meaning that the association between FQP policy and bacteremia rates did not vary by the center location or FQ resistance rate in the community.

Post-engraftment bacteremia

In the univariate analysis, center location other than northwestern Europe, underlying non-malignant disease, HSCT in center not providing FQP, engraftment within 14 days and HSCT in center not JACIE/FACT accredited were associated with increased risk of GNRB.

GVHD was not associated with increased risk of bacteremia. This parameter, however, was assessed only in the minority of cases as among 721 patients reported with GVHD in 59 centers in 22 countries, the exact date of GVHD onset was missing in 484 patients in 48 centers in 20 countries.

In the multivariate analysis, transplantation in centers not located in northwest Europe; underlying non-malignant disease, not providing FQP and never JACIE/FACT accredited, were significantly associated with the GNRB development.

Total GNR bacteremia

In the univariate analysis, center location other than northwestern Europe, mismatched donor, positive CMV serology in both donor and recipient, cord blood source, low Karnofsky/Lansky score and steroids given for the GVHD prophylaxis were associated with increased risk of bacteremia during six months following allogeneic HSCT.

In the multivariate analysis, transplantation in centers not located in northwest Europe; cord blood source, and low Karnofsky/Lansky score were significantly associated with the GNRB development.

MDR vs. non-MDR bacteremia before and after engraftment (Supplementary Table 3)

In the subgroup multivariate analysis of risk factors for the pre-engraftment MDR GNRB, the following risk factors revealed significant association: south-eastern Europe center location, underlying disease not at complete remission at the time of HSCT, cord blood source, and lower Karnofsky/Lansky score. While south-eastern Europe center location was the only risk factor significantly associated with non-MDR pre-engraftment bacteremia.

The post-engraftment MDR GNRB was significantly associated with center location other than northwestern Europe, nonmalignant underlying diseases and time to engraftment ≤ 14 days. While non-MDR post-engraftment bacteremia was associated with center location other than northwestern Europe and center policy of not providing FQP.

Mortality following allogeneic HSCT (Table 2)

Overall 6-months post-HSCT mortality was 18% (95%CI 16–20%). Pre-engraftment MDR bacteremia, southeast Europe center location, cord blood stem cell source, second or more HSCT, older age and lower Karnofsky/Lansky score were significantly associated with mortality before engraftment. Mortality after engraftment was significantly higher in patients with pre-engraftment MDR bacteremia, post-engraftment bacteremia, following second or more HSCT, older age and lower Karnofsky/Lansky score.

Table 3
Background characteristics and factors associated with pre-engraftment Gram-negative rods bacteremia in autologous-HSCT.

	All HSCTs n=3152 (%)	Pre engraftment GNR bacteremia				
		Number with bacteremia	Univariate		Multivariate	
		205	HR (95% C.I.)	p	HR (95% C.I.)	p
Center location						NS
Northwest Europe	870 (27.6)	69	1.00			
Southeast Europe	2202 (69.9)	136	0.76 (0.57–1.02)	0.07		
Other	80 (2.5)	0				
Sex						NS
Male	1893 (60.1)	122	1.00			
Female	1259 (39.9)	83	1.03 (0.78–1.36)	0.86		
Age at HSCT (years)	Median 56.1 (range 0.5–79.6)					
10-year increase			1.14 (1.02–1.27)	0.017	1.18 (1.02–1.37)	0.03
Underlying disease						
Plasma cell disorder	1648 (52.3)	91	1.00	0.0003*	1.00	<0.0001*
Malignancies	1469 (46.6)	106	1.38 (1.04–1.82)	0.02	1.76 (1.15–2.68)	0.009
Autoimmune diseases	35 (1.1)	8	4.44 (2.01–9.82)	0.0002	7.51 (3.12–18.08)	<0.0001
Missing data	0	0				
Status of the disease at transplant						NS
Complete remission	1149 (38.6)	79	1.00			
Other status	1827 (61.4)	116	0.91 (0.68–1.22)	0.52		
Missing data	176	10				
HSCT number						NS
First	2713 (86.1)	183	1.00			
Second or more	439 (13.9)	22	0.74 (0.47–1.16)	0.18		
Ex-vivo manipulation of the cells						NS
None	2472 (97.8)	156	1.00			
Yes	55 (2.2)	5	1.44 (0.51–4.07)	0.49		
Missing data	625	44				
Karnofsky or Lansky status	Median 90 (range 40–100)					NS
10-point increase			0.94 (0.82–1.07)	0.35		
Missing data	251	10				
Center provides fluoroquinolone prophylaxis						NS
No	399 (25.3)	44	1.00			
Yes	1178 (74.7)	61	0.47 (0.32–0.69)	0.0001		
Missing data	1575	100				
Infection control team						
No	552 (20.3)	67	1.00		1.00	
Yes	2166 (79.7)	130	0.47 (0.35–0.64)	<0.0001	0.52 (0.35–0.79)	0.002
Missing data	434	8				
Conditioning regimen						NS
Melphalan only	1559 (50.0)	83	1.00	0.0045*		
BEAM	733 (23.5)	57	1.54 (1.10–2.16)	0.01		
Melphalan + other (not BEAM)	181 (5.8)	8	0.85 (0.41–1.74)	0.65		
Other	643 (20.6)	55	1.72 (1.21–2.44)	0.002		
Missing data	36	2				
JACIE/FACT accreditation 2016						NS
Accredited	1805 (57.3)	113	1.00			
Not accredited	1347 (42.7)	92	1.09 (0.83–1.44)	0.55		
Missing data	0	0				

GNR Gram-negative rod; HSCT hematopoietic stem cell transplantation; BEAM: B – BiCNU, carmustine; E - etoposide; A - cytarabine; M - melphalan; NS – not significant
* overall comparison

Autologous HSCT

Participating centers and bacteremia rates

Sixty-seven centers from 24 countries performed auto-HSCT; of them, 46 centers performed it in adults, 13 in children and eight in both. Three centers from two middle-outcome countries participated in our study; others were from high-outcome countries. All three centers from middle-outcome countries; and 27/64 centers from high-outcome countries, were never JACIE/FACT accredited. ICT was involved in 46/64 auto-HSCT centers in high-outcome countries; and in all three centers in middle-outcome countries.

1178/1577 (74.7%) of patients were transplanted in centers providing FQP; 2166/2718 (79.7%) of patients were transplanted in centers with ICT operating. Among 1244 patients transplanted in 24 centers where both information on FQP policy and ICT involvement was available, 680 (54.7%) were from 15 centers where both ICT operated and FQP was provided; and 156 (12.5%) - from one center where ICT was not involved and FQP was not provided.

Background information on 3152 auto-HSCTs performed during the study period, is presented in Table 3. The GNRB incidence was 7.2% (95% CI 6.3–8.2) following adult‘ and 6.8% (95% CI 3.4–11.8) following pediatric auto-HSCT; rates per country are presented in Supplementary Table 4. The incidence was 8.4% (95% CI 6.7–10.4) in the north-western vs. 6.8% (95% CI 5.8–7.9) in south-eastern Europe; two of 80 auto-HSCT patients in other countries developed GNRB.

The cumulative incidence of pre-engraftment GNRB was 6.6% (95%CI: 6–7%); and post- engraftment GNRB 0.7% (95%CI: 0.4–1.1%).

Microbiological results

A total of 239 GNRs were isolated, including 182 (76.2%) *Enterobacteriaceae*, 44 (18.4%) non-fermentative GNRs and 13 (5.4%)

Table 4
Factors associated with mortality in autologous HSCT (multivariate analysis).

Parameter	Numbers (%)	Pre-engraftment mortality HR (95% C.I.)	p	Post-engraftment mortality HR (95% C.I.)	p
Pre-engraftment GNR bacteremia					
No	2938 (94.1)	1.00		1.00	
Yes, MDR	35 (1.1)	1.13 (0.33–3.84)	0.85	0.88 (0.20–3.80)	0.86
Yes, non-MDR	149 (4.8)	1.56 (0.91–2.68)	0.11	1.72 (0.99–3.00)	0.055
Missing data	23				
Post-engraftment GNR bacteremia			Not relevant		
No	3070 (99.5)			1.00	
Yes, MDR	6 (0.2)			4.03 (1.11–14.63)	0.034
Yes, non-MDR	10 (0.3)			1.90 (0.20–17.74)	0.58
Missing data	59				
Karnofsky or Lansky status					
10-point increase	2894	0.69 (0.62–0.78)	<0.0001	0.70 (0.62–0.79)	<0.0001
Missing data	251				
Conditioning regimen					
Melphalan only	1559 (50.1)	1.00	0.0001*	1.00	0.0002*
BEAM	730 (23.5)	1.47 (1.03–2.09)	0.03	1.35 (0.93–1.97)	0.11
Melphalan + other (not BEAM)	181 (5.8)	2.18 (1.32–3.60)	0.002	2.37 (1.40–4.02)	0.001
Other	639 (20.6)	1.99 (1.42–2.80)	<0.0001	2.01 (1.40–2.88)	0.0002
Missing data	36				
JACIE / FACT accreditation 2016					
Accredited	1800 (57.2)	1.00		1.00	
Not accredited	1345 (42.8)	0.58 (0.42–0.81)	0.001	0.55 (0.39–0.78)	0.0007

GNR – Gram-negative rods; MDR – multidrug resistant; BEAM: B – BiCNU, carmustine; E - etoposide; A - cytarabine; M - melphalan
* overall comparison.

other GNRs. The cumulative incidence of *Enterobacteriaceae* bacteremia in auto-HSCT patients was 5.3% (95% CI: 4.5–6.1) and of non-fermentative rods was 1.1% (95% CI: 0.8–1.5).

The distribution of pathogens in the pre- and post-engraftment period are presented in Supplementary Table 2. Median time to GNRB was 14 (range 0–143) days; it was 14 (range 0–92) for monomicrobial *Enterobacteriaceae* and 16 (range 8–143) for monomicrobial non-fermentative rods (p=0.02). The incidence of episodes in autologous transplants is presented in Supplementary Fig. 2.

Risk factors for Gram-negative bacteremia

Pre-engraftment bacteremia *(Table 3)*. In the univariate analysis, older age, underlying autoimmune or malignant disease vs. plasma cell disorder, HSCT in center not providing FQP, absence of ICT, and type of conditioning regimen predisposed to pre-engraftment GNRB.

In the multivariate analysis, older age, underlying autoimmune or malignant disease vs. plasma cell disorder and absence of ICT were significantly associated with pre-engraftment bacteremia.

MDR vs. non-MDR bacteremia before engraftment *(supplementary Table 5).* The following factors were significantly associated with MDR pre-engraftment bacteremia in the multivariate analysis: Karnofsky or Lansky status and conditioning other than melphalan only.

None of the factors were found significantly associated with non-MDR pre-engraftment bacteremia in the multivariate analysis.

Among 23 post-engraftment episodes of GNRB, 16 occurred in patients with malignancies and seven with plasma cell disorders. Eighteen occurred in patients where ICT was operating. Risk factor analysis of the post-engraftment GNRB was not performed due to the limited number of such episodes.

Mortality following autologous HSCT (Table 4)

Overall 6-months post-HSCT mortality was 5.0% (95%CI 4–6%). Mortality either before and after engraftment following auto-HSCT was significantly higher in patients with lower Karnofsky/Lansky score, receiving conditioning other than melphalan monotherapy and in centers JACIE/FACT accredited. Mortality after engraftment was higher in patients with post-engraftment MDR bacteremia.

Discussion

HSCT is a curative treatment for increasing numbers of malignant and non-malignant diseases. Bacterial infections, especially those due to GNR, adversely affect the outcome of HSCT patients. During the past decade, increasing numbers of HSCT have been performed in populations considered at higher risk for infectious complications, such as patients with advanced malignancies and with alternative donors.[21] In such situations, an up-to-date analysis of GNRB risk factors is important. In this large intercontinental study, we report on the rates and factors associated with increased GNRB risks during the pre- and post-engraftment periods, following either allogeneic or autologous HSCT.

Center‘ policy recommending FQP was not associated with decreased risk of pre-engraftment bacteremia in allo-HSCT patients in our study. Several reports from Canada, Germany, and Italy have shown that FQP does not reduce bacteremia rates in children and adults following allo-HSCT.[13,22,23] Other studies demonstrated an increase in MDR pathogens colonization and infection rates among HSCT patients receiving FQP.[15,24–27]. Recently published meta-analysis demonstrated that FQP did not affect mortality.[28] These more recent data and the results of our study suggest, therefore, that the benefit of FQP prophylaxis is questionable with current changes of the epidemiological scenario for bacterial infections and should be checked in a prospective multicenter study. The decreased benefit of the FQP can be explained by the increase in fluoroquinolone resistance among GNR.[15,18,29] While benefit of FQP in neutropenic patients with a long pre-transplant history (as most of allo-HSCT recipients) is doubtful; it is still can be useful in patients with a short pre-transplant history with few previous hospitalizations and limited use of antibiotics. For example, patients with multiple myeloma submitted to auto-HSCT following induction chemotherapy generally administered on an outpatient basis and rarely complicated by infections requiring antibiotic therapy. In these patients, the intestinal flora is still presumably susceptible to FQ decontamination effect and this may explain the persistence of the effectiveness of prophylaxis in this population, as demonstrated in Italian multicenter study[13] and meta-analysis.[30] Our study was not, however, designed to analyze whether FQP influences the risk of bacteremia. While the association between FQP and bacteremia rates was analyzed based on each center general prophylaxis policy, personal per-patient decisions regarding prophylaxis could differ, and this data was unavailable. Data on FQP policy in patients during induction chemotherapy was missing.

Cord blood stem cell source was associated with higher bacteremia risks, similar to Italian data.[2,13] Being at complete remission at HSCT was not associated with lower GNRB risks in these studies; this factor was, however, significant in our experience.

In the majority of studies, GNRB in the post-engraftment period in allo-HSCT patients is mainly associated with severe acute or chronic, specifically gastrointestinal, GVHD.[14,31–33] Studies in children, however, do not correlate GVHD with an increased risk of any kind of bacteremia.[34] Although we observed no increased bacteremia risk in patients following GVHD, its influence cannot be excluded, as data on GVHD onset were unavailable for the majority of patients.

Similarly to the data from prospective countrywide Spanish and Italian studies, we demonstrated that older age and underlying malignancy predispose to pre-engraftment GNRB in auto-HSCT patients.[5,13] Interestingly, whereas GNRB rates were generally lower in auto- as compared with allo-HSCT patients, we found a very high bacteremia rate (23%) in a small cohort of auto-HSCT patients transplanted because of autoimmune diseases. This can probably be related to a long interval between initial diagnosis and the HSCT, during which patients are exposed to immunosuppressive therapy, involving biological agents; conditioning including antithymocyte globulin and T-cell depletion. Our findings shall be verified by prospective follow-up after infection complications in these patients, as HSCT is increasingly performed for autoimmune diseases.[35]

Interestingly, we demonstrated a lower pre-engraftment bacteremia risks in auto-HSCT patients in centers with active ICT during the study period. Although adherence to infection control guidelines, as well as the involvement of ICT in each patient, were not checked in our study, and these factors may correlate with other advances that reduce GNRB rates, this association may indicate the importance of strict adherence to protocols and infection control measures in bacteremia prevention, as was demonstrated by other studies.[36] The fact that we demonstrated a significant association between this parameter and bacteremia in auto-HSCT patients only, may be explained by the stronger influence of other factors in more immune-suppressed allo-HSCT patients, e.g. stem cell source.

We also demonstrated lower post-engraftment bacteremia risks in allo-HSCT patients in JACIE/FACT-accredited centers. Implementation of a quality management system was previously described as being associated with improved survival after allogeneic stem cell transplantation.[37]

In our study, the GNRB rate in allo-HSCT patients was three times higher in south-eastern European countries compared with those in the north-west. Our previous study demonstrated higher GNR resistance rates in south-eastern Europe than in the continent's north-west.[15] This data, on the background of the striking increase in allo-HSCT activity in some East European countries,[38] underscores the importance of infection control measures. Interestingly, a significant increase in GNRB rates was demonstrated during the last decade in the northern European countries.[12]

In our previous paper, we analyzed risk factors for the MDR GNRB by prospective comparison of MDR vs. non-MDR episodes.[15] In this manuscript, a comparison to the non-bacteremic patients revealed additional associations. Among them, the association of MDR GNRB before engraftment with being not at complete remission; and after engraftment – with nonmalignant underlying diseases. In our study, GNRB, and specifically MDR phenotype, was associated with increased mortality following transplantation. Pre-engraftment GNRB was an independent risk factor for post-transplant mortality in two Italian studies.[2,13] The association between bacteremia and mortality following neutrophil recovery is less clear. Several studies report similar post-HSCT survival rates in patients with and without post-engraftment bacteremia,[3,39–41] while others demonstrated opposite results.[31,32] Our data underline the importance of appropriate management of patients with GNRB and the prevention of infections by resistant bacteria for patients‘ outcomes.

Our study has several limitations. Data for non-bacteremic patients were obtained from the ProMise EBMT database, and some pertinent information was missing. We could not assess the association between bacteremia rates and the presence and severity of mucositis and GVHD; and the bacterial colonization status. For the reasons mentioned above, conclusions regarding a decreased benefit of FQP cannot be directly drawn from our findings.

Our research also has important strengths. It is the first prospective, intercontinental study summarizing GNRB rates and risk factors data in children and adult HSCT populations. This sizable database enabled risk factor analysis in either allogeneic or autologous HSCT recipients, separately before and after engraftment, uncovering important correlations that should be investigated in further prospective research. To summarize, we demonstrated that:

(a) In allo-HSCT patients, GNRB rates were higher centers located not in north-western Europe; pre-engraftment bacteremia rates were higher in patients transplanted not at complete remission, and from cord blood source; while post-engraftment GNRB rate was higher in centers not providing FQP, never JACIE/FACT accredited and in patients with underlying non-malignant disease;
(b) In auto-HSCT patients, GNRB rates were higher in patients with older age, autoimmune and malignant underlying disease,
(c) GNRB, especially with MDR bacteria, was associated with increased mortality.

The partial results of this study were presented orally at the 44th annual EBMT Conference, Lisbon, Portugal, 2018.

Declarations of Competing Interest

HA declares receiving a research grant from MSD; speaker grant from Gilead, MSD, Pfizer. Other co-authors have no conflicts of interest to declare relevant to this study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

This is a multicenter study performed as a collaborative effort of the Gram-negative bacteremia group. We are deeply indebted to the members of the Infectious Diseases Working Party of the European Bone Marrow Transplantation group for fruitful discussions and to all collaborators, who are (in alphabetic order of countries and contributors):

Austria: Susanne Matthes;
Belgium: Yves Beguin;
China: Depei Wu;
Czech Republic: Petra Keslova, Milan Navratil, Antonin Vitek;
Croatia: Radovan Vrhovac;

Cyprus: Frederiki Melanthiou;
Denmark: Henrik Sengeloev;
Finland: Marja Sankelo;
France: Aziza Abaza Nedhif, Emmanuel Bachy, Alienor Xhaard;
Germany: Andreas Groll, Gerda Silling;
Greece: Stelios Graphakos;
Israel: Lev Shvidel;
Italy: Laura Cudillo, Edoardo Lanino, Francesco Lanza, Francesca Patriarca, Roberto Raimondi, Fulvio Porta, Ivana Sator, Milena la Spina, Michele Vespignani, Ottavio Ziino;
Lithuania: Jelena Rascon;
Netherlands: Tom Wolfs, Michel Schaap;
Poland: Jolanta Gozdzik;
Portugal: Antonio Campos;
Russia: Valentina Pirumova;
Slovakia: Firas Al Sabty;
Spain: Isabel Ruiz Camps, José López, Rafael Rojas;
Turkey: Alphan Kupesiz;
UK: Rachel Hall, Srinivas Pillai;

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2020.11.002.

References

1. Chang AK, Foca MD, Jin Z, Vasudev R, Laird M, Schwartz S, et al. Bacterial bloodstream infections in pediatric allogeneic hematopoietic stem cell recipients before and after implementation of a central line-associated bloodstream infection protocol: a single-center experience. *Am J Infect Control* 2016;**44**(12):1650–5.
2. Mikulska M, Raiola AM, Galaverna F, Balletto E, Borghesi ML, Varaldo R, 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):109–18.
3. Almyroudis NG, Fuller A, Jakubowski A, Sepkowitz K, Jaffe D, Small TN, et al. Pre- and post-engraftment bloodstream infection rates and associated mortality in allogeneic hematopoietic stem cell transplant recipients. *Transpl Infect Dis Off J Transpl Soc* 2005;**7**(1):11–17.
4. Choeyprasert W, Hongeng S, Anurathapan U, Pakakasama S. Bacteremia during neutropenic episodes in children undergoing hematopoietic stem cell transplantation with ciprofloxacin and penicillin prophylaxis. *Int J Hematol* 2017;**105**(2):213–20.
5. Pinana JL, Montesinos P, Martino R, Vazquez L, Rovira M, Lopez J, et al. Incidence, risk factors, and outcome of bacteremia following autologous hematopoietic stem cell transplantation in 720 adult patients. *Ann Hematol* 2014;**93**(2):299–307.
6. Srinivasan A, McLaughlin L, Wang C, Srivastava DK, Shook DR, Leung W, et al. Early infections after autologous hematopoietic stem cell transplantation in children and adolescents: the St. Jude experience. *Transpl Infect Dis Off J Transpl Soc* 2014;**16**(1):90–7.
7. Poutsiaka DD, Price LL, Ucuzian A, Chan GW, Miller KB, Snydman DR. Blood stream infection after hematopoietic stem cell transplantation is associated with increased mortality. *Bone Marrow Transpl* 2007;**40**(1):63–70.
8. Poutsiaka DD, Munson D, Price LL, Chan GW, Snydman DR. Blood stream infection (BSI) and acute GVHD after hematopoietic SCT (HSCT) are associated. *Bone Marrow Transpl* 2011;**46**(2):300–7.
9. Sanz J, Cano I, Gonzalez-Barbera EM, Arango M, Reyes J, Montesinos P, et al. Bloodstream infections in adult patients undergoing cord blood transplantation from unrelated donors after myeloablative conditioning regimen. *Biol Blood Marrow Transpl* 2015;**21**(4):755–60.
10. Mikulska M, Viscoli C, Orasch C, Livermore DM, Averbuch D, Cordonnier C, et al. Aetiology and resistance in bacteraemias among adult and paediatric haematology and cancer patients. *J Infect* 2014;**68**(4):321–31.
11. Gudiol C, Bodro M, Simonetti A, Tubau F, Gonzalez-Barca E, Cisnal M, et al. Changing aetiology, clinical features, antimicrobial resistance, and outcomes of bloodstream infection in neutropenic cancer patients. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis* 2013;**19**(5):474–9.
12. Weisser M, Theilacker C, Tschudin Sutter S, Babikir R, Bertz H, Gotting T, et al. Secular trends of bloodstream infections during neutropenia in 15 181 haematopoietic stem cell transplants: 13-year results from a European multicentre surveillance study (ONKO-KISS). *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis* 2017;**23**(11):854–9.
13. Girmenia C, Bertaina A, Piciocchi A, Perruccio K, Algarotti A, Busca 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 Off Publ Infect Dis Soc Am* 2017;**65**(11):1884–96.
14. Mitchell AE, Derrington P, Turner P, Hunt LP, Oakhill A, Marks DI. Gram-negative bacteraemia (GNB) after 428 unrelated donor bone marrow transplants (UD-BMT): risk factors, prophylaxis, therapy and outcome. *Bone Marrow Transpl* 2004;**33**(3):303–10.
15. Averbuch D, Tridello G, Hoek J, Mikulska M, Akan H, Yanez San Segundo L, 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 Off Publ Infect Dis Soc Am* 2017;**65**(11):1819–28.
16. Transplantation ESfBaM. MED-AB forms manual (a guide to the completion of the EBMT HSCT Med-AB forms). 2018 https://www.ebmt.org/sites/default/files/2018-03/MED-AB%20Forms%20Manual.pdf.
17. Lipsitz SR, Fitzmaurice GM, Orav EJ, Laird NM. Performance of generalized estimating equations in practical situations. *Biometrics* 1994;**50**(1):270–8.
18. Leibovici L, Paul M, Cullen M, Bucaneve G, Gafter-Gvili A, Fraser A, et al. Antibiotic prophylaxis in neutropenic patients. *Cancer* 2006;**107**(8):1743–51.
19. ECDC. Surveillance atlas of infectious diseases. 2015 https://www.ecdc.europa.eu/en/surveillance-atlas-infectious-diseases.
20. WHO. Antimicrobial resistance: global report on surveillance 2014 https://www.who.int/drugresistance/documents/surveillancereport/en/.
21. Passweg JR, Baldomero H, Bader P, Bonini C, Duarte RF, Dufour C, et al. Use of haploidentical stem cell transplantation continues to increase: the 2015 European society for blood and marrow transplant activity survey report. *Bone Marrow Transpl* 2017;**52**(6):811–17.
22. Alexander S, Fisher BT, Gaur AH, Dvorak CC, Villa Luna D, Dang H, et al. Effect of levofloxacin prophylaxis on bacteremia in children with acute leukemia or undergoing hematopoietic stem cell transplantation: a randomized clinical trial. *JAMA* 2018;**320**(10):995–1004.
23. Kern WV, Weber S, Dettenkofer M, Kaier K, Bertz H, Behnke M, et al. Impact of fluoroquinolone prophylaxis during neutropenia on bloodstream infection: Data from a surveillance program in 8755 patients receiving high-dose chemotherapy for haematologic malignancies between 2009 and 2014. *J Infect* 2018;**77**(1):68–74.
24. Satlin MJ, Chavda KD, Baker TM, Chen L, Shashkina E, Soave R, et al. Colonization with levofloxacin-resistant extended-spectrum beta-lactamase-producing enterobacteriaceae and risk of bacteremia in hematopoietic stem cell transplant recipients. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2018;**67**(11):1720–8.
25. Mikulska M, Averbuch D, Tissot F, Cordonnier C, Akova M, Calandra T, et al. Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines. *J Infect* 2018;**76**(1):20–37.
26. Liss BJ, Vehreschild JJ, Cornely OA, Hallek M, Fatkenheuer G, Wisplinghoff H, et al. Intestinal colonisation and blood stream infections due to vancomycin-resistant enterococci (VRE) and extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBLE) in patients with haematological and oncological malignancies. *Infection* 2012;**40**(6):613–19.
27. Hakki M, Humphries RM, Hemarajata P, Tallman GB, Shields RK, Mettus RT, et al. Fluoroquinolone prophylaxis selects for meropenem non-susceptible Pseudomonas aeruginosa in patients with hematologic malignancies and hematopoietic-cell transplant recipients. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2018;**68**(12):2045–52.
28. Egan G, Robinson PD, Martinez JPD, Alexander S, Ammann RA, Dupuis LL, et al. Efficacy of antibiotic prophylaxis in patients with cancer and hematopoietic stem cell transplantation recipients: a systematic review of randomized trials. *Cancer Med* 2019;**8**(10):4536–46.
29. Flowers CR, Seidenfeld J, Bow EJ, Karten C, Gleason C, Hawley DK, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American society of clinical oncology clinical practice guideline. *J Clin Oncol Off J Am Soc Clin Oncol* 2013;**31**(6):794–810.
30. Gafter-Gvili A, Fraser A, Paul M, Vidal L, Lawrie TA, van de Wetering MD, et al. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. *Cochrane Database Syst Rev* 2012;**1**:CD004386.
31. Mori Y, Yoshimoto G, Nishida R, Sugio T, Miyawaki K, Shima T, et al. Gastrointestinal graft-versus-host disease is a risk factor for postengraftment bloodstream infection in allogeneic hematopoietic stem cell transplant recipients. *Biol Blood Marrow Transpl* 2018;**24**(11):2302–9.
32. Levinson A, Pinkney K, Jin Z, Bhatia M, Kung AL, Foca MD, et al. Acute gastrointestinal graft-vs-host disease is associated with increased enteric bacterial bloodstream infection density in pediatric allogeneic hematopoietic cell transplant recipients. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2015;**61**(3):350–7.
33. Bock AM, Cao Q, Ferrieri P, Young JA, Weisdorf DJ. Bacteremia in blood or marrow transplantation patients: clinical risk factors for infection and emerging antibiotic resistance. *Biol Blood Marrow Transpl* 2013;**19**(1):102–8.
34. Castagnola E, Bagnasco F, Bandettini R, Caviglia I, Morreale G, Lanino E, et al. Role of acute graft-versus-host disease in the risk of bacteremia and invasive fungal disease after allogeneic hemopoietic stem cell transplantation in children. Results from a single-center observational study. *Biol Blood Marrow Transpl* 2014;**20**(7):1068–73.
35. Kelsey PJ, Oliveira MC, Badoglio M, Sharrack B, Farge D, Snowden JA. Haematopoietic stem cell transplantation in autoimmune diseases: From basic science to clinical practice. *Curr Res Transl Med* 2016;**64**(2):71–82.
36. Toscano CM, Bell M, Zukerman C, Shelton W, Novicki TJ, Nichols WG, et al. Gram-negative bloodstream infections in hematopoietic stem cell transplant patients: the roles of needleless device use, bathing practices, and catheter care. *Am J Infect Control* 2009;**37**(4):327–34.
37. Gratwohl A, Brand R, McGrath E, van Biezen A, Sureda A, Ljungman P, et al. Use

of the quality management system "JACIE" and outcome after hematopoietic stem cell transplantation. *Haematologica* 2014;**99**(5):908–15.
38. Passweg JR, Baldomero H, Bader P, Bonini C, Cesaro S, Dreger P, et al. Hematopoietic stem cell transplantation in Europe 2014: more than 40 000 transplants annually. *Bone Marrow Transpl* 2016;**51**(6):786–92.
39. Kikuchi M, Akahoshi Y, Nakano H, Ugai T, Wada H, Yamasaki R, et al. Risk factors for pre- and post-engraftment bloodstream infections after allogeneic hematopoietic stem cell transplantation. *Transpl Infect Dis Off J Transpl Soc* 2015;**17**(1):56–65.
40. Zajac-Spychala O, Wachowiak J, Pieczonka A, Siewiera K, Fraczkiewicz J, Kalwak K, 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. *Transplant Infect Dis Off J Transpl Soc* 2016;**18**(5):690–8.
41. Gudiol C, Garcia-Vidal C, Arnan M, Sanchez-Ortega I, Patino B, Duarte R, et al. Etiology, clinical features and outcomes of pre-engraftment and post-engraftment bloodstream infection in hematopoietic SCT recipients. *Bone Marrow Transpl* 2014;**49**(6):824–30.