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Prevalence of intestinal colonization by multidrug-resistant bacteria and related bloodstream infections in patients with hematological malignancies

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RESEARCH ARTICLE

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ABSTRACT

The aim of this study was to investigate the prevalence of intestinal colonization by major multidrug-resistant (MDR) bacteria and fungi in patients with hematological malignancies (HM) and its relationship with subsequent bloodstream infections (BSIs). The study was performed between December 2023 and June 2024 at the University Hospital "Saint Marina", Varna, Bulgaria. A total of 180 HM patients were screened for intestinal colonization by 3rd generation cephalosporin-resistant (3rdGCephR) and carbapenem-resistant (CR) *Enterobacterales*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, Vancomycin-Resistant Enterococci (VRE) and *Candida* sp. according to our own protocol. Blood cultures were taken according to clinical indications. Multiplex PCR was used to detect beta-lactamase genes in all invasive *Enterobacterales* isolates. A total of 100 patients (55.6%) were colonized by one or more of the screened agents. Among these, 88 patients were MDR carriers (48.9%, 88/180) and the highest colonization rates were found for CR *Klebsiella pneumoniae* (CRKP) (42%), *Candida* sp. (34%), VRE (25%) and 3rdGCephR *Escherichia coli* (23%). A total of 29 patients (16.1%; 29/180) developed BSIs, with *K. pneumoniae* responsible for 44.8%. Of these, 76.9% (10/13) were CR and bla_{NDM} positive isolates. Related BSIs were diagnosed in 57.9% of the MDR carriers with BSIs (11/19). The related BSIs percentage according to the colonizing agent was 21.4% for CRKP (9/42), 7.1% for 3rdGCephR *K. pneumoniae* (1/14) and 25% for *P. aeruginosa* (1/4). CRKP colonization was significantly higher among patients with CRKP BSIs than those with non-CRKP BSIs ($P < 0.001$). The MDR intestinal colonization, specifically by CRKP is an important source for subsequent BSIs in this high-risk patient population.

KEYWORDS

hematological malignancy, opportunistic pathogens, MDR bacteria, intestinal colonization, bloodstream infections

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INTRODUCTION

Patients with hematological malignancies (HM) are a population at particularly high risk for developing infectious complications caused by different pathogens [1]. Bloodstream infections (BSIs) are among the most common types of infection, affecting between 11 and 40%

of the neutropenic HM patients [2]. The reported mortality rate from BSIs ranges from 5% to 100% [3–7]. Patients after Hematopoetic Stem Cell Transplantation (HSCT) are a specific subgroup at a very high risk for infectious complications, and BSIs in particular, which is related to the severe immune deficiency they experience during transplantation [8, 9]. Infections are the third most common cause of early mortality after HSCT (< day 100) and the second most common after relapse (after day +100) [10]. The reported BSI incidence in this patient population is between 14 and 39%, and the associated mortality exceeds 50% in cases associated with multidrug resistant (MDR) pathogens [11–15].

Currently the etiological spectrum of BSIs among patients with HM is dominated by Gram-negative bacteria, with *Enterobacterales* and Gram-negative non-fermenting bacteria (*Pseudomonas aeruginosa, Acinetobacter baumannii, Stenotrophomonas maltophilia*, etc.) being the leading causative agents [16–18]. Although detected in relatively low rate, the fungi are also considered important agents, still associated with high mortality among HM patients [19, 20].

Over the past 20 years, following the trends in the general population, in the group of Gram-negative bacteria, the MDR isolates have been shown to dominate as etiological agents of BSIs [1, 2, 21–25]. Among these, Carbapenem-Resistant *Enterobacterales* (CRE), recognized by the WHO as pathogens of critical priority, are the most common, and *Klebsiella pneumoniae*, being the most frequently detected CRE [26–29]. Other MDR pathogens of significance as causative agents of BSIs currently include CR *P. aeruginosa,* CR *A. baumannii*, and Vancomycin-Resistant Enterococci (VRE) [28].

Multiple factors have been identified as risk factors for BSIs in patients with hematological malignancies. Neutropenia, especially the profound ($<0.5.10^9$/L) and prolonged neutropenia (> 7days), is among the most important [9, 30]. Other risk factors are the high-dose chemotherapy and the mucosal barrier injury, directly associated with immune deficiencies, dysbiosis, severe mucositis, increased permeability of the intestinal mucosa and thus with microbial translocation from the intestinal tract into the bloodstream [31–33]. In this context, particular attention should be paid to gut colonization with opportunistic organisms, especially those that are difficult to treat due to their MDR, extensively drug-resistance (XDR), and pandrug-resistance (PDR). The MDR intestinal colonization is recognized as a major risk factor for subsequent BSIs among HM patients [34–37]. The reported BSI incidence among colonized patients is significantly higher than the incidence among non-colonized individuals (50% vs. 7.5%) [38]. Approximately 30% of HSCT patients develop BSIs caused by the same MDR colonizing agent [36]. The thirty-day mortality rates associated with MDR related BSIs vary widely, reaching 71% for CR *K. pneumoniae* BSIs [39].

The aim of this study was to investigate the prevalence of intestinal colonization by MDR bacteria and fungi in patients with HM and its relationship with subsequent BSIs.

MATERIAL AND METHODS

This study was performed between December 1st, 2023, and June 30th, 2024, at the University Hospital "Saint Marina", Varna, a 1,400-beds hospital in Northeastern Bulgaria. A total of 180 patients with HM, admitted to the Hematology Department and the Pediatric Hematology Department of the hospital were included. Fecal samples collected from each patient on admission and when clinically indicated were screened for 3rd generation cephalosporin-resistant and carbapenem-resistant Gram-negative bacteria, *P. aeruginosa* (irrespective of its resistance profile), *S. maltophilia*, VRE and *Candida* sp. according to our own protocol.

The specimens were inoculated on CHROMagar^{TM} CPE (Franklin Lakes, NJ, USA), Agar Brilliance^{TM} CRE (Thermo Fisher Diagnostics B.V.), MacConkey agar with 1 mg L^{-1} cefotaxime, Agar Brilliance VRE^{TM} (Thermo Fisher Diagnostics B.V.) and Sabouroux agar (Oxoid, Hampshire, UK) and were incubated at 37 °C for 24 h.

Species identification was done by MALDI Biotyper Sirius (Bruker, Bremen, Germany).

When clinically indicated, blood cultures were analyzed by BACTEC FX40 automated system (BD, USA). The blood samples were incubated for 5 days according to the standard protocol or for 10–14 days for patients suspicious for fungal infection. In case of positivity in the blood culture instrument, the positive blood culture bottle was first subjected to Gram stain evaluation and rapid identification by MBT Sepsityper IVD (Bruker, Bremen, Germany) and further confirmed after obtaining short microbial subculture on solid media (after 5–7 h) by MALDI Biotyper Sirius (Bruker, Bremen, Germany).

The antimicrobial susceptibility testing was carried out by VITEK 2 COMPACT (BioMérieux, France) and Bayer Kirby disk-diffusion method. The results were interpreted according to the EUCAST guidelines 2023/2024 [40].

The invasive *Enterobacterales* isolates were tested for presence of beta-lactamase genes, encoding extended-spectrum beta-lactamases (ESBLs), AmpC type beta-lactamases and carbapenemases (bla_{SHV}, $bla_{CTX\text{-}M\text{-}1/9groups}$, $bla_{CTX\text{-}M\text{-}2/8groups}$, $bla_{CMY\text{-}2}$, bla_{KPC}, bla_{VIM}, bla_{NDM}, bla_{IMP}, $bla_{OXA\text{-}23\text{-}like}$, $bla_{OXA\text{-}48\text{-}like}$) by Multiplex Real-time PCR Molecular mouse (GRAM NEG RES chip, Alifax S.r.l) directly from the positive blood culture bottle after Gram stain evaluation and rapid identification by MBT Sepsityper IVD or from a short microbial subculture on solid media (5–7 h) according to the manufacturer recommendations.

Definitions

BSI was defined as an isolation of bacterial or fungal pathogen, which is not part of the resident microbial flora. In case of skin colonizers (Coagulase Negative Staphylococci, *Corynebacterium* spp., *Bacillus* spp., *Micrococcus* spp.), at least two consecutive positive blood cultures with the same organism, obtained within 48 h, were required, accompanied by clinical symptoms [41].

The BSIs were determined as related (RelBSIs) when the same species and resistance profile were isolated from both the blood sample and the prior fecal sample. Multidrug Resistance was defined as previously described [42].

Statistical methods

Descriptive statistical methods were used to summarize the study variables. Frequencies and percentages were reported for categorical variables and median with IQR were presented for numerical variables, after evaluation for normality through visual inspection of the histograms and Q-Q plots and using the Kolmogorov-Smirnov test. The chi-square test of independence and Fisher's exact test were used to assess the association between two categorical variables. Additionally, a chi-square goodness-of-fit test was employed to test the observed distribution of a qualitative variable. All analyses were considered significant at $P < 0.05$. Data were analyzed using SPSS version 23.0 (IBM Corp.NY).

RESULTS

Epidemiology of intestinal pathogen colonization

From December 2023 to June 2024, a total of 459 stool samples from 180 patients with HM, including 28 transplanted individuals (15.5%) were screened for intestinal colonization by 3rd generation cephalosporin and carbapenem-resistant Gram-negative bacteria, VRE, *P. aeruginosa* (irrespective of the resistance profile) and *Candida* sp.

The characteristics of the entire group of tested patients and the group of colonized individuals are presented in Table 1.

During the study period a total of 100 patients (55.6%, 100/180) were identified with fecal colonization by one or more of the screened microbial agents. Among these, 88 patients were colonized by MDR organisms (88%), corresponding to 48.9% from the whole studied group (88/180). Among the colonized patient group, 13% were HSCT patients (13/100).

Carbapenem-resistant Gram-negative bacteria were detected as colonizing organisms in 42/180 (23.3%), 3rd generation cephalosporin resistant *Enterobacterales* (3rd GCephRE) in 46/180 (25.5%) patients. Vancomycin-resistant enterococci, presented exclusively by *Enterococcus faecium*, were identified in the fecal samples of 25/180 (13.9%) patients. Colonization by *P. aeruginosa* (wild type) and *Candida* sp. was confirmed in 4/180 (2.2%) and 34/180 (18.9%) patients, respectively. No *A. baumannii*/MDR *A. baumannii*, MDR *P. aeruginosa* and *S. maltophilia* were detected as intestinal colonizers.

The following colonization rates were found among the colonized patients ($n = 100$): CR *K. pneumoniae* (42%), *Candida* sp. (34%), VRE (25%), 3rdGCephR *Escherichia coli* (23%), 3rd GCephR *K. pneumoniae* (14%), 3rd GCephR *Citrobacter freundii* (6%), 3rd GCephR *Enterobacter cloacae* (3%) and *P. aeruginosa* wild type (4%).

The frequency of intestinal colonization by the screened microbial agents according to the hematological disease is presented in Table 2.

MDR organisms were found as single colonizing agents in 46 patients (46/100, 46%) as follows: CR *K. pneumoniae* in 28%, 3rd GCephRE (6 *K. pneumoniae*; 8 *E. coli* and 1 *C. freundii*) in 15% and VRE – in 3%. Representatives of genus *Candida* were detected as sole colonizing agents in 11 patients (11%).

Carbapenem-resistance was detected only among isolates of *K. pneumoniae.*

A total of 43 patients (43/100, 43%) were colonized by more than one problematic organism. VRE were detected simultaneously with CR *K. pneumoniae* in 16.7% (7/42) and with 3rd GCephRE in 21.7% (10/46). Eleven patients (11/100, 11%) were colonized by multiple agents (≥3).

Prevalence of BSIs

A total of 29 patients (16.1%) in the whole studied group of 180 patients developed BSIs during the 7th-month period (Table 3). Gram-negative bacteria (17 *Enterobacterales* and 1 *P. aeruginosa*) were responsible for 62% of the cases. *K. pneumoniae* was the causative agent of 13/29 BSIs

Table 1. Characteristics of hematological patients, screened for intestinal pathogen colonization ($n = 180$)

Variables	All patients *n* (%)	Colonized, *n* (%)	Not colonized, *n* (%)	*p*
All patients with HM	180 (100.0)	100 (55.6)	80 (44.4)	0.157
Male	100 (55.5)	53 (53.0)	47 (58.8)	0.440
Median age, years (IQR)	59.5 (47–71)	56 (43.5–69)	63 (55–71)	0.005
Hematological disease				
Acute myeloid leukemia (AML)	57 (31.7)	36 (36.0)	21 (26.3)	0.162
Non-Hodgkin lymphoma (non-HL)	48 (26.7)	23 (23.0)	25 (31.3)	0.214
Multiple myeloma (MM)	22 (12.2)	9 (9.0)	13 (16.3)	0.140
Acute lymphocytic leukemia (ALL)	19 (10.6)	14 (14.0)	5 (6.3)	0.093
Chronic myeloid leukemia (CML)	11 (6.1)	5 (5.0)	6 (7.5)	0.487
Chronic lymphocytic leukemia (CLL)	10 (5.6)	6 (6.0)	4 (5.0)	0.771
Hodgkin lymphoma (HL)	5 (2.8)	1 (1.0)	4 (5.0)	0.105
Aplastic anemia (AA)	5 (2.8)	5 (5.0)	0 (0.0)	0.043
Myelodysplastic disease (MD)	3 (1.7)	1 (1.0)	2 (2.5)	0.435

Table 2. Frequency of different types of colonizing microbial agents in patients with HM according to the diagnosis

Diagnosis	CRKP *n* (%)	3rd GCephRE *n* (%)	PA *n* (%)	VRE *n* (%)	CA *n* (%)
AML	17 (40.5)	14 (30.4)	–	12 (48.0)	15 (44.1)
Non-HL	12 (28.5)	9 (19.5)	–	5 (20.0)	7 (20.6)
MM	1 (2.3)	4 (8.7)	2 (50.0)	1 (4.0)	4 (11.7)
ALL	3 (7.1)	13 (28.2)	2 (50.0)	5 (20.0)	2 (5.8)
CML	3 (7.1)	1 (2.1)	–	–	1 (2.9)
CLL	2 (4.8)	2 (4.3)	–	–	3 (8.8)
HL	–	2 (4.3)	–	–	–
AA	3 (7.1)	1 (2.1)	–	2 (8.0)	2 (5.8)
MD	1 (2.3)	–	–	–	–
Total number of patients	**42 (100.0)**	**46 (100.0)**	**4 (100.0)**	**25 (100.0)**	**34 (100.0)**

Abbreviations: **CRKP**, Carbapenem resistant *K. pneumoniae*; **3rdGCephRE**, 3rd Generation Cephalosporin Resistant *Enterobacterales*; **PA**, *P. aeruginosa*; **VRE**, Vancomycin-resistant *E. faecium*; **CA**, *Candida* sp.; **AML,** Acute myeloid leukemia; **non-HL,** non-Hodgkin lymphoma; **MM,** Multiple myeloma; **ALL,** Acute lymphocytic leukemia; **CML,** Chronic myeloid leukemia; **CLL,** Chronic lymphocytic leukemia; **HL,** Hodgkin lymphoma; **AA,** Aplastic anemia; **MD**, Myelodysplastic disease.

(44.8%). Of these, 76.9% were CR *K. pneumoniae* BSIs (10/13).

Overall, 19/100 colonized patients (19%) developed BSIs, corresponding to 65.5% (19/29) of the whole group with BSIs (Table 3).

A total of 11/19 colonized patients (57.9%) developed BSIs caused by the same microbial agents indicating related BSIs (RelBSIs) [(9 CR *K. pneumoniae*, one 3rd GCR *K. pneumoniae* and one *P. aeruginosa* wild type)] (Table 4) and the positive colonization status preceded the infectious

Table 3. Characteristics of BSIs related to the etiological agent, hematological diagnosis and the intestinal colonization status

BSIs		Patients, *n* (%)	Diagnosis (*n*)	Colonization status (*n*)
Gram negative bacteria				
Causative agent	Genetic mechanism of β-lactam resistance (*n*)			
CR *K. pneumoniae*	(bla_{SHV} + bla_{NDM}) (9) (bla_{SHV} + bla_{NDM} + bla_{OXA48}) (1)	10* (34.5)	AA (3) AML (3) non-HL (4)	CRKP (6) (CRKP + *Candida* sp.) (2) (CRKP + 3rdGCephR *C. freundii* + VRE) (1) (3rdGCephRKP + VRE + Candida sp.) (1)
3rd GCephR *K. pneumoniae*	(bla_{SHV} + $bla_{CTX\text{-}M\text{-}1/9\ group}$) (1)	1 (3.4)	ALL (1)	(3rdGCephRKP + VRE + *Candida* sp.) (1)
K. pneumoniae (wt)	Negative	2 (6.8)	AML (2)	Not colonized (2)
E. coli (wt)	Negative	3 (10.3)	MM (2) ALL (1)	Not colonized (3)
S. marcescens (wt)	Negative	1 (3.4)	AML (1)	Not colonized (1)
P. aeruginosa (wt)	nt	3 (10.3)	MM (2) AA (1)	(*P. aeruginosa* + *E. coli*) (1) (CRKP + VRE) (1) Not colonized (1)
Gram positive bacteria				
S. epidermidis		2 (6.8)	MM (2)	*Candida* sp. (1) (*Candida* sp. + *P. aeruginosa*) (1)
S. warneri		1 (3.4)	HML (1)	(CRKP + 3rdGCephR *E. coli*) (1)
E. faecium (wt)		2 (6.8)	non-HL (2)	(3rdGCephR *C. freundii* + *Candida* sp.) (1) Not colonized (1)
Streptococcus agalactiae		1 (3.4)	MM (1)	Not colonized (1)
S. viridans		1 (3.4)	non-HL (1)	*Candida* sp. (1)
Clostridium perfringens		1 (3.4)	AML (1)	Not colonized (1)
Fungi				
C. tropicalis		1 (3.4)	AML (1)	3rd GCephR KP (1)
Total number of patients, n (%)		29 (100.0)		

*One patient with polymicrobial BSI [CRKP + *E. coli* (wt)]; **CRKP**, Carbapenem-Resistant *K. pneumoniae*; **3rdGCephRKP**, 3rd Generation Cephalosporin Resistant *K. pneumoniae*; **wt**, wild type; ***n***, indicates the number of patients; **nt**, not tested.

Table 4. Related and unrelated BSIs in colonized patients according to the colonizing microbial agent

Colonizing microbial species	Colonized patients with BSIs *n*, (%)	Related BSI *n* (%)	Unrelated BSI *n*, (%)
CR *K. pneumoniae*	11 (100.0)	9 (81.8)	2 (18.2)
3rdGCR *K. pneumoniae*	3 (100.0)	1 (33.3)	2 (66.7)
3rdGCR *E. coli*	2 (100.0)	0	2 (100.0)
3rdGCR *C. freundii*	2 (100.0)	0	2 (100.0)
P. aeruginosa	2 (100.0)	1 (50.0)	1 (50.0)
VRE	4 (100.0)	0	4 (100.0)
Candida sp.	8 (100.0)	0	8 (100.0)

complication. In all 11 patients, the RelBSIs occurred during severe neutropenia and in 7 of these (63.6%) – during profound neutropenia (<0.1.10^9/L). The percentage of the RelBSIs according to the colonizing agent was 21.4% for CR *K. pneumoniae* (9/42), 7.1 % for 3rd GCephR *K. pneumoniae* (1/14) and 25% for *P. aeruginosa* (1/4).

The comparison between the patients with CR *K. pneumoniae* BSIs and those with BSIs, caused by pathogens, different from CR *K. pneumoniae*, showed that CR *K. pneumoniae* intestinal colonization was significantly higher among patients, diagnosed with CR *K. pneumoniae* BSIs ($P < 0.001$) (Table 5).

Unrelated BSIs (un-RelBSIs) were diagnosed in 8/100 colonized patients (8%), corresponding to 27.6% of all patients with BSIs (8/29) and were presented by 2 *Staphylococcus epidermidis*, 1 *Staphylococcus warneri*, 1 *Streptococcus viridians*, 1 *E. faecium*, 1 (CR *K. pneumoniae* + *E. coli*), 1 *P. aeruginosa* and 1 *Candida tropicalis* (Table 3).

Additionally, 10 patients, who were not colonized (10/29, 34.5%), also developed BSIs (Table 3). As with the RelBSIs, most of the patients in these two groups (colonized patients with un-RelBSIs and non-colonized patients with BSIs) developed the infectious complication during severe neutropenia (77.7%, 14/18).

Table 5. Characteristics of patients with CR *K. pneumoniae* BSIs and non-CR *K. pneumoniae* BSIs

Variables	CRKP BSIs ($n = 10$)	non-CRKP BSIs ($n = 19$)	*P*-value
Age, median years (IQR)	59.5 (54–65.8)	59 (51–64)	0.663
Male	5 (50.0)	12 (63.1)	0.494
Hematology disease			
AML	3 (30.0)	5 (26.3)	0.833
Non-HL	4 (40.0)	3 (15.8)	0.148
MM	0 (0.00)	7 (36.8)	**0.028**
ALL	0 (0.00)	2 (10.5)	0.288
CML	0 (0.00)	1 (5.3)	0.460
AA	3 (30.0)	1 (5.3)	0.066
CR *K. pneumoniae* intestinal colonization, *n* (%)			
Positive	9 (90.0)	2 (10.5)	**<0.001**
Negative	1 (10.0)	17 (89.5)	

Abbreviations: **CRKP**, Carbapenem resistant *K. pneumoniae*; **AML,** Acute myeloid leukemia; **Non-HL,** non-Hodgkin lymphoma; **MM,** Multiple myeloma; **ALL,** Acute lymphocytic leukemia; **CML,** Chronic myeloid leukemia; **AA,** Aplastic anemia.

Genetic mechanisms responsible for beta-lactam resistance

All 17 invasive *Enterobacterales* isolates (13 *K. pneumoniae*, 3 *E. coli* and 1 *Serratia marcescens*) were subjected to Multiplex PCR to detect the presence of genes encoding resistance to 3rd generation cephalosporins and carbapenems. The bla_{SHV} and bla_{NDM} were detected in all 3rd generation cephalosporin and carbapenem resistant *K. pneumoniae* isolates ($n = 10$) (Table 3). One of these isolates was also positive for $bla_{OXA\text{-}48\text{-}like}$. One 3rd generation cephalosporin-resistant but carbapenem-susceptible isolate of *K. pneumoniae* carried bla_{SHV} and $bla_{CTX\text{-}M\text{-}1/9\ group}$. No resistance genes were found in 6 *Enterobacterales* isolates (2 *K. pneumoniae*, 3 *E. coli* and 1 *S. marcescens*), all demonstrating the wild type phenotype (Table 3). Wild type resistance phenotype was also identified in the three cases of *P. aeruginosa* associated BSIs (Table 3).

DISCUSSION

The present study evaluates the prevalence of intestinal colonization by difficult-to-treat opportunistic organisms (including MDR) in patients with HM and the relationship between the colonization status and subsequent BSIs. A high proportion of patients, colonized by clinically significant opportunistic organisms (bacteria and fungi) was found, with a high prevalence of MDR gut colonization (48.9%). The patients with acute myeloid leukemia, followed by those with non-Hodgkin's lymphoma, were the most frequently colonized. Among the colonized patients, CR *K. pneumoniae* was the dominant colonizing agent (42%), followed by VRE (25%) and 3rdGCephR *E. coli* (23%). Over 40% of the colonized individuals were found to be carriers of multiple problematic organisms. A similar study in Spain, conducted between 2020 and 2022, reported significantly lower levels of intestinal colonization by MDR pathogens among HM patients (27.5%), with leading colonizing agents *E. coli* (49.3%), *K. pneumoniae* (24.9%), and *P. aeruginosa* (7.2%) [35]. The reported proportion of CR *Enterobacterales*-colonized patients (14.6%) among all MDR-colonized patients is lower than our result [35]. A large study, also involving HM patients from 18 Italian hematological institutions documented 6.5% incidence of MDR colonization and higher rates of CRE (59%) and ESBL carriage (44.4%), as well as 6.3% VRE gut colonization [34]. In a recent study, B. Kömürcü also reported much lower rectal CRE colonization rate (8.8%) among HM patients with febrile neutropenia in a Turkish hospital, but higher rates for ESBL-*Enterobacterales* (40.4%) [43]. Studies from China, evaluating the intestinal CRE prevalence and the subsequent BSIs among HM patients, incl. patients undergoing allogenic HSCT, reported gut CRE prevalence between 10.3, 23.8 and 29.6%, with *E. coli* and

K. pneumoniae being the dominant CRE colonizers, followed by *Klebsiella oxytoca*, *Enterobacter hormaechi* and other *Enterobacterales* representatives [5, 38, 44]. In contrast to this, the high prevalence of CRE as a colonizing agent in our study (23.3%) is entirely associated with *K. pneumoniae*. A systemic review and meta-analysis conducted by H. Luo reported 21.7% pooled CRE and 19.2% ESBL colonization rate among 21,402 HM patients from several WHO regions [23]. The highest CRE pooled prevalence was found for Southeast Asia (57.4%), followed by Americas (15.5%), Eastern Mediterranean region (14.9%) and the lowest was reported for Europe (8.9%) [23]. Differences were also found in the prevalence of the pooled ESBL colonization rate according to the geographic region – between 15% for Americas and 18.9–20.4% for Eastern Mediterranean and Europe [23]. The detected CR *Enterobacterales* (23.3%) and 3rd GCephR *Enterobacterales* prevalence (25.5%) in our study exceeded the respective pooled prevalence reported for the European region in the study of H. Luo, reflecting the regional, national, and local specificities related to antimicrobial resistance. In a recent Bulgarian study Markovska reported 30.2% ESBL and 3% CRE gut carriers [45]. Importantly, the author found that the prevalence of the fecal ESBL carriers among hospitalized patients was statistically higher compared to that in the community (42.4% vs 25.5%) [45]. Based on this data for Bulgaria, our results demonstrate that prevalence of 3rd GCephR *Enterobacterales* gut carriers in this high-risk patient population is close to that in the general population, but the CRE prevalence is much higher. In the context of the regional differences and trends, a very recent study by Karakosta from Greece, a country neighboring Bulgaria, assessing the MDR colonization status of over 4,000 hospitalized patients from 3 hospitals (including HM patients and transplant recipients), also reported a high relative proportion of CRE (31.1%) and VRE colonized patients (15.6%). However, in contrast to our findings, Karakosta also reported a very high relative proportion of CR *A. baumannii* (30.1%) and CR *P. aeruginosa* (5.8%) [46].

As reported by other authors [1, 2, 22, 24, 25], our study confirmed the Gram-negative bacteria as dominant etiological agents of BSIs in HM patients, with CR *K. pneumoniae* being the leading pathogen. Our findings are consistent with the ECDC reported data for a significantly increasing trend for both the CR *K. pneumoniae* BSIs incidence in the EU (by over 50%) and the EU mean percentage for carbapenem resistance in this species from 10.4% in 2019 to 13.3% in 2023 [47]. Greece, Bulgaria, and Romania are the countries with carbapenem-resistance levels among invasive isolates of *K. pneumoniae* above 50% [47].

In the whole cohort, we diagnosed 16.1% patients, who developed BSIs, corresponding to 19% in the colonized group. A similar result was reported by Pizzaro et al., who identified 19.3% patients with this infectious complication, with 54% of them, colonized with MDR organisms and 46% non-colonized individuals [35]. Other studies found a higher proportion of MDR colonized patients who developed subsequent BSIs (25.7%) [34]. An important finding in our study is the high proportion of RelBSIs among colonized patients who developed BSIs (57.9%), a result, which is similar to that reported by Cattaneo (62.2%), but higher than the reported by other authors (47.8%) [34, 35]. We identified CR *K. pneumoniae* as the most common causative agent of BSIs but also responsible for over 80% of all RelBSIs. Furthermore, *K. pneumoniae* was the only carbapenem-resistant Gram-negative organism responsible for intestinal colonization and subsequent BSIs. In our study the CR *K. pneumoniae* carriers that developed RelBSI were 21.4% (9/42), which is close to that reported by Cattaneo et al. (21.6%), Kömürcü et al. (20%), X. Chen et al. (18.4%) and W. Cao et al. (15.9%), but lower than that reported by Girmenia et al. (30%). In addition, most authors identified CR *K. pneumoniae* as the leading CRE colonizer, responsible for subsequent BSIs [5, 22, 34, 38, 43].

Although targeting a broader population of high-risk patients (HM, ICU and transplant recipients, patients with a history of hospitalization), Karakosta also reported a relatively high proportion of CRE colonized patients who developed subsequent BSIs (15.6%) [46]. In a meta-analysis, assessing the incidence of subsequent CR *K. pneumoniae* infections among CR *K. pneumoniae* rectal carriers, H. Wang reported a pooled incidence of 10.1% for CR *K. pneumoniae* BSIs, although a high variability between countries was found [48].

Furthermore, the present study identified the CRE RelBSI significantly more common in the CR *K. pneumoniae* colonized group compared to the CR *K. pneumoniae* non-colonized patients, confirming the CR *K. pneumoniae* gut colonization as an important risk factor for subsequent CRE BSIs, a finding also reported by other authors [38, 46]. In a study by Girmenia on patients with allogeneic HSCT, it was demonstrated that the colonization by resistant Gram-negative organisms was associated with a significantly increased risk of pre-engraftment BSIs caused by the same colonizing agent, with the probability of such infection being particularly high in carriers of carbapenem not-susceptible *K. pneumoniae* (32.5% in colonized vs. 0.1% in non-colonized; $P < 0.001$) [36]. The same was found for the patients with autologous HSCT (19% vs. 0.01%; $P < 0.001$) [36].

Regardless of the variety of colonizing agents, identified in our study, RelBSIs were caused in 9/11 cases by CR *K. pneumoniae*, a result, demonstrating the greater propensity of this difficult-to-treat MDR pathogen to cause BSIs compared to other colonizing agents, most probably related to higher virulence, invasive ability, and epidemic potential [49–51]. These findings underscore the importance of performing regular CRE fecal screening among this patient population, especially during neutropenia periods. The timely identification of high-risk patients for CRE infectious complications, initiation of preemptive targeted treatment, and cohorting the patients to prevent transmission and intrahospital dissemination of these difficult-to-treat pathogens are the potential benefits of the regular screening approach [26, 52, 53]. The carbapenem-resistance in all CR *K. pneumoniae* blood isolates was mediated by NDM beta-

lactamase, with one isolate both bla_{NDM} and bla_{OXA-48} positive. Based on the identical resistance profiles of the invasive and fecal CR *K. pneumoniae* isolates, associated with RelBSI cases, we can assume that the colonizing isolates are also NDM-producers. As part of the CHIMERA study, performed among 677 patients with rectal CR *K. pneumoniae* colonization, hospitalized in medical, surgical and ICU departments, Falcone et al. reported 56.4% NDM, 36.5% KPC, 5.8% VIM and 1.3% OXA-48 carriers [54]. Interestingly, this Italian study also found a higher rate of BSIs among NDM rectal carriers compared with KPC and VIM carriers (15.4% vs 8.1% and 2.6%, $P = 0.004$) and identified NDM rectal colonization as an independent risk factor for BSIs [54]. On the contrary, a Chinese prospective study on the epidemiology and outcomes of CR *K. pneumoniae* infections (incl. BSIs) among HM patients reported domination of KPC-2 producing strains, while Metallo-beta-lactamase (MBL) (IMP-4, NDM-5) and OXA-48-positive *K. pneumoniae* were detected rarely [55]. The study of Kang et al. from Korea, despite conducted among 1,174 CRE colonized patients from the general hospital population, also confirmed the rectal KPC *K. pneumoniae* (or CR *K. pneumoniae*) colonization independently associated with CPE BSIs in colonized patients [56]. The same study identified the hematological malignancies as an independent risk factor for subsequent BSIs among CRE-carriers [56].

Despite the high proportion of patients colonized with 3rd GCephR *Enterobacterales*, only one colonized patient, developing RelBSI, was diagnosed, and this case was also associated with *K. pneumoniae*. Similarly, despite the high relative proportion of VRE colonized patients, our study did not identify any VRE RelBSI. In contrast, an Italian study reported 11.1% VRE (1/9) and 15.6% ESBL RelBSIs (10/65) among VRE and ESBL colonizers respectively [34].

The fungi were one of the opportunistic organisms which were screened in this study. Despite the high relative proportion of patients, colonized by *Candida* (the third most commonly detected colonizer after CR *K. pneumoniae* and 3rd GCephR *Enterobacterales*), only a single patient with *Candida* BSI was diagnosed and this was not related to the colonization status of the patient.

Importantly, regardless of the BSI type (related, unrelated or in not colonized individuals), more than 80% of the patients in our study developed this infectious complication during severe neutropenia, a result, that clearly demonstrates and confirms the neutropenia as an important underling condition in these high-risk patients, a finding, which is in concordance with other similar studies [34].

CONCLUSION

To the best of our knowledge this is the first report on the prevalence of intestinal colonization by major MDR bacteria and related BSIs in patients with hematological malignancies in Bulgaria. Out study revealed 48.9% of the patients colonized by MDR pathogens, with carbapenem resistant *K. pneumoniae*, 3rd generation cephalosporin resistant *E. coli* and vancomycin-resistant *E. faecium* being the most common colonizers. Compared to the European average, a higher prevalence of CR *K. pneumoniae* intestinal colonization was found in this patient population. Related BSIs were diagnosed in 57.9% of the MDR colonized patients who developed BSIs. In our study CR *K. pneumoniae* was the dominant colonizing species, responsible for most of the related BSIs. The intestinal colonization by MDR pathogens, specifically carbapenem resistant *K. pneumoniae*, was confirmed as an important source for subsequent infectious complications in this high-risk patient population.

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