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ORIGINAL ARTICLE

Bloodstream infections with gram-negative organisms and the impact of multidrug resistance in patients with hematological malignancies

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Abstract

Infections and especially blood stream infections (BSI) with gram-negative bacteria (GNB) represent a major threat for patients with hematological diseases undergoing chemotherapy and mainly contribute to morbidity and mortality. In this retrospective single-center study, we analyzed the impact of BSI with different gram-negative multidrug-resistant bacteria (MDRGN) compared to BSI with antibiotic susceptible gram-negative bacteria. Data of 109 patients with hematological malignancies and GNB BSI were analyzed with overall survival (OS) 30 days after BSI being the primary endpoint. BSI with non-fermentative gram-negative bacteria were found in 26.6% of all patients and 73.4% suffered from a BSI with an *Enterobacteriaceae*. Thirty-two of 109 patients suffered from BSI with MDRGN. Characteristics of MDRGN and non-MDRGN BSI patients did not differ besides the fact that significantly more patients received an immunosuppressive therapy in the MDRGN BSI group. OS (30 days after BSI) of patients with MDRGN BSI was significantly lower (85.6 vs. 55.9%; $p < 0.001$) compared to patients with non-MDRGN BSI. Patients with MDRGN BSI with non-fermentative pathogens had a worse OS after 30 days compared to MDRGN BSI with *Enterobacteriaceae* and the same holds true for non-MDRGN BSI. In multivariate analysis of MDRGN BSI, non-fermenters and ICU admission were independently associated with increased 30-day mortality. Our data demonstrate the negative impact of non-fermentative gram-negative pathogens causing BSI compared to *Enterobacteriaceae* in hematological patients and thereby underlining the heterogeneity of gram-negative BSI.

Keywords Hematological malignancies · Bloodstream infections · Gram-negative bacteria · Multidrug-resistant organisms

Introduction

In patients with hematological malignancies like leukemia and lymphoma, infections represent a frequent clinical challenge due to chemotherapy-related neutropenia, mucositis, and disease-related immunosuppression. Regular use of central venous catheters, long hospitalization, and hematopoietic stem cell transplantation further increase the risk to suffer from infections. Bloodstream infections (BSI) represent one of the most common types of invasive infections and occur in approximately 20–25% of neutropenic patients [1, 2]. Furthermore, BSI are associated with a high mortality up to 40% [3, 4].

In the last years, a shift of bacterial species from gram-positive to gram-negative bacteria (GNB) as the causative agents of BSI was observed [5, 6] with a higher mortality in patients suffering from GNB BSI [6]. Additionally, the increase of *Enterobacteriaceae* with an extended spectrum β-lactamase (ESBL) phenotype with further resistance to fluoroquinolones and non-fermentative pathogens like *Pseudomonas aeruginosa* and *Acinetobacter baumannii* with multidrug-resistance raises concerns in all fields of healthcare, particularly in patients with hematological malignancies.

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Some strains have been reported to be only susceptible to colistin or amikacin [7], which use is limited due to toxicity in critical ill patients receiving chemotherapy.

The influence of GNB BSI with and without antibiotic resistance on early outcomes of hematological patients is controversially discussed: Some authors demonstrated a worse outcome of multidrug-resistant gram-negative bacteria (MDRGN) BSI compared to susceptible gram-negative bacteria BSI [6, 8–10], whereas others did not could not confirm such differences [11–13]. Furthermore, several studies addressed questions regarding the outcomes of patients with BSI with one distinct pathogen, e.g., *Escherichia coli* or *Klebsiella pneumoniae* [8, 9, 11, 14], but systematic data comparing different bacterial species on outcomes is still lacking.

Therefore, we retrospectively investigated early outcomes of patients with hematological malignancies treated at our department suffering from BSI with GNB with and without multidrug-resistance. We addressed the question of mortality caused by *Enterobacteriaceae* in comparison to non-fermentative pathogens such as *P. aeruginosa* and *A. baumannii.*

Methods

Study design, patients and definitions

We conducted a retrospective analysis of 109 patients with hematological malignancies and BSI with gram-negative rods treated at the University Hospital Frankfurt, Germany, between January 2008 and December 2016. Patients' records were reviewed to obtain the data. Blood cultures were taken in case of fever or other signs of infections if indicated by the treating physicians and blood was collected into culture bottles (BD BACTEC Lytic/10 Anaerobic/F and BD BACTEC Plus Aerobic/F, Becton Dickinson, Heidelberg, Germany). All patients with at least one episode of gram-negative BSI were included into the study. In patients with more than one BSI, the first BSI was considered. Primary endpoint was overall survival (OS) 30 days after BSI. Severe neutropenia was defined as absolute neutrophil count (ANC) < 500 neutrophils/μl. Patients with estimated prolonged neutropenia routinely received an antibiotic prophylaxis with levofloxacin; patients undergoing allogeneic hematopoietic stem cell transplantation received cefotaxime as prophylaxis. Empirical antibiotic treatment was chosen according to the guidelines for the treatment of febrile neutropenia [15], usually with piperacillin/tazobactam or a carbapenem. The initial antimicrobial treatment was retrospectively considered to be inadequate, if the organism recovered from blood culture demonstrated in vitro resistance against the empiric antibiotic therapy. Regarding the pre-existing conditions, the Charlson comorbidity index was assessed [16, 17]. Mucositis was assessed and graded according to the common terminology criteria for adverse events (CTCAE) [18]. The use of medical records was approved by local ethics committee (approval SHN-10-2017).

Microbiological testing and definitions

MDRGN was defined as *Enterobacteriaceae*, *Acinetobacter baumannii*, or *Pseudomonas aeruginosa* with resistance against at least three out of four antibiotic classes: piperacillin as indicator agent for penicillins, cefotaxime and/or ceftazidime as indicator agent for cephalosporins, imipenem and/or meropenem as indicator agents for carbapenems and ciprofloxacin as indicator agent for fluoroquinolones as previously described [19–21]. For identification of different species, matrix-assisted-laser desorption ionization–time of flight analysis (MALDI–TOF; VITEK MS, bioMérieux, Nürtingen, Germany) was used. Testing for antibiotic susceptibility was performed using VITEK 2 and/or antibiotic gradient tests (bioMérieux). In case of carbapenem-resistant *Enterobacteriaceae* or *A. baumannii*, detection of genes encoding carbapenemases (i.e., NDM, VIM, IMP, OXA-48 like, and KPC for *Enterobacteriaceae* as well as OXA–23, OXA–24, OXA–58 and NDM for *A. baumannii*) was routinely performed via PCR analysis and subsequent sequencing [22, 23]. MDRGN BSI was defined as at least one blood culture that grew any MDRGN. In case of more than one BSI with MDRGN, the first BSI was considered. Polymicrobial BSI was defined as the detection of at least two different pathogens from blood culture specimens taken within 24 h. All clinical microbiology procedures were performed under quality assured conditions (accredited standards according to ISO 15189:2007; certificate number D–ML–13102–01–00, valid through January 25th, 2021). Nosocomial acquisition of BSI was defined as onset of BSI > 72 h after admission to hospital.

All patients were routinely screened for colonization with multidrug-resistant organisms including MDRGN on day of admission as well as weekly during inpatient entire stay. Screening swabs for MDRGN were taken from rectal and pharyngeal site. Colonization with MDRGN was defined as MDRGN detection from any of the pre-mentioned localizations. Patients with known colonization status were placed under contact isolation measurements. Patients with known colonization received antibiotics covering the colonizing MDRGN in case of fever. If a colonizing MDRGN was only susceptible to colistin and/or amikacin, these antibiotics were used at fever only in case of clinical deterioration and clinical signs of sepsis. *Stenotrophomonas maltophilia*, *Sphingomonas paucimobilis*, and *Pseudomonas alcaligenes* are not covered by the German MDRGN definitions [20], have a comparably low virulence [24] and due to their susceptibility to standard antibiotics, e.g., fluoroquinolones or cephalosporins, they were added to the non-MDRGN group.

Statistics

SPSS (Version 24.0; IBM, SPSS Institute Inc., Chicago, USA) was used for statistical analysis. Continuous variables were compared using Mann-Whitney *U* test, categorical variables by Fisher's exact test and chi-square test, respectively. Kaplan-Meier plots were compared by log-rank test. Cox proportional hazards were calculated for multivariate analysis. All factors with a p value < 0.1 in univariate analysis were included into multivariate analysis and male sex as a control. All p values were two sided and considered to be significant if < 0.05.

Results

Patient characteristics

Between January 2008 and December 2016, in 109 patients with hematological malignancies at least one BSI with a gram-negative rod was detected. These pathogens were identified to belong to five different species of *Enterobacteriaceae* (*Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae/asburiae*, *Proteus mirabilis* and *Serratia marcescens*) and five species of non-fermentative bacteria (*Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Pseudomonas alcaligenes, Acinetobacter baumannii* and *Sphingomonas paucimobilis*). From 109 patients, 32 patients suffered from BSI with MDRGN. Patients with MDRGN suffered mostly from BSI caused by *P. aeruginosa* (12/32; 37.5%) followed by *E. coli* (11/32; 34.4%) and *K. pneumoniae* (8/32; 25%). The most common pathogen in patients with non-MDRGN BSI ($n = 77$) was *E. coli* (54/77 patients, 70.1%) followed by *P. aeruginosa* (10/77 patients, 13%). Distribution of different BSI caused by *Enterobacteriaceae* and non-fermentative bacteria over time according to their resistance phenotype is displayed in Fig. 1.

Table 1 shows baseline patient characteristics. The median age of the population was 56 years (range 17–78) with predominantly male patients (66.1%). Most patients suffered from acute myeloid leukemia (57/109; 52.3%) followed by lymphoma (23/109; 21.1%), acute lymphoblastic leukemia (17/109; 15.6%), multiple myeloma (8/109; 7.3%), and myeloproliferative diseases (4/109; 3.7%). Regarding the stage of the underlying disease, 67/109 (61.5%) were newly diagnosed at BSI, 3/109 (2.8%) in complete remission and 39/109 (35.8%) after relapse or with refractory disease. In 79.8% of patients, the therapy at BSI was curatively intended. 12/109 (11%) patients underwent autologous hematopoietic stem cell transplantation (auto-HSCT) and 17/109 (15.6%) allogeneic HSCT (allo-HSCT), 7/109 were patients post-HSCT (1 post auto-HSCT and 6 post allo-HSCT). Concerning the comorbidities, 11.9% had diabetes mellitus, 8.3% a human immunodeficiency virus infection, 3.7% a liver disease, 0.9% chronic renal failure, 16.5% heart and 10.1% lung disease. Median Charlson comorbidity score was 4 (range 0–11). 49.5% of all patients had another hospital admission within 30 days before BSI/were treated as inpatients since 30 days and 62.4% had another hospital admission/were treated as inpatients within 90 days, respectively. 4.6% were admitted to ICU within 90 days prior to BSI. 76.1% of all patients had an indwelling central catheter during BSI (16.5% with a port-catheter and 59.6% with a central venous catheter). Corticosteroids were administered in 35.8% of all patients within 7 days before BSI, 9.2% were receiving parenteral nutrition and 10.1% an immunosuppressive therapy at BSI. There were no statistical differences in baseline patient characteristics between patients with non-MDRGN and MDRGN BSI except that significantly more patients with MDRGN BSI received an immunosuppressive therapy (21.9 vs. 5.2%; $p = 0.014$) and more patients in the MDRGN BSI group underwent allo-HSCT (28.1 vs. 10.4%; $p = 0.064$).

Infection-related characteristics

Infection-related characteristics are summarized in Table 2. Overall, 26.6% of all patients suffered from a BSI with a non-fermentative pathogen and 73.4% from a BSI due to *Enterobacteriaceae*. 85.3% of all BSI were nosocomial-acquired. BSI originates in the majority of the patients (50.5%) as primary BSI without a detectable primary site, followed by lung (29.4%), soft tissue (8.3%), urinary tract (7.3%) and abdominal infections (4.6%) as source of BSI, respectively. 4/109 patients had a polymicrobial BSI (two patients with an additional *Enterococcus faecium*, one with an *Enterobacter cloacae* and one with a coagulase-negative *Staphylococcus*). The vast majority of all patients (90.8%) was in severe neutropenia (ANC < 500/μl) at the time of BSI with a median duration of neutropenia of 15 days (range 3–125 days). Median CRP was 9.15 mg/dL and 25.7% had an elevated creatinine level at onset of BSI. 18/109 patients (16.5%) suffered from a mucositis grade 3/4. 61/109 patients (56%) received an antibiotic prophylaxis either with fluoroquinolones or cefotaxime in the setting of allo-HSCT. Of 17 patients undergoing allo-HSCT, 12 microbial isolates (70.6%) revealed a resistance against the cefotaxime prophylaxis scheme. Furthermore, 44/109 patients received a fluoroquinolone prophylaxis. Of these 44 patients, 35 (79.5%) pathogens were resistant against fluoroquinolones. Additionally, of all bacteria causing BSI, 24/109 (22%) presented with a gentamicin, 20/109 (18.3%) with a tobramycin and 7/109 (6.4%) with an amikacin resistant phenotype, respectively. 23/109 (21.1%) patients were treated empirically with inadequate antibiotics. 23.9% of patients were admitted to the ICU immediately after BSI. In 12.8% of all patients, another BSI was detected within 7 previous days before GNB BSI. Regarding the colonization

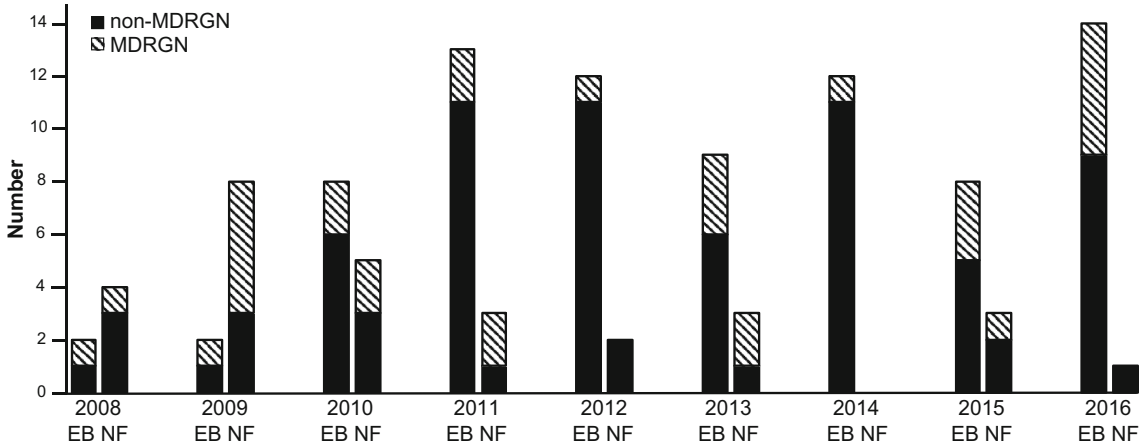

Fig. 1 Distribution of BSI due to *Enterobacteriaceae* (EB) and non-fermentative bacteria (NF) over time according to their resistance phenotype

status with MDRGN, 32.1% ($n = 35/109$) were colonized by any MDRGN and 21/35 of these patients by the MDRGN causing the BSI (19.3% of all patients).

In patients with MDRGN BSI compared to patients with non-MDRGN BSI significantly more non-fermentative bacteria (40.6 vs. 20.8%) and less *Enterobacteriaceae* (59.4 vs. 79.2%) were detected as causatives of BSI ($p = 0.027$). The primary site of MDRGN BSI was more often a lung infection (MDRGN 40.6%; non-MDRGN 24.7%) with a statistical tendency ($p = 0.062$). Patients with MDRGN BSI had comparable durations of severe neutropenia (ANC < 500/μl) until BSI compared to non-MDRGN BSI patients (7 vs. 6 days; $p = 0.819$). 46.9% of MDRGN BSI patients and 10.4% of non-MDRGN patients received an inappropriate initial antibiotic therapy ($p < 0.001$). As an indicator for clinical deterioration, more patients of the MDRGN group had to be admitted to the ICU (40.6 vs. 16.9%; $p = 0.013$).

Outcomes

Table 3 displays an overview of patient outcomes. The early OS (30 days after BSI) was 76.8% (95% CI 68.8, 84.8). OS of patients with MDRGN BSI was significantly lower ($p < 0.001$) from 7 days (MDRGN: 65.6%, 95% CI 49.1, 82.1 vs. non-MDRGN: 90.9%, 95% CI 76.4, 90.6) up to 30 days (MDRGN: 55.9%, 95% CI 38.7, 73.1 vs. non-MDRGN: 85.6%, 95% CI 77.8, 93.4) compared to patients with non-MDRGN BSI. The median time between BSI and death was 4 days (range 0–28). More patients with MDRGN BSI compared to non-MDRGN BSI died during neutropenia (37.5 vs. 10.4%; $p = 0.002$) and more fatal outcomes in the MDRGN group were bacteremia-related (37.5 vs. 13%; $p = 0.007$; one patient each in the non-MDRGN BSI group and MDRGN BSI group, respectively, died due to relapse of AML and one patient death in the MDRGN BSI group was caused by tumor lysis). 9/14 patients (64.3%) who died due to their MDRGN BSI were not identified as colonized before BSI with the particular pathogen of BSI. Patients with known colonization status prior to MDRGN BSI had a significantly better OS after 30 days compared to patients with first appearance of MDRGN in BSI (previously known: 75.6% OS, 95% CI 57.0, 94.2 vs. previously unknown: 18.2%, 95% CI 0–40.9; $p < 0.001$). In the subgroup of patients with *Enterobacteriaceae* BSI, MDRGN BSI lead to a worse survival compared to non-MDRGN BSI (73% (95% CI 56.2, 93.4) vs. 88.7% (95% CI 80.9, 96.5) (Fig. 2a). The same effects were observed in the subgroup of patients with non-fermentative bacteria caused BSI (MDRGN: 30.8% (95% CI 5.7, 55.9) vs. non-MDRGN: 71.4% (95% CI 47.7, 95.1) (Fig. 2b). Patients with MDRGN BSI with non-fermentative pathogens had a worse OS after 30 days compared to patients with MDRGN *Enterobacteriaceae* BSI (non-fermentative bacteria: 30.8% [95% CI 5.7, 55.9] vs. *Enterobacteriaceae:* 73.0% [95% CI 52.6, 93.4]; $p = 0.008$) as well as patients with non-MDRGN BSI (non-fermentative bacteria: 75% [95% CI 53.8, 96.2] vs. *Enterobacteriaceae* 88.4% [95% CI 80.4, 96.4]; $p = 0.130$) (Fig. 2c, d).

Regarding the risk factors for death after 30 days (Table 4) age > 65 years ($p = 0.005$), MDRGN BSI ($p = 0.002$), non-fermentative pathogen as causative of BSI ($p = 0.001$), ICU admission ($p < 0.001$), ANC duration until BSI ($p = 0.006$) and a Charlson comorbidity index > 4 points ($p = 0.005$) were identified in univariate analysis as significant risk factors. Furthermore, antibiotic prophylaxis was identified as a protective factor for death ($p = 0.083$). MDRGN BSI (hazard ratio (HR) 2.741; 95% CI 1.067–7.039; $p = 0.036$), BSI by non-fermentative pathogen (HR 3.632; 95% CI 1.321–9.985; $p = 0.012$) and ICU admission (HR 2.968; 95% CI 1.183–7.445; $p = 0.020$) were independently associated with 30-day mortality in the multivariate analysis (Table 4) while there was no longer a significant association between fatal outcome and Charlson comorbidity index > 4 points, ANC duration until BSI and antibiotic prophylaxis. Of note, antibiotic prophylaxis was not confirmed as an independent protective factor in multivariate analysis ($p = 0.244$).

Table 1 Baseline patient characteristics

Characteristics	All patients ($n = 109$)	Non-MDRGN BSI ($n = 77$)	MDRGN BSI ($n = 32$)	P value
Male sex, *n* (%)	72 (66.1)	49 (63.6)	23 (71.9)	0.507
Age at BSI, median (range)	56 (17–78)	55 (19–72)	56.5 (17–77)	0.947
Underlying hematological malignancy, *n* (%)				0.189
- AML	57 (52.3)	35 (45.5)	22 (68.8)	
- ALL	17 (15.6)	15 (19.5)	2 (6.3)	
- Lymphoma	23 (21.1)	17 (22.1)	6 (18.8)	
- Multiple myeloma	8 (7.3)	7 (9.1)	1 (3.1)	
- MPN	4 (3.7)	3 (3.9)	1 (3.1)	
Stage of hematological malignancy, *n* (%)				0.279
- Newly diagnosed	67 (61.5)	51 (66.2)	16 (50)	
- In complete remission	3 (2.8)	2 (2.6)	1 (3.1)	
- After relapse/refractory	39 (35.8)	24 (31.2)	15 (46.9)	
Curative treatment approach, *n* (%)	87 (79.8)	62 (80.5)	26 (81.3)	1.000
Therapy line, *n* (%)				0.185
- 1st line	62 (56.9)	47 (61)	15 (46.9)	
- 2nd line	30 (27.5)	21 (27.3)	9 (28.1)	
- Further lines	17 (15.6)	9 (11.7)	8 (25)	
HSCT at BSI, *n* (%)				0.064
- Autologous	12 (11)	10 (13)	2 (6.3)	
- Allogeneic	17 (15.6)	8 (10.4)	9 (28.1)	
Post-HSCT, *n* (%)				1.000
- After autologous	1 (0.9)	1 (1.3)	0	
- After allogeneic	6 (5.5)	3 (3.9)	3 (9.4)	
Comorbidities, *n* (%)				
- Diabetes mellitus	13 (11.9)	11 (14.3)	2 (6.3)	0.338
- HIV	9 (8.3)	6 (7.8)	3 (9.4)	0.720
- Liver disease	4 (3.7)	1 (1.3)	3 (9.4)	0.075
- Renal failure	1 (0.9)	0	1 (3.1)	0.294
- Heart disease	18 (16.5)	12 (15.6)	6 (18.8)	0.778
- Lung disease	11 (10.1)	7 (9.1)	4 (12.5)	0.728
Charlson comorbidity index, median (range)	4 (0–11)	4 (0–11)	4 (1–9)	0.890
Hospital within 30 days prior to BSI, *n* (%)	54 (49.5)	35 (45.5)	19 (59.4)	0.212
Hospital admission within 90 days prior to BSI, *n* (%)	68 (62.4)	44 (57)	24 (75)	*0.088*
ICU admission within 90 days prior to BSI, *n* (%)	5 (4.6)	4 (5.2)	1 (3.1)	1.000
Indwelling central catheter, *n* (%)				0.226
- Port-catheter	18 (16.5)	17 (22.1)	1 (3.1)	
- Central venous catheter	65 (59.6)	39 (50.6)	26 (81.3)	
Corticosteroids within 7 days prior to BSI, *n* (%)	39 (35.8)	27 (35.1)	12 (37.5)	0.829
Parenteral nutrition, *n* (%)	10 (9.2)	8 (10.4)	2 (6.3)	0.720
Immunosuppressive therapy, *n* (%)	11 (10.1)	4 (5.2)	7 (21.9)	0.014

BSI, bloodstream infection; non-MDRGN, multidrug-susceptible gram-negative bacteria; MDRGN, multidrug-resistant gram-negative bacteria; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MPN, myeloproliferative neoplasia; HSCT, hematopoietic stem cell transplantation; HIV, human immunodeficiency virus; ICU, intensive care unit. *P* values indicate differences between non-MDRGN BSI and MDRGN BSI

Table 2 Infection-related characteristics

Characteristics	All patients ($n = 109$)	Non-MDRGN BSI ($n = 77$)	MDRGN BSI ($n = 32$)	P value
Species of BSI, *n* (%)				0.055
- Nonfermenter	29 (26.6)	16 (20.8)	13 (40.6)	
- *Enterobacteriacae*	80 (73.4)	61 (79.2)	19 (59.4)	
Nosocomial aquisition of BSI, *n* (%)	93 (85.3)	67 (87)	26 (81.3)	0.553
Primary site of BSI, *n* (%)				0.062
- Lung	32 (29.4)	19 (24.7)	13 (40.6)	
- Urinary tract	8 (7.3)	7 (9.1)	1 (3.1)	
- Abdominal	5 (4.6)	5 (6.5)	0	
- Soft tissue	9 (8.3)	4 (5.2)	5 (15.6)	
- Primary BSI	55 (50.5)	42 (54.5)	13 (40.6)	
Polymicrobial BSI, *n* (%)	4	2	2	0.579
ANC < 500/μl until BSI, *n* (%)	99 (90.8)	70 (90.9)	29 (90.6)	1.000
ANC < 500/μl duration until BSI (days), median (range)	7 (1–64)	6 (1–47)	7 (1–64)	0.819
ANC < 500/μl for > 10 days, *n* (%)	63 (57.8)	41 (53.2)	22 (68.8)	0.201
CRP (mg/dL), median (range)	9.15 (0.53–50.68)	9.25 (0.53–50.68)	8.875 (0.56–48.22)	0.353
Creatinine over upper limit, *n* (%)	28 (25.7)	17 (22.1)	11 (34.4)	0.229
Severe (grade 3/4) mucositis at BSI, *n* (%)	18 (16.5)	13 (16.9)	5 (15.6)	1.000
Antibiotic prophylaxis, *n* (%)	61 (56)	44 (57.1)	17 (53.1)	0.833
Inappropriate empirical antimicrobial therapy, *n* (%)	23 (21.1)	8 (10.4)	15 (46.9)	< 0.001
ICU admission, *n* (%)	26 (23.9)	13 (16.9)	13 (40.6)	0.013
Other BSI within 7 days prior to gram-negative BSI, *n* (%)	14 (12.8)	8 (10.4)	6 (18.8)	0.345
Prior colonization with any MDRGN, *n* (%)	35 (32.1)	10 (13)	25 (78.1)	< 0.001
Prior colonization with MDRGN detected as BSI, *n* (%)	21 (19.3)	0	21 (65.6)	< 0.001

BSI, bloodstream infection; non-MDRGN, multidrug-susceptible gram-negative bacteria; MDRGN, multidrug-resistant gram-negative bacteria; ANC, absolute neutrophil count; CRP, C-reactive protein; ICU, intensive care unit. *P* values indicate differences between non-MDRGN BSI and MDRGN BSI

Discussion

In our retrospective study, we analyzed the outcomes of patients with GNB BSI and hematological malignancies in respect of multidrug-resistance and the group of gram-negative pathogens. The patient population in our study revealed no differences in baseline patient characteristics between patients with MDRGN and non-MDRGN BSI except for immunosuppressive therapy, which was significantly more frequent in MDRGN patients. Of note, immunosuppressive therapy was not identified as a risk factor for 30-day death in univariate analysis. Furthermore, especially the underlying diseases and the Charlson comorbidity index were well balanced between MDRGN and non-MDRGN patients.

Of overall 109 patients, 32 (29.4%) suffered from BSI with MDRGN. Other studies reported rates of ESBL strains in 26–32% of *E. coli* BSI [10–12], which is in line with our data, but due to other definitions of MDRGN in our study not readily comparable. Trecarichi et al. reported for *K. pneumoniae* a carbapenem resistance rate of nearly 58% in an Italian population [14] and for non-fermenters such as *P. aeruginosa* drug resistance rates up to 70% (defined as resistance in at least three antimicrobial categories) [6]. The differences in the studies might be due to different definitions of "multidrug-resistance." As mentioned above, we defined MDRGN as pathogens with resistance against at least three out of four antibiotic classes, whereas other studies considered bacteria expressing an ESBL phenotype already to be MDRGN which we did not. Furthermore, there are strong geographical differences in the prevalence of MDRGN even within Europe, e.g., in an Italian study, more than 50% of *K. pneumoniae* strains leading to BSI are carbapenem resistant [14] whereas in Germany the carbapenem resistance rate for *K. pneumoniae* is < 5% [25]. In addition, in different studies, the underlying

Table 3 Outcomes

Characteristics	All patients ($n = 109$)	Non-MDRGN BSI ($n = 77$)	MDRGN BSI ($n = 32$)	P value
Overall survival, % (95% CI)				< 0.001
- 7 days	83.5 (76.4, 90.6)	90.9 (84.4, 97.4)	65.6 (49.1, 82.1)	
- 21 days	80.7 (73.4, 88)	88.3 (81, 95.6)	62.5 (45.6, 79.4)	
- 30 days	76.8 (68.8, 84.4)	85.6 (77.8, 93.4)	55.9 (38.7, 73.1)	
Death in neutropenia, *n* (%)	20 (18.3)	8 (10.4)	12 (37.5)	0.002
Bacteremia-related death, *n* (%/% of all death within 30 days)	22 (20.2/88)	10 (13/90.9)	12 (37.5/85.-7)	0.007
BSI to death (days), median (range)	4 (0–28)	4 (0–27)	2.5 (0–28)	0.536
Bacteremia-related death without previous colonization with BSI-MDRGN, *n* (%)	9/25 (36)	0/11	9/14 (64.3)	< 0.001

BSI, bloodstream infection; non-MDRGN, multidrug-susceptible gram-negative bacteria; MDRGN, multidrug-resistant gram-negative bacteria. *P* values indicate differences between non-MDRGN BSI and MDRGN BSI

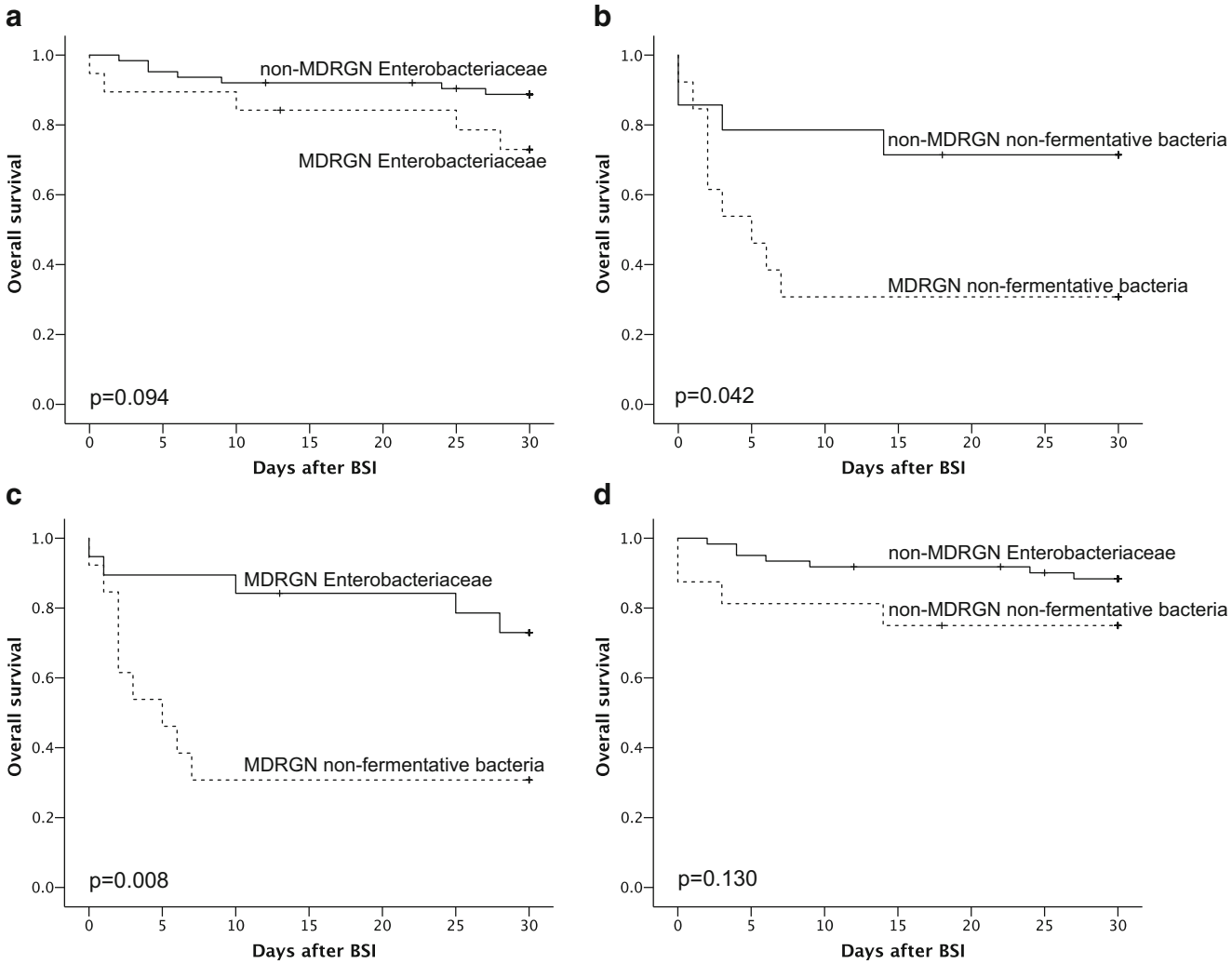

Fig. 2 Kaplan-Meier plot for overall survival after bloodstream infection. **a** Patients with *Enterobacteriaceae* and **b** non-fermentative bacteria BSI stratified each MDRGN and non-MDRGN and **c** in MDRGN and **d** non-MDRGN patients stratified each for *Enterobacteriaceae* and non-fermentative pathogens

Table 4 Univariate and multivariate analysis of risk factors for death after 30 days

Characteristics	Univariate analysis			Multivariate analysis		
	Survivors (30 days) ($n = 84$)	Non-survivors (30 days) ($n = 25$)	*P* value	Hazard ratio	95% CI	*P* value
Male sex	55 (65.5)	17 (68)	1.000	0.718	0.349–2.067	0.849
Age > 65 years	18 (21.4)	13 (52)	0.005	2.099	0.804–5.479	0.130
MDRGN BSI, *n* (%)	18 (21.4)	14 (56)	0.002	2.741	1.067–7.039	0.036
Nonfermenter BSI, *n* (%)	14 (16.7)	13 (52)	0.001	3.632	1.321–9.985	0.012
Polymicrobial BSI, *n* (%)	2 (2.4)	2 (8)	0.225	–	–	–
HSCT at BSI, *n* (%)			0.166	–	–	–
- Autologous	11 (13.1)	1 (4)				
- Allogeneic	15 (17.9)	2 (8)				
- No HSCT	58 (69)	22 (88)				
Newly diagnosed (de novo) disease, n (%)	54 (64.3)	13 (52)	0.257			
ANC < 500/μl duration until BSI (days), median (range)	8 (1–64)	3 (1–28)	0.006	0.954	0.895–1.016	0.143
Severe (grade 3/4) mucositis at BSI, *n* (%)	15 (17.9)	3 (12)	0.759	–	–	–
Antibiotic prophylaxis, *n* (%)	52 (61.9)	9 (36)	0.083	0.570	0.222–1.466	0.244
Breaktrough BSI, *n* (%)	14 (16.7)	1 (4)	0.183	–	–	–
ICU admission, *n* (%)	12 (14.3)	14 (56)	< 0.001	2.968	1.183–7.445	0.020
Other BSI within 7 days prior to gram-negative BSI, *n* (%)	10 (11.9)	5 (20)	0.328	–	–	–
Charlson > 4 points, *n* (%)	29 (34.5)	17 (68)	0.005	1.997	0.699–5.703	0.196
Indwelling central catheter, *n* (%)	64 (76.2)	19 (76)	1.000	–	–	–
Corticosteroids within previous 7 days, *n* (%)	32 (38.1)	7 (28)	0.477	–	–	–
Parenteral nutrition, *n* (%)	10 (11.9)	0	0.112	–	–	–
Immunosuppressive therapy, *n* (%)	10 (11.9)	1 (4)	0.451	–	–	–

CI, confidence interval; MDRGN, multidrug-resistant gram-negative bacteria; HSCT, hematopoietic stem cell transplantation; ANC, absolute neutrophil count; ICU, intensive care unit; Charlson, Charlson comorbidity index. *P* values indicate differences between survivors and non-survivors

malignancies differ strongly and therefore, in patients with more previous hospital stays due to their disease, a higher colonization rate with MDRGN could be assumed. Patients with MDRGN BSI revealed a significant lower OS (65.6 vs. 82.1%) and a clinical deterioration leading to significantly more ICU admissions compared to patients with BSI with non-MDRGN.

In the subgroup of *Enterobacteriaceae* and non-fermenters, respectively, MDRGN patients had a lower OS than non-MDRGN BSI patients. In multivariate analysis, BSI with non-fermentative bacteria (HR 3.632; 95% CI 1.321–9.985; $p = 0.012$) as well as BSI with MDRGN (HR 2.741; 95% CI 1.067–7.039; $p = 0.036$) were independent risk factors for death after 30 days. Some studies cannot prove a negative impact of MDRGN in patients with BSI [11–13] but many others demonstrated higher mortality rates of MDRGN BSI in patients with hematological malignancies [8–10, 14, 26–28], which is in line with our results. We demonstrate in patients with hematological malignancies a negative impact of non-fermentative gram-negative pathogens compared to *Enterobacteriaceae* in both, MDRGN (30.8 vs. 73%) and non-MDRGN BSI (75 vs. 88.4%). There is evidence that *P. aeruginosa* might have a higher negative impact on survival than others due to a higher hazard ratio for early death at 21 days after BSI (HR 4.40) [6], but the authors did not distinguish between MDRGN and non-MDRGN. In our study, *P. aeruginosa* was the most frequent non-fermentative pathogen. Cattaneo et al. demonstrated a higher mortality of BSI with *P. aeruginosa (up to 36.4% 30-day mortality)* compared to other gram-negative organisms (11.3% 30-day mortality) [29]. The

same results were also described in children with hematological diseases with a mortality of 35.8% with resistant *P. aeruginosa* rods [30]. Therefore, the negative impact on survival of non-fermentative bacteria might be due to *P. aeruginosa* BSI. The relatively small sample size in our study does not allow further subgroup analysis to address this question. Satlin et al. investigated BSI in patients with hematologic malignancies and compared *P. aeruginosa*, ESBL-expressing *Enterobacteriaceae* and carbapenem-resistant rods and found an increased mortality in patients with carbapenem-resistant bacteria and a slight increased mortality in patients with *P. aeruginosa.* However, the authors describe no differences between ESBL-expressing *Enterobacteriaceae* and multi-susceptible *Enterobacteriaceae* [28]. One explanation for the differences between *Enterobacteriaceae* and non-fermentative pathogens in our study might be the preferential site of infection for the different bacterial groups: Since *Enterobacteriaceae* as gut colonizers are more typical of causing BSI after translocation through intestinal mucosa lesions, non-fermenters as *P. aeruginosa* target typically the respiratory system leading then to BSI with higher mortality due to pulmonary infections.

Assessing the colonization status, 21/32 (65.6%) patients were found to be colonized intestinally before BSI by MDRGN causing BSI. However, the sensitivity of rectal screenings to detect a colonization with MDRGN remains unclear. Interestingly, 10/77 patients with non-MDRGN BSI were previously colonized by a MDRGN and might be overtreated with empirical antibiotic therapy. 9/14 (64.3%) patients with fatal BSI were found to be not previously colonized by the pathogen detected in blood culture and the empirical antimicrobial treatment was inadequate in 46.9% of patients with MDRGN BSI reflecting the unknown colonization status and therefore choosing an inappropriate treatment, since it is well known that a delay of the appropriate antimicrobial treatment is associated with an increased mortality [31]. However, 35.7% of MDRGN BSI patients died from bacteremia related with known colonization of the pathogen before BSI even if the guidelines recommend antibiotics covering the resistance profile of the colonizing bacteria. One reason for death with known previous colonization might be due to the susceptibility of the pathogens only to last-resort and/or toxic antibiotics as colistin and amikacin. Those antibiotics were only used at our center if the patients reveal signs of severe sepsis and some patients in our study might not have shown any signs of sepsis at the early onset of infection. However, they might deteriorate so rapidly that the later escalation of antibiotic treatment was too late to rescue the patients, since the median time from BSI to death was only 2.5 days in the MDRGN group.

Knowing that it is difficult to draw general conclusions from a retrospective study with a relatively small sample size, in our study, we demonstrate a negative impact of non-fermentative pathogens compared to *Enterobacteriaceae* in hematological patients in a relatively homogenous patient population. Additionally, our data show that colonization with MDRGN should be considered when choosing empirical antibiotic treatment which may has an impact on survival.

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Author contributions SS and BS designed the study. SS and SW collected data. SS, SW, CR, TAW, MH, VAJK, JK, HS and BS interpreted the data. SS, BS and SW wrote the manuscript. All authors read and approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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