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Dissecting bloodstream infections in febrile neutropenic patients with hematological malignancies, a decade-long single center retrospective observational study (2009–2019)

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ABSTRACT

Background: The use of ill-suited antibiotics is a significant risk factor behind the increase in the mortality, morbidity, and economic burden for patients who are under treatment for hematological malignancy (HM) and bloodstream infections (BSI). Such unfitting treatment choices intensify the evolution of resistant variants which is a public health concern due to possible healthcare-associated infection spread to the general population. Hence, this study aims to evaluate antibiograms of patients with BSI and risk factors associated with septicemia.
Methods: A total of 1166 febrile neutropenia episodes (FNE) among 513 patients with HM from the National Center for Cancer Care and Research (NCCCR), Qatar, during 2009–2019 were used for this study. The socio-demographic, clinical, microbial, and anti-microbial data retrieved from the patient's health records were used.
Results: We analyzed the sensitivity of gram-negative and gram-positive bacilli reported in HM-FN-BSI patients. Out of the total 512 microorganisms isolated, 416 (81%) were gram-negative bacteria (GNB), 76 (15%) were gram-positive bacteria (GPB) and 20 (4%) were fungi. Furthermore, in 416 GNB, 298 (71.6%) were *Enterobacteriaceae sp.* among which 121 (41%) were ESBL (Extended Spectrum Beta-Lactamase) resistant to Cephalosporine third generation and Piperacillin-Tazobactam, 54 (18%) were Carbapenem-resistant or multidrug-resistant organism (MDRO). It's noteworthy that the predominant infectious agents in our hospital include *E. coli*, *Klebsiella species*, and *P. aeruginosa*. Throughout the study period, the mortality rate due to BSI was 23%. Risk factors that show a significant correlation with death are age, disease status, mono or polymicrobial BSI and septic shock.
Conclusion: Decision pertaining to the usage of antimicrobials for HM-FN-BSI patients is a critical task that relies on the latest pattern of prevalence, treatment resistance, and clinical outcomes. Analysis of the antibiogram of HM-FN-BSI patients in Qatar calls for a reconsideration of currently followed empirical antibiotic therapy towards better infection control and antimicrobial stewardship.

Introduction

Increased risk of infections, especially bloodstream infections (BSIs) is the primary factor that hinders the successful management of hematological malignancies (HM) [1]. Along with the unfavorable immune system changes caused by the underlying hematological malignancy, treatment (especially due to chemotherapy)-induced cytotoxicity, immunosuppression, and damage in the

Abbreviations: ESBL, Extended -spectrum B- lactamase producing Enterobacteriaceae; MDR, Gram-negative bacteria are reported as MDR if not susceptible to at least 3 of the following antimicrobial categories: antipseudomonal penicillin, cephalosporins, carbapenems, aminoglycosides or fluoroquinolones [33]; MDRO, MDR organism; MSSA, methicillin sensitive staph. aureus; MRSA, methicillin -resistant staphylococci; VRE, vancomycin-resistant enterococci

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gastrointestinal system are other reasons that lead to the development of febrile neutropenia (FN) in HM patients [2]. HM patients who underwent stem cell transplantation are put on immunosuppressive treatment for months to make sure that the host body does not reject the graft, this is yet another reason that induce neutropenia and increase susceptibility to infections [3]. Clinically, an absolute neutrophil count (ANC) < 500 cells/mm^3 is interpreted as neutropenia and if presented with fever (≥38.3ºC) it becomes FN. Handling FN is critical as it otherwise results in poor management of underlying HM, prolongs hospital stay, and increases treatment expenses. Fever in patients with diminished neutrophil count is a fatal complication and constitutes a medical emergency that cause significant morbidity and mortality in HM patients [4]. Studies suggest that neutropenia that persist for more than one week provides a very conducive environment for the infectious agents (microbes) often leading to serious infections [5]. While the causative microbes behind the infection can be bacteria, viruses, fungi, and parasites, the site of infection can be blood, colon, chest, skin, sinus, or/and urinary tract.

As per a few recent studies, the incidence of FN in HM patients is as high as 80%, and that of BSI is 16% (1424/9080) during the period 2002–2015 [6]. Out of the broad spectrum of causative microbes, bacteraemia (bacteria in bloodstream) is the most prevalent BSI constituting 10–25% of the total BSIs [6]. Hospitals device empirical antibiotic regimen for HM-FN-BSI patients based on the regional microbial prevalence and antibiotic susceptibility which often changes over time. The need for an up-to-date comprehensive report on such trends is the primary motivation for this research. For instance, with-in bacteremia, the proportion of gram-negative and gram-positive bacteria (GNB and GPB) behind the clinical event (FN) has changed from 71% and 29% (1973–1978) to 33% and 67% (1992–1994) over time. BSI epidemiology in neutropenic patients showed a global trend of gram-negative bacteria (GNB), particularly *Pseudomonas syringae pv. actinidiae* and *Enterobacteriaceae* between 1960 and 1970 [7]. Afterward, gram-positive micro-organisms become the most common pathogens in neutropenic patients led by *Staphylococcus coagulase negative* (SCON), *Streptococci viridans* and *S. aureus* [8]. This tendency was reverted again and, GNB re-emerged as leading pathogens in cancer patients [9]. Based on the type of causative organism and pattern of drug sensitivity/resistance, the empirical antibacterial treatment included active agents against GNB (eg. *P. aeruginosa*), and in certain cases MRSA (methicillin -resistant *staphylococci*) and *Viridans streptococci*. Hence, clinicians, pharmacists, and policymakers largely rely on local antibiograms to list out empiric antimicrobial selection criteria, especially while waiting for microbiology culture results. However, predominant causative microorganisms varied with type of treatment (chemotherapy, targeted therapy, immunotherapy), indwelling catheters used, and antimicrobial prophylaxis administration. Moreover, many other poorly explained factors including environmental conditions, emerging resistance patterns, disease severity, and phase of treatment influenced the antibiogram of HM-FN-BSI patients [10]. However, there is a lack of the latest data related to this [11]**.** Hence, this study aims to conduct a retrospective evaluation to depict the currently unclear picture of the epidemiological and microbiological profile of HM-FN-BSI patients in Qatar.

Patients and methods

Study design and patient cohort

To identify the epidemiological and microbiological characteristics of BSI in HM-FN patients along with the outcome and resistance patterns for various antimicrobial treatments, a retrospective review of patient Case Report Form (electronic CRF and paper) was conducted using the patients' records which included sociodemographic data, clinical treatment records, pathogen details, and antimicrobial susceptibility results. Patient files/electronic health records (EHR) used for this study were retrieved from Cerner Millennium® EHR platform and paper records from the hematology department in the National Center for Cancer Care and Research (NCCCR), Doha, Qatar for the period January 2009 to December 2019. HM patients who are > 15 years presented with chemotherapy-induced FN were eligible. One thousand one hundred sixty-six (1166) febrile neutropenia episodes (FNEs) in 513 adult patients were identified, out of these 256 patients (427 episodes) reported BSI. Maximum, minimum, and average number of FN episodes reported per patient were 6, 1, and 2. Out of 256 BSI patients, 107 patients reported multiple episodes and 149 patients reported at least 1 episode during the period of study. The local ethics committee of Hamad Medical Corporation (HMC) approved this study, under the reference number MRC-01-22-551.

We followed a thorough multi-step methodology to identify data of patients with FN and BSI. This involved a meticulous process utilizing paper records and EMR viewer for patients enrolled between 2009 and 2015. Whereas for the period 2016–2019, we exclusively relied on the Cerner Millennium® EHR platform. Additionally, records from the microbiology lab, pharmacy, and quarterly quality control reports were consistently maintained throughout this period. Our approach included an initial review of microbiology lab reports to identify positive blood cultures. We then correlated these positive cultures with clinical data indicative of malignant hemopathy, specific treatment regimens, and infection, such as fever, and cross-verified with supporting documentation in physician notes.

As shown in the flow chart diagram (Fig. 1), the study's inclusion criteria encompassed cases of febrile neutropenia characterized by a positive blood culture, individuals with a malignant hematologic condition, and patients experiencing profound neutropenia, denoted by a count of fewer than 500 cells per microliter, persisting for a duration exceeding 7 days. Conversely, exclusion criteria comprised instances of febrile neutropenia where blood cultures yielded negative results, as well as patients with solid tumors and benign hematologic conditions. Additionally, individuals with neutropenia of brief duration, lasting fewer than 7 days, were also excluded from the study (Fig. 1).

Microbiological analysis

For our study, we collected blood cultures from a peripheral vein and from the catheters used. Samples collected were inoculated into BactAlert® culture media (bioMérieux). The bacterial species in each culture sample were detected using routine biochemical tests. Moreover, antimicrobial susceptibility analysis on identified isolates was conducted using VITEK 2.0 AST cards and E-test strips (bioMérieux). Both the bacterial identification and antimicrobial susceptibility results are reconfirmed by additional tests at the central microbiology laboratory of HMC, using BD Phoenix™, using Clinical Laboratory Standards Institute breakpoints as previously described by [12].

Definitions

The definitions of febrile neutropenia, fever, neutropenia, high risk neutropenia, septicemia, bloodstream infection, central line-associated bloodstream infection (CLABSI), colonization, empirical antimicrobial therapy, multi-drug resistant GNB, Polymicrobial BSI was defined as any blood isolate with more than 1 bacterial or fungal species are summarized in Supplementary Table 1.

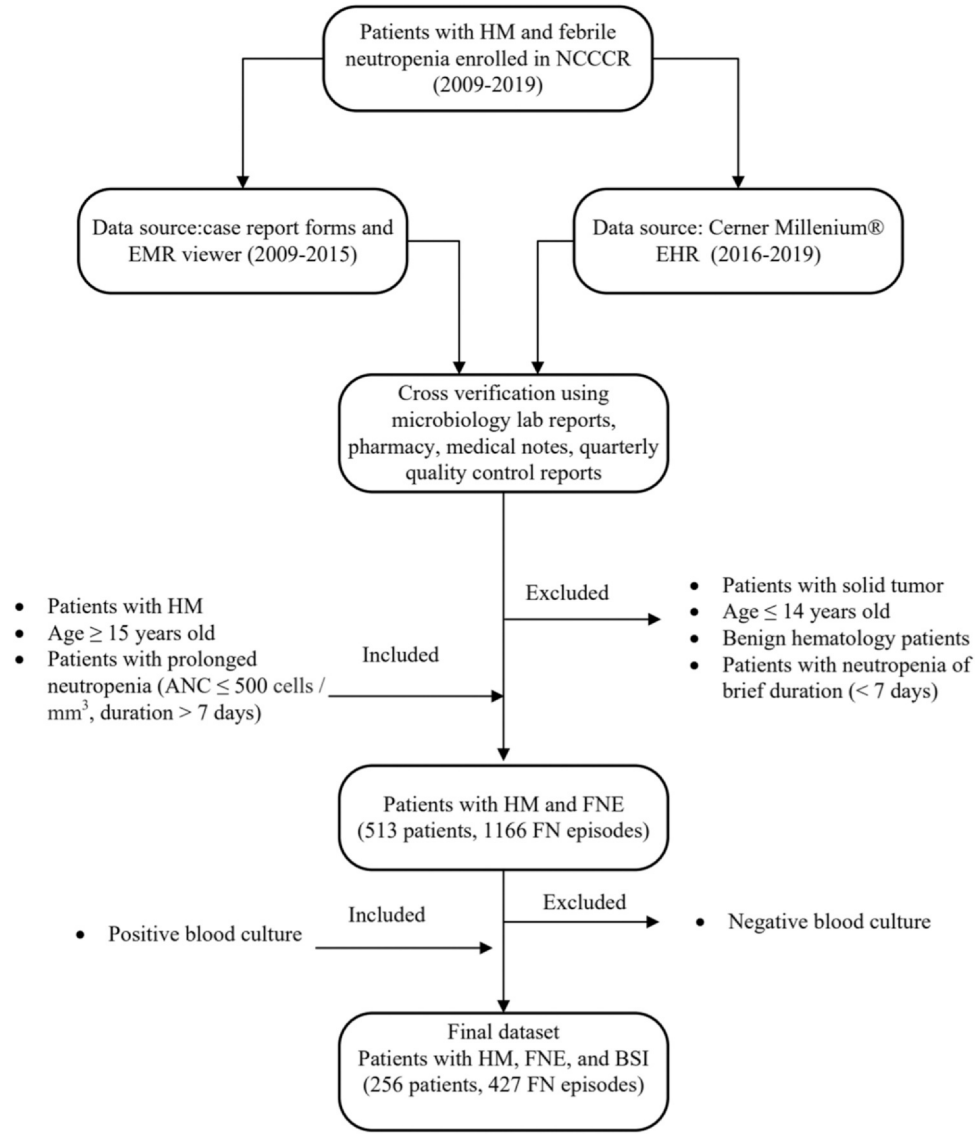

Fig. 1. Inclusion and exclusion criteria for data collection.

Antibiotic use policy

At NCCCR Hospital in Qatar, we adhere to a robust quarterly review process for our antimicrobial policy, consistently achieving a commendable compliance rate of over 90%. This meticulous supervision extends to critical performance indicators, including the promptness of initial antibiotic administration, the judicious selection of antibiotics, and the incidence of transfers to the Intensive Care Unit (ICU) or mortality rates. Moreover, in managing patients with Febrile Neutropenia (FN), we rely on a combination of clinical practice guidelines, local protocols based on Qatari epidemiological data, and bacterial resistance patterns to inform our empirical therapy choices. For cases of Febrile Neutropenic Episodes (FNE), our standard empirical antibiotic therapy regimen with piperacillin/tazobactam, and amikacin was administrated, followed by reassessments after 3–5 days. Once the causative microbial agent was isolated, the antibiotic used was adjusted accordingly. In the event of failure to identify the causative agent and persistent fever, a second-line empirical antibiotic agent (meropenem) was administrated. Furthermore, if the patient reports hemodynamic instability or pneumonia or if a catheter-related infection is suspected, and/or if there is a history of MRSA (Methicillin-resistant *Staphylococcus aureus*) infection, then glycopeptides were added to the regimen. Note that, on the 5th treatment day, if fever persisted in spite of treatment with recommended systemic antibiotics, empirical antifungal treatment (liposomal amphotericin B or echinocandin such as caspofungin) was added. An early increase in antibiotics and antifungal was administered to patients whose conditions worsened rapidly before the 5th day of treatment. Other indications for antifungal addition in our center are (i) persistent fever despite broad spectrum antibiotics therapy, (ii) broncho-pneumonia, (iii) sinusitis, (iv) severe mucositis, and (v) esophagitis or positivity of serum galactomannan.

Antimicrobial prophylaxis

Antimicrobial prophylaxis (AP) is recommended to prevent primary or secondary infection and to limit colonization of microbes, however, should be used only based on well-accepted indications. Otherwise, AP may increase treatment expense, toxicity, and antimicrobial resistance [14]. In our center, antimicrobial prophylaxis is not routinely used. Only trimethoprim/sulfamethoxazole (160/800 mg) 3 times/week is used against *Pneumocystis jirovecii*. In lymphoid malignancy and for antifungal prophylaxis treatment, we

use posaconazole for acute myeloid leukemia, and fluconazole or liposomal amphotericin B for lymphoma (LYM) and acute myeloid leukemia (AML).

Results

In this section, we discuss the socio-demographic, clinical, microbiological, and antibiotic susceptibility profiles related to 1166 FNE reported in 513 HM patients.

Epidemiological study of BSI in neutropenic patients with HM: demographic distribution and bacteremia frequency

Out of 1166 FNE, 427 (36.6%) were documented with positive blood culture or BSI. Of the 513 neutropenic patients evaluated, 40.5% were from South Asia, 39.6% from MENA and 13.6% from East Asia. The mean patient age was 40.3 years and 78.1% of patients were male. As per our data, 89% of FNE occurred in patients aged less than 60 years (Table1). Note that, 43% of the FN-BSI is reported during post-induction/consolidation phase, which can be due to the effect of prior therapy sessions as well as the high dose regimen during the consolidation phase. Also, 85% of them appeared during the active phase of treatment which included pretreatment, induction, and post induction therapy. Studying the incidence of FN-BSI with respect to the status of the underlying disease revealed an incidence of 47% in patients who achieved CR/PR and 17% in those who are under palliative care and salvage therapy; treatment response of 36% were not evaluable. Looking at the subtype-wise distribution, 52% of febrile episodes were observed in patients with AML, 23% with Acute lymphocytic leukemia (ALL), 22% with lymphoma and 2.9% with Myelodysplastic syndromes (MDS). Similarly, BSI were reported in 54.7% of AML, 24.6% of ALL, and 19% of LYM, mainly during the active phase of treatment (pretreatment, induction, and post-induction therapy).

Microbiological profile of BSI in neutropenic patients

Among the 427 BSI reports, 353 (82.7%) were monomicrobial and 74 (17.3%) were polymicrobial infection. For the entire duration of the study, five hundred twelve (512) microorganisms were isolated from 427 blood cultures; 416 (81%) were GNB; 76 (15%) were GPB and 20 (4%) were fungi (Table2) (Fig. 2). Dominant GNB

Table 2
Microbiological profile of BSI in neutropenic patients.

Family	Organism	N	%	Total	%
Gram-negative	*E-Coli*	143	34.4%	417	81%
	Klebsiella pnumoniae	116	27.9%		
	Pseudomonas aeruginosa	66	15.9%		
	Aeromonas species	19	4.6%		
	Stenotrophomonas maltophilia	19	4.6%		
	Enterobacter cloacae	19	4.6%		
	Serratia marcescens	9	2.2%		
	Acinetobacter baumannii	6	1.4%		
	Salmonella species	5	1.2%		
	Other	15	3.5%		
Gram-positive	*Staphylococcus aureus*	16	21%	76	15%
	Staphylococcus coagulase negative	16	21%		
	Streptococcus species	16	21%		
	Enterococcus species	9	12%		
	Others	19	25%		
Fungi	*Candida species*	15	79%	19	4%
	Fusarium	3	15.7%		
	Tricosporon asahii	1	5.2%		

Table 1
Socio-demographic and clinical characteristics of patients with BSI.

`	Total Population			BSI- Population		% (BSI/Total)
Number of patients	513			256		50%
Number of episodes	1166			427		37%
Gender	Male	401	78.10%	204 (79.7%)	79.7%	51%
	Female	112	21.80%	52 (20.3%)	20.3%	46%
Age	Mean age	40.3 (14–91)	Percent	39.9 (14–91)	Percent	
	< 20	29	5.7%	13	5%	45%
	[21–30]	124	24.2%	61	24%	49%
	[31–40]	131	25.5%	69	27%	53%
	[41–50]	100	19.5%	55	22%	55%
	[51–60]	72	14.0%	33	13%	46%
	[61–70]	42	8.2%	22	9%	52%
	> 70	15	2.9%	3	1%	20%
Geographic origin	South Asia	208	40.5%	115	45%	55%
	MENA	203	39.6%	87	34%	43%
	East Asia & Pacific	70	13.6%	34	13%	49%
	Sub-Saharan Africa	16	3.1%	12	5%	75%
	Europe	7	1.4%	4	2%	57%
	North America	6	1.2%	3	1%	50%
	Others	3	0.6%	1	0%	33%
Underlying disease	AML	266	51.9%	140	55%	53%
	ALL	118	23.0%	63	25%	53%
	LYM	114	22.2%	48	19%	42%
	MDS	15	2.9%	5	2%	33%
Phase of treatment	Pre-treatment	166	14%	34	8%	20%
	Induction	323	28%	88	21%	27%
	Post induction/ Consolidation	507	43%	239	56%	47%
	Salvage therapy / Relapse	51	4%	19	4%	37%
	Palliative Tx.	119	11%	47	11%	39%
Status of disease	NE	424	36%	108	25%	25%
	CR/PR	548	47%	231	54%	42%
	Refractory/Relapse	194	17%	88	21%	45%
Septic shock	No	937	80%	262	61%	28%
	Yes	229	20%	165	39%	72%
Death	Yes	103	20%	59	23%	57%
	No	410	80%	197	77%	48%

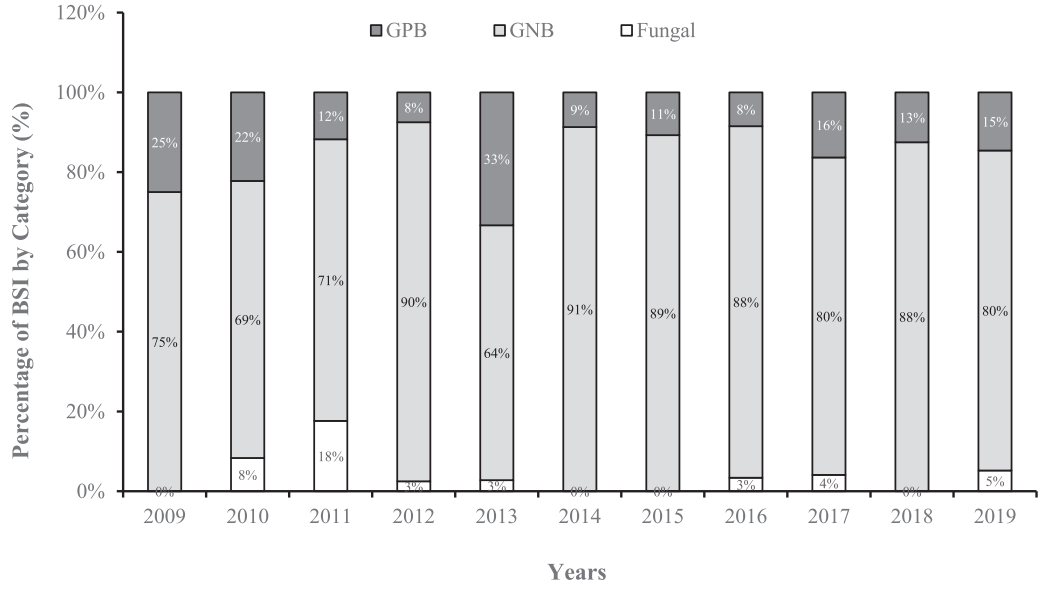

Fig. 2. Annual distribution of BSI causative microbial agents' categories in neutropenic patients.

was *E. Coli* (34.4%), followed by *Klebsiella sp.* (27.9%) and *Pseudomonas aeruginosa* in 15.9%. Concerning GPB, the three major organisms isolated were *Staphylococcus coagulase negative*, *S. aureus* and *Streptococci sp.* The annual distribution of BSI causative microbial agents' shows the same micro-biological pattern during the whole period of the study. GNB ranked first with a frequency varying between (64–91%), followed by GPB with a frequency varying between (8–33%) (Fig. 2).

Bacteremia antibiotic susceptibility profile

Antibiotic sensitivity pattern in GNB is reported in Table 3. Among 298 (71.6%) of the *Enterobacteriaceae* isolated, 123 (41%) were sensitive, 121 (41%) were ESBL resistant to cephalosporine third generation and piperacillin-tazobactam, 54 (18%) were Carbapenem resistant or MDRO. Regarding *P. aeruginosa*, the organism was found to be sensitive in 74% and MDRO in 26%. The yearly sensitivity of GNB showed same pattern during the whole period of the study. There is no increase in antibiotic resistance (Fig. 3). Concerning GPB, *S. aureus* was found to be sensitive to Methicillin in 69% of isolates and 31% were found MRSA. *Staphylococcus coagulase negative* and *streptococci sp.* were found to be sensitive in all isolates (100%). *Enterococci* were found to be susceptible in 78% of isolates, while VRE was found in only 22% of isolates (Table 4).

Risk factors for septic shock and death in patients with BSI

Throughout the study period, the mortality rate due to BSI was 23%, varying between a minimum of 5% reported in 2012 and maximum of 60% in 2009 (Fig. 4). This mortality was related to polymicrobial BSI in 27% of cases, and to monomicrobial BSI in 73%. Death was reported in 32 AML cases, 19 lymphomas, 6 ALL and 2 MDS (Table 5). While, 42 (71%) death was recorded in the active phase of treatment (pre-treatment, induction and post induction therapy), for palliative treatment and salvage therapy it was 17 (29%). The correlation (bivariate analysis) between mortality from septicemia and risk factors reveals that yearly episodes, phase of treatment, status of disease, septic shock, and mono/polymicrobial septicemia was significant ($p = 0.002$, $p < 0.01$, $p < 0.01$, $p < 0.01$, $p = 0.03$, respectively).

We also used multivariate logistic regression analyze to identify the risk factors that influence the likelihood of two clinical events, septic shock and death (both are binary dependent variables) using a set of independent variables given in Table 7. We used logit model (Maximum Likelihood Estimation (MLE)) to fit a model for analyzing the dependent variable septic shock, the algorithm converged, and P-value is 0.00042 indicating the model is significant. However, the measure of goodness of fit Pseudo R square error (0.055) is less questioning the ability of the model in explaining the variation in the data. In Table 7, the coefficient values represent the estimated

Table 3
Sensitivity of gram-negative bacteremia in neutropenic patients.

Organism	Sensitive (n, %)		ESBL (n, %)		MDRO (n, %)		Total (n, %)	
E-Coli	55	38%	57	40%	31	22%	143	34.4%
Klebsiella sp.	59	51%	42	36%	15	13%	116	27.9%
Enterobacter sp.	1	5%	15	79%	3	16%	19	4.6%
Serratia marcescens	0	0%	7	78%	2	22%	9	2.2%
Acinetobacter sp.	3	50%	0	0%	3	50%	6	1.4%
Salmonella sp.	5	100%	0	0%	0	0%	5	1.2%
Total Enterobacteriaceae	**123**	**41%**	**121**	**41%**	**54**	**18%**	**298**	**71.6%**
P. aeruginosa	49	74%	0	0%	17	26%	66	15.9%
Aeromonas sp.	19	100%	0	0%	0	0%	19	4.6%
S. maltophilia	0	0%	0	0%	19	100%	19	4.6%
Others	6	43%	0	0%	8	57%	14	3.4%
Total	197	47%	121	29%	98	24%	416	100.0%

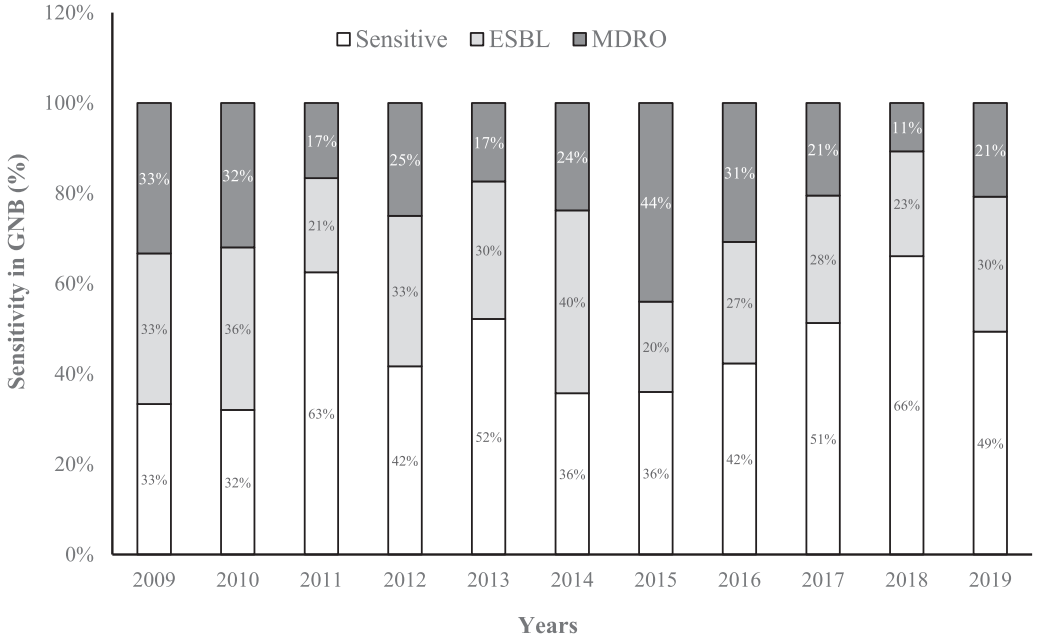

Fig. 3. Yearly distribution of sensitivity in GN bacteremia in neutropenic patients.

Table 4
Sensitivity of gram-positive bacteremia in neutropenic patients.

Organism	MSSA (n, %)		MRSA (n, %)		VRE (n, %)		Total (n, %)	
S. aureus	11	69%	5	31%	0	0%	16	21.1%
S. coagulase negative	16	100%	0	0%	0	0%	16	21.1%
Streptococcus sp.	16	100%	0	0%	0	0%	16	21.1%
Enterococcus sp.	7	78%	0	0%	2	22%	9	11.8%
Other	16	84%	0	0%	3	16%	19	25.0%
Total	66	87%	5	7%	5	7%	76	100.0%

impact of each predictor on the log-odds of experiencing "Septic Shock". Based on our dataset, Treatment Phase, Status of Disease, BSI_Mono_Poly, Type of BSI (organism type) and Line (related or not) are the predictors which have statistically significant impact in predicting the outcome septic shock. In the case of predicting the outcome death using 11 independent variables (variable Septic Shock -yes/no included), p-value is 4.48e-25, indicating the model is significant and Pseudo R square error is 0.4118. Age, Age-Category,

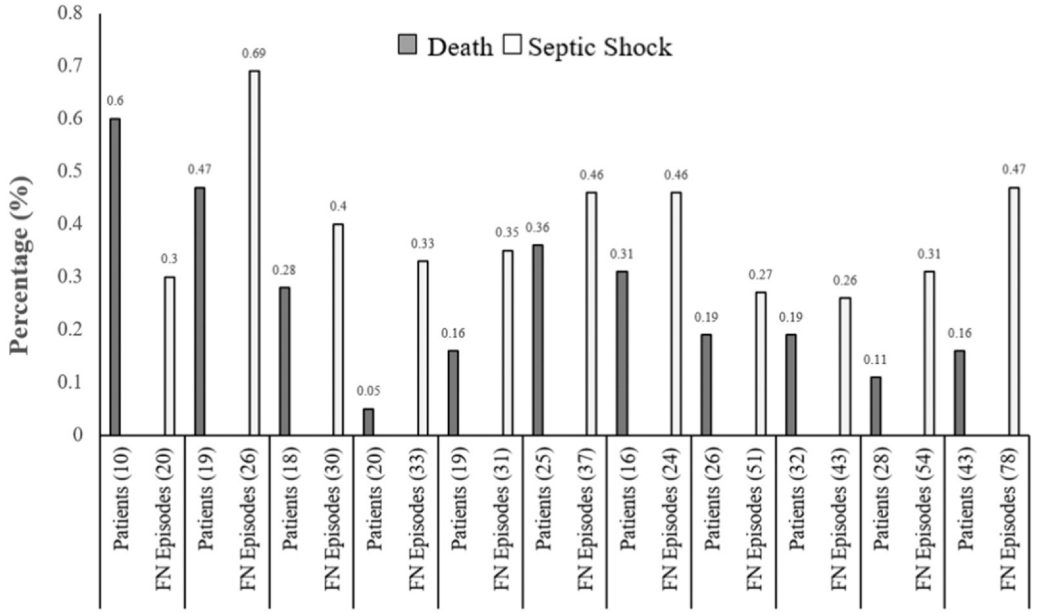

Fig. 4. Yearly frequency of septic shock and death in neutropenic patients.

Table 5
Correlation of different parameters with death in FN patients.

Parameter		Death		Total	p-value
		No	Yes		
Episode Year	2009	14	6	20	**0.002***
	2010	17	9	26	
	2011	25	5	30	
	2012	32	1	33	
	2013	28	3	31	
	2014	28	9	37	
	2015	19	5	24	
	2016	46	5	51	
	2017	37	6	43	
	2018	51	3	54	
	2019	71	7	78	
Age	< 20	22	1	23	0.1
	[21–30]	84	11	95	
	[31–40]	88	13	101	
	[41–50]	90	14	104	
	[51–60]	55	8	63	
	[61–70]	23	10	33	
	> 70	6	2	8	
Sex	F	75	16	91	0.241
	M	293	43	336	
Region	South Asia	155	23	178	0.735
	MENA	125	21	146	
	East Asia & Pacific	51	11	62	
	Sub-Saharan Africa	27	3	30	
	North America	7	0	7	
	Europe	2	1	3	
	Others	1	0	1	
Underlying disease	ALL	71	6	77	0.186
	AML	207	32	239	
	LYM	81	19	100	
	MDS	9	2	11	
Phase of Treatment	Pre-Treatment	24	10	34	**< 0.01***
	Induction	78	10	88	
	Post induction/ Consolidation	217	22	239	
	Salvage therapy/ Relapse	17	2	19	
	Palliative Tx.	32	15	47	
Monomicrobial Y/N	Yes	58	16	74	**0.032***
	No	310	43	353	
Line related (Yes/No)	No	195	34	229	0.507
	Yes	173	25	198	
Septic shock	No	259	3	262	
	Yes	109	56	165	**< 0.01***
Response/ status of disease	CR/PR	221	10	231	
	NE	82	26	108	**< 0.01***
	Refractory / Relapse	65	23	88	

Status of Disease, BSI, and Septic shock are predictors that exhibit statistically significant impact on predicting death. When the variable Septic shock -yes/no is dropped, the Pseudo R-square error dropped to 0.1514, in this case, Age, Age-Category, Status of disease, and BSI_Mono_Poly, have statistically significant impact on the dependent variable death. Furthermore, as shown in Fig. 5, the reported mortality was attributed to monomicrobial septicemia in 73% of cases and 27% of polymicrobial, GNB BSI was responsible for death as a single agent in 35/59 (59%) and in combination with other microorganisms in 16/59 (27%), GPB as a single agent in 4/59 (7%) and in combination with other microorganisms in 5/59 (8.5%). Fungi BSI were responsible for death in 4/59 (7%) as a single agent and in combination with others in 5/59 (8.5%) (Fig. 5). Resistant Enterobacteriaceae related death was reported in 25.5% (15/59) as a single agent and in 17% (10/59) in combination with other microorganisms, similarly, resistant *P. aeruginosa* related death was reported in 8.5% (5/59) as a single agent and 5% (3/59) in polymicrobial BSI. *Stenotrophomonas maltophilia* was identified as the causative organism behind mortality in 8.5% (5/59) and 5% (3/59) in monomicrobial and polymicrobial BSI respectively (Table 6).

Discussion and conclusion

This retrospective study examined 11 years data collected from 2009 to 2019 from 513 patients with hematology malignancy, neutropenia, and fever. We found that BSI was prevalent in 37% of cases, which is higher than what was earlier reported (10–25% of all FNE) with previous studies [15], and recent studies [16]. However, Dandoy et al., 2017 report a higher incidence in patients who underwent hematopoietic stem cell transplantation (13–60%) [17].

In our study, 83% of the BSIs were monomicrobial and 17% were polymicrobial; it is reported that the incidence of polymicrobial BSI varies between 5% and 15% and is responsible for high mortality [18]. However, as per Rolston et al., 2007, caution in interpreting the figures of incidence of polymicrobial BSI is warranted due to the lack of a common and standardized definition [19]**.** In this study, GNB is the most causative agent (81% GNB, 15% GPB, 4% others); dominated by the 3 most prevalent pathogens (*E. coli*, *K. pneumoniae and P. aeruginosa*). This result is comparable to older studies conducted in western countries [5] as well as in Lebanon [20], Iran [21]**,** and Saudi Arabia [22]. However, recent studies from western countries have shown the emergence of GNB septicemia worldwide, but the prevalence does not exceed 60%, and no significant gap between GNB and GPB isolates [18]. In our hospital, the pattern of the causative organism in FNE patients was stable. There is no change in the etiology of BSI from 2009 to 2019. The discrepancy in the observed higher incidence of GNB bacteremia may be attributed to the limited presence and infrequent use of anti-bacterial (anti-GNB) prophylaxis with fluoroquinolone or co-trimoxazole compared to previous studies [23]**.** Additionally, a significant portion of the patient cohort hails from low-income countries, particularly Southeast Asia (SEAN) accounting for 45%, and the Middle East and North Africa (MENA) region (39%). These regions may serve as reservoirs for drug-resistant microorganisms in their communities, potentially leading to primary or secondary infections. Studies on international travelers, including those with hematological malignancies, showed the acquisition of MDR *Enterobacteriaceae*, and noted that traveling to SEAN posed the highest risk (29–88%) for MRE, subsequently, other Asian countries (18–67%) and North Africa (31–57%) also report considerable travel related bacterial acquisition; the colonization is considered in up than 70% and persisted more than 6 months [24–27]**.** Moreover, it was previously documented that the administration of intensive chemotherapy in the treatment of malignant hematologic disorders leads to significant myelosuppression and mucosal ulceration. This, in turn, increases the likelihood of GNB. Estimates suggest that approximately 40–50% of bloodstream infections in cancer patients can be attributed to compromised mucosal barriers [41].

As mentioned by Wisplinghoff et al., 2003, usually, neutropenic patients with indwelling lines developed GPB bacteremia mainly SGN and S. aureus [8]. The majority of our patients had a central line-associated BSI, 81% of them developed GN bacteremia and 47% had catheter-related bacteremia. This fact could be explained by some factors related to the host and/or the environment, such as: the colonization of the line by endogenous organisms from the gastrointestinal tract or skin flora [28]. In addition, regional changes in infection control initiatives, climate, humidity, and several other factors influence the etiology of infections [29,30]**.** For example, as per Ramphal et al., 2004, *P. aeruginosa* infections appear to be more prevalent in a warm climate [31]. *Aeromonas sp*. infection appears to be observed in countries using desalination of water [29,30]. Following a global shift in bacterial susceptibility, cancer patients have also witnessed a significant increase in infections caused by resistant microorganisms; this highlights the significance of our study and substantiate the need for more similar region-specific research in this area.

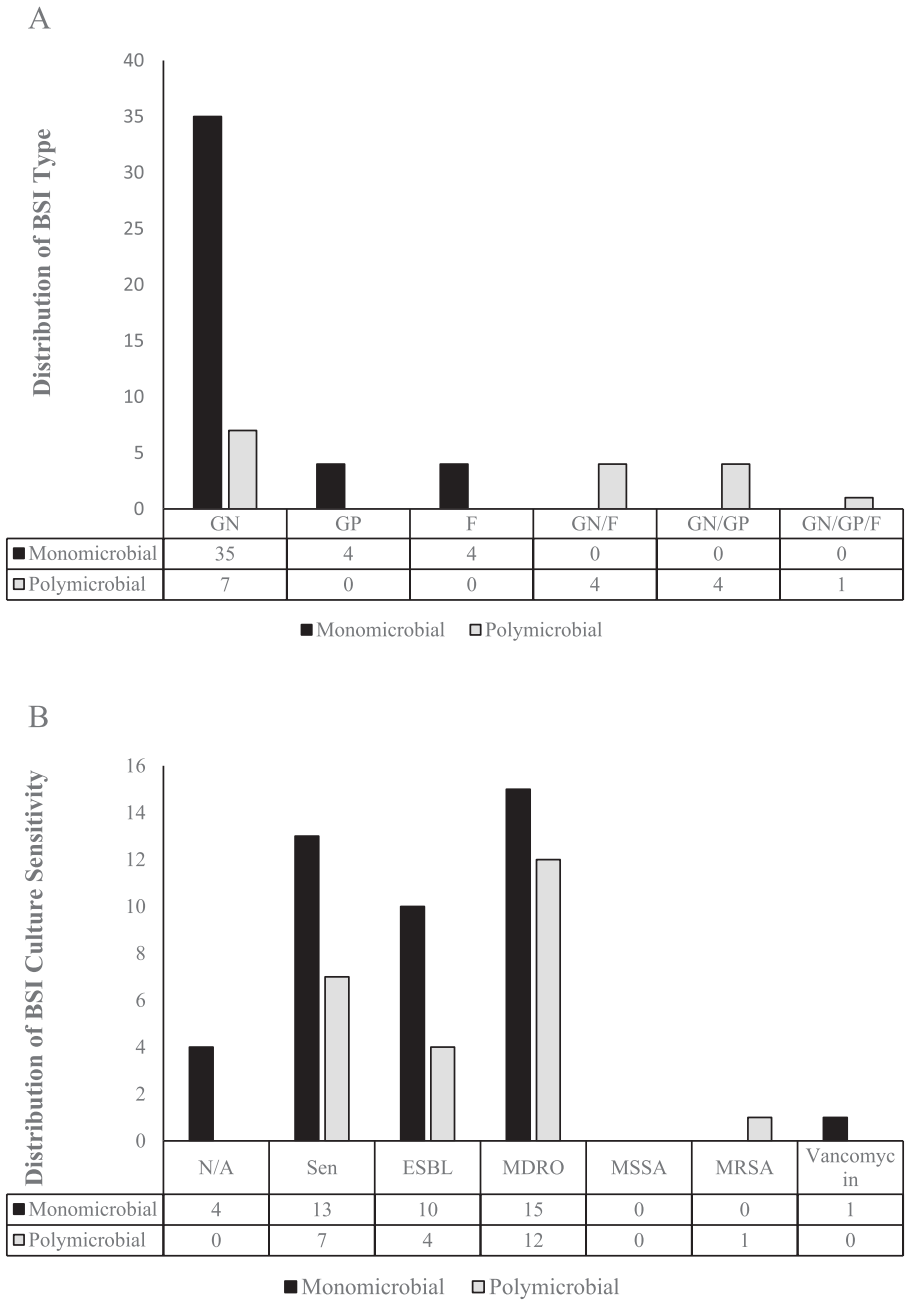

Fig. 5. BSI-related death classification by type (A) and by sensitivity (B).

Table 6
BSI-related death classification by antibiotic resistance bacteria species.

	Monomicrobial (n = 43)*	Polymicrobial (n = 16)**
ESBL	• *E. coli* (n = 6) • *Klebsiella pneumonia* (n = 3) • *Klebsiella oxytoca* (n = 1)	• *E. coli* + others (n = 3) • *Pseudomonas aeruginosa* + others (n = 2) • *Enterobacter cloacae* + others (n = 1)
MDRO	• *E. coli* (n = 4) • *Pseudomonas aeruginosa* (n = 5) • *Strenotrophomonas maltophilia* (n = 5) • *Klesiella pneumoniae* (n = 1)	• *E. coli* + others (n = 4) • *Klebsiella pneumoniae* + others (n = 2) • *Strenotrophomonas maltophilia* + others (n = 3) • *Pseudomonas aeruginosa* + others (n = 3) • *Entrecoccus faecium* + others (n = 2)

*: The remaining monomicrobial agents (n=18) were sensitive (n=17) and VCE (n=1)
**: The remaining polymicrobial agents (n=7) were very heterogenous and of low occurrence.

Table 7
Multivariate logistic regression analysis of risk factors of septic shock and death in patients with BSI.

	Septic Shock		Death (Variable Septic Shock not included)		Death (Variable Septic Shock included)	
Predictors	Coefficients	p-value	Coefficients	p-value	Coefficients	p-value
Intercept	-1.6174	0.031	-3.7023	0.001	-5.9548	0.000
Age	-0.0454	0.197	-0.1539	0.005	-0.1710	0.004
Age-Category	0.4937	0.154	1.5908	0.003	1.7371	0.004
Sex	-0.3511	0.175	-0.3126	0.383	-0.0753	0.859
Region	-0.0516	0.605	-0.1401	0.360	-0.0023	0.990
Underlying Disease	-0.1253	0.411	0.0997	0.647	0.1244	0.637
Treatment Phase	0.2544	0.016	0.0920	0.521	-0.1000	0.539
Status of Disease	0.4603	0.001	1.0515	0.000	1.0991	0.000
BSI_Mono_Poly	0.5916	0.029	0.8544	0.018	0.5107	0.238
Type of BSI	-0.1710	0.036	-0.1928	0.121	-0.1353	0.349
Line Related	0.3673	0.087	-0.0532	0.867	-0.5221	0.172
Septic Shock	-	-	-	-	4.0364	0.000
Model p-value	4.2e-04		9.34e-08		4.48e-25	

*: Model used Logit, Method: maximum likelihood estimation (MLE), Number of observations: 427 FN episodes with BSI.

The presence of MDR bacteria in neutropenic patients is reportedly increasing in many centers in the world, limiting the treatment options. On the other hand, the emergence of multi-resistant GN microorganisms suggests the use of new antibiotics [32] and reconsidering old-generation antibiotics such as colistin/polymyxin B, fosfomycin, and tigecyclines [33,34]. Similarly, as many GPB reports reduced susceptibility to glycopeptides, other antimicrobial agents such as daptomycin, linezolid, and tigecycline are used for hematology patients [33].

In our results, the study population is predominantly male (80%), with a relatively young age range, where 78% of participants are between 14 and 50 years old (mean age: 40 years). This demographic makeup aligns closely with the demographic trend seen in the Qatari population, which is characterized by its youthfulness (with a mean age of 33.0 years) and a higher proportion of males (70.7%) (Table 1). The overall susceptibility rate of GNB was 47%, and resistance rate was 53% (SBL resistance to Cephalosporin third generation and Piperacillin-Tazobactam was 29%, carbapenem-resistant (MDRO)) was 24%); among GNB, *Enterobacteriaceae* which represented 71.6% (41.2% Sensitive, 40.6% ESBL, and 18.2% MDRO). *E. coli* was the most prevalent microorganism with 34.4% followed by *Klebsiella sp.* 27.9%. There were 40% ESBL producing *E. coli* strains, and 36% *Klebsiella sp.* which are not effectively targeted by the standard empirical anti-therapy (piperacillin-tazobactam or cephalosporins 3rd generation) (Table 3), these results invite us to change the antibiotic therapy strategy. Similar statistics related to carbapenem-resistant *E. coli* (22%) and *Klebsiella sp*. (13%) are reported in many studies [35].

According to our data, *P. aeruginosa* was responsible for 16% of BSI, *P. aeruginosa* was sensitive to antibiotics in 74%, resistant to carbapenem in 26%, MDRO *P. aeruginosa* caused mortality in 13.5% of cases as single agent or in combination with other microorganisms. In our study, SM was related to mortality (13.5%) as single agent or in combination with other microorganisms. *Aeromonas sp.* is a GN anaerobic bacteria mainly present in aquatic environments; and it causes infection in immunocompromised patients [36,37]. In fact, BSI can be life-threatening and invasive, resulting in a high mortality rate approaching 70% [29,30]. Even though the anti-microbial resistance among GPB involving methicillin in *Staphylococci* and vancomycin in *Enterococci* was identified, reportedly this issue is not a concern compared to MDR GN bacteria [13].

When we evaluated antimicrobial susceptibility among GPB, we found that the rate of MSSA for *Staphylococcus coagulase negative* (100% vs 15.7% and 20%) and for *S. aureus* (69% vs 63.5% and 44%) was lower than that reported by [9], and. However, the rate of *Enterococci* resistant to vancomycin (22% vs 10.8% and 23%) were higher or similar to both previous studies. To compare the resistance of hematology versus NCCCR and HMC; the evolution of resistance by year and category; Sensitive 40% 2014–68% (2011, 2018); ESBL 18% (2011), 38% (2014); MDRO 14% 2011, 41% (2018).

In our study, the 30-day mortality rate was 23% (5–60%), consistent with older studies [8], and higher than the reported mortality rate in other studies [20,38–40]. Mortality at 30 days was secondary to monomicrobial BSI in 73% and polymicrobial in 27%, among monomicrobial BSI (GNB: 35/59 =59%, GPC: 4/59 =7% and fungi 7%). We also found that yearly episodes, phase of treatment, response to treatment, type of BSI, and septic shock influence morbidity and mortality in patients with BSI. In the present study, the relation between these factors and mortality was statistically significant.

The current study exhibits several notable limitations that could influence the interpretation and applicability of the findings. These limitations encompass: (i) The study's single-center nature, which may restrict the generalizability of the results beyond the specific study site, (ii) the retrospective design, reliant on historical data, introduces the potential for incomplete or insufficient data collection regarding pertinent risk factors impacting patient outcomes, (iii) lack of data concerning the MASCC score (Multinational Association of Supportive Care in Cancer), which could impede the assessment of patient risk for complications related to febrile neutropenia. Consequently, risk stratification was not included in our study's analysis, (iv) The conventional microbiological identification methods displayed limitations, particularly in the detection of carbapenem resistance. While molecular methods are preferred for acquiring such critical information, their extended processing time could pose a risk to patients' care, and (v) finally it is crucial to acknowledge that initiating empirical antimicrobial therapy may potentially have adverse effects on the outcomes of patients with bloodstream infections caused by multi-drug resistant pathogens, particularly when compared to a promptly targeted antimicrobial selection. This underscores the intricate decision-making process in clinical practice, where balancing the urgency of treatment with the risk of promoting drug-resistant strains is of paramount importance. Several studies in the related field have examined various aspects of infection, such as sepsis among children [42], viridans streptococci lead infections in adults [43], the prevalence of gram-negative bacilli (GNB) in HSCT patients [44], the risk of recurrent febrile neutropenia due to early discontinuation of antibiotics [45], the effectiveness of Vancomycin for febrile neutropenia [46], and candidemia-related mortality [47]. However, our study offers a more comprehensive analysis of the spectrum of causative organisms and the associated risk factors related to septic shock and mortality. Notably, this is the first documented study that dissects bloodstream infections episodes among neutropenic blood cancer patients in Qatar.

In conclusion, our study showed a high prevalence of GN-BSI among patients with hematological malignancies and highlighted an increased presence of antimicrobial resistance among GNB

particularly *E. coli* and *Klebsiella sp.* to all antimicrobial agents that are recommended for empirical treatment, we also observed a high mortality rate for patients in their active phase of treatment (induction and consolidation therapy).

Our analysis of the regional distribution pattern and susceptibility of pathogens as well as the resulting complications in the course of treatment with deteriorated patient outcomes invites us (i) to change our strategy of empirical anti-therapy targeting resistant GNB proportion in particular *E. coli* and *Klebsiella sp.*; (ii) to establish an active and time-effective surveillance for resistant bacteria (e.g MRSA, VRE, ESBL and MDRO); (iii) to screen patients on initial and subsequent admissions as they come from geographical regions with high rates of MDR pathogens, and (iv) to treat colonized patients, introduce vigilant antibiotic prophylaxis in our center, strengthen infection control interventions, and be committed with stewardship program [48,49].

Declaration of Competing Interest

Authors declare no conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2023.11.017.

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