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Epidemiology and Antibiotic Resistance of Bacterial Bloodstream Infections in Hematological Malignancies: A 7-Year Study from Northeastern Iran

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ABSTRACT

Background: Bacterial bloodstream infections (BSIs) are a major challenge in patients with hematological malignancies. This study aimed to evaluate the epidemiology and antimicrobial susceptibility patterns of bacterial pathogens causing BSI in a tertiary care center in Northeastern Iran.

Methods: We conducted a retrospective study of 107 BSI episodes in patients with hematological malignancies (2011–2018). Neutropenia was defined as an absolute neutrophil count (ANC) <1500/µL. Antimicrobial susceptibility testing (AST) was performed using the disk diffusion method in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines. Data were analyzed using descriptive statistics, and group comparisons were performed using the Chi-square or Fisher's exact test.

Results: Among 107 BSI episodes, 62 (57.9%) patients were neutropenic. Acute myeloid leukemia (41.1%) was the most frequent underlying malignancy. Predominant isolates were Staphylococcus aureus (15.9%), Acinetobacter spp. (15.0%), Enterococcus spp. (13.1%), and Staphylococcus epidermidis (12.1%). Neutropenia was significantly associated with S. aureus and Escherichia coli infections ($P < 0.05$). S. epidermidis showed high susceptibility to vancomycin (92.3%), and Enterococcus spp. to linezolid (78.6%). Significant variations in susceptibility patterns were observed, reflecting the need for region-specific empirical therapy.

Conclusion: The distinct antimicrobial resistance patterns observed in our study, particularly concerning *S. aureus* and *Enterococcus* spp., underscore the critical need for region-specific empirical therapy in patients with hematological malignancies. Our findings highlight the significant burden of *S. aureus* and *E. coli* infections in both neutropenic and non-neutropenic patients, emphasizing the importance of vigilant monitoring and tailored treatment strategies. Ongoing surveillance and the judicious use of agents like vancomycin against susceptible pathogens remain essential for improving clinical outcomes in this vulnerable population.

Keywords: Antibiotics, Multidrug resistance, Hematological malignancy, Resistance patterns.

Introduction

Infections remain a major cause of morbidity and mortality among patients with various neoplasms. Advances in infection prevention and management programs for cancer patients have significantly reduced infection-related mortality. Prompt initiation of appropriate antimicrobial therapy is particularly effective in lowering mortality among patients with leukemia and bacteremia, while the administration of broad-spectrum prophylactic antibiotics to afebrile neutropenic patients has been shown to markedly reduce both the incidence of febrile neutropenia and the risk of severe infectious complications. Nevertheless, the widespread use of prophylactic and empiric broad-spectrum antibiotics has contributed to the emergence of multidrug-resistant (MDR) pathogens, posing new challenges in the management of bloodstream infections (BSIs) among patients with hematological malignancies (1, 2).

Bloodstream infections (BSIs) are a serious and frequent complication in immunocompromised individuals with

hematological disorders, especially those undergoing hematopoietic stem cell transplantation or intensive chemotherapy (3, 4). These infections contribute to prolonged hospitalization, treatment delays, and increased mortality, thereby worsening patient prognosis (3). Both Gram-positive and Gram-negative bacteria are major causative agents of BSIs in this patient population (3, 5, 6).

The reported prevalence of bacteremia in patients with hematological malignancies varies across studies, ranging from 11% to 38% (7). Although the exact global burden is unclear, mortality rates have been reported between 14% and 20% (8). The epidemiology of BSIs among patients with hematological malignancies differs geographically, with higher mortality rates observed in low- and middle-income countries. This disparity is largely attributed to delays in initiating therapy and the high prevalence of resistance to commonly used antimicrobials (9).

Given the significant regional variations in microbial epidemiology and the evolving landscape of antimicrobial resistance, localized studies are essential to inform effective clinical practices. In many regions, including the Middle East, the shifting patterns of both Gram-positive and Gram-negative pathogens necessitate continuous surveillance to optimize empirical antibiotic therapy and improve patient outcomes.

Effective selection of empirical antibiotic regimens requires comprehensive knowledge of the causative organisms and their antimicrobial resistance profiles. Research in this area is crucial to guide screening, prevention, and empirical treatment strategies (10). The present study aims to identify the bacterial pathogens responsible for BSIs and evaluate their antimicrobial resistance patterns in patients with hematological malignancies at a major referral center in northeast Iran.

Method

This retrospective study was conducted in the Hematology Department of Imam Reza Hospital, Mashhad, Iran, covering the period from 2011 to 2018. Eligible participants included all patients with a confirmed diagnosis of hematological malignancies and bacteremia. Data were obtained from both electronic medical records and physical patient charts.

Information was systematically collected using a standardized checklist, which included demographic details, type of hematological malignancy, relevant medical history, microbiological findings, treatment regimens, antibiotic resistance profiles, clinical manifestations of the current infection, and patient outcomes. Cases with incomplete or missing essential data were excluded from the analysis.

Statistical analysis was performed using SPSS software (version 26; IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was applied to assess the normality of data distribution. Continuous variables were summarized as mean ± standard deviation (SD), along with minimum and maximum values, while categorical variables were expressed as frequencies and percentages. Comparisons of pathogen distribution between groups were conducted using the independent t-test. A p-value <0.05 was considered statistically significant.

susceptibility testing was conducted following the most recent CLSI guidelines available at the time of each specimen's analysis, ensuring that all interpretations were consistent with the clinical standards of that specific year.

Antimicrobial susceptibility testing was performed using the Kirby-Bauer Disk Diffusion method with standardized antibiotic discs which adhere to the exact concentrations specified by the CLSI guidelines.

Results

A total of 107 single BSI episodes in patients with hematological malignancies were included in the analysis, with each patient representing one episode. Of these, 60 episodes (56.1%) involved male patients, with a mean age of 43.8 ± 18.6 years. The most common hematological malignancy was acute myeloid leukemia (AML), accounting for 44 cases (41.1%), followed by acute lymphoblastic leukemia (ALL) in 26 cases (24.3%). The mean duration of hospitalization was 20 ± 1.3 days. During the study period, 68 patients (64%) survived until discharge.

Microbiological analysis revealed that the most frequently isolated pathogen was *Staphylococcus aureus* (15.9%), followed by *Acinetobacter* spp. (15%), *Enterococcus* spp. (13.1%), and *Staphylococcus epidermidis* (12.1%). The complete distribution of pathogens is presented in Table 1.

Table 1. Distribution of bacterial pathogens isolated from patients with hematological malignancies and bacteremia

Pathogen type	Number of episodes (n)	Percentage (%)
Staphylococcus aureus	17	15.9
Acinetobacter spp.	16	15.0
Enterococcus spp.	14	13.1
Staphylococcus epidermidis	13	12.1
Klebsiella pneumoniae	10	9.3
Escherichia coli	10	9.3
Other cases*	10	9.3
Pseudomonas spp.	7	6.5
Staphylococcus lugdunensis	2	1.9
Total	99	100.0

***Includes *Bacillus, Proteus mirabilis, Pneumococcus, Klebsiella oxytoca,* Unidentified Gram-positive Bacilli, *Streptococcus viridans*, and *Micrococcus*.**

Table 2. Distribution of bacterial pathogens in neutropenic and non-neutropenic patients

Pathogen type	Neutropenic patients (N= 62)	Non-neutropenic patients (N= 45)	P value**
Staphylococcus aureus	10 (58.8%)	7 (41.2%)	0.042
Acinetobacter	8 (50.0%)	8 (50.0%)	0.99
Enterococcus	11 (78.6%)	3 (21.4%)	0.08
Staphylococcus Epidermidis	6 (46.2%)	7 (53.8%)	0.74
Klebsiella pneumoniae	6 (60%)	4 (40.0%)	0.71
Escherichia coli	9 (90%)	1 (10.0%)	0.01
Pseudomonas spp.	3 (42.9%)	4 (57.1%)	0.67
Staphylococcus lugdunensis	2 (100%)	0 (0.0%)	0.50
Other pathogens	4 (40.0%)	6 (60.0%)	0.442
Total	59	40	-

***Includes *Bacillus, Proteus mirabilis, Pneumococcus, Klebsiella oxytoca,* Unidentified Gram-positive Bacilli, *Streptococcus viridans*, and *Micrococcus*.**

Percentages are calculated based on the 99 culture-positive episodes. The 8 culture-negative cases were excluded from the pathogen distribution analysis.

It should be noted that Neutropenia was defined as an absolute neutrophil count (ANC) <1500/µL, encompassing mild, moderate, and severe neutropenia. Using this definition, neutropenia was present in 62 episodes (42.1%). The distribution of pathogens between neutropenic and non-neutropenic groups is presented in Table 2. Notably, neutropenic episodes demonstrated a significantly higher incidence of infections caused by Staphylococcus aureus and *Escherichia coli* (P<0.001).

Antibiotic susceptibility testing demonstrated that vancomycin exhibited the highest susceptibility, with 92.3% of *Staphylococcus epidermidis* and 82.35% of *Staphylococcus aureus* isolates classified as susceptible. Furthermore, *Enterococcus* species showed 78.6% sensitivity to linezolid, while *S. aureus* isolates displayed 52.9% susceptibility to ciprofloxacin. Comprehensive susceptibility profiles for all tested antibiotics are summarized in Table 3.

Discussion

This investigation aimed to delineate the microbial spectrum and antibiotic resistance patterns in BSI episodes among patients with hematological malignancies. The most frequently identified pathogens in our study population were *Staphylococcus aureus* and *Acinetobacter* spp. Notably, *Staphylococcus epidermidis* exhibited high susceptibility to vancomycin (92.3%), underscoring the need for ongoing monitoring of resistance trends. We observed a statistically significant association between neutropenia and infections caused by *S. aureus* and *Escherichia coli*. While neutropenia is a critical predisposing factor for these infections, our findings highlight that non-neutropenic patients also constitute a significant proportion of the infected population, necessitating vigilant screening and empirical management in this subgroup as well.

Table 3. The sensitivity of common pathogens to various antibiotics

Antibiotics (n=17)	*S. epidermidis* (n=13)	*Enterococcus* (n=14)	*Acinetobacter* (n=16)	*S. aureus*
Vancomycin	12 (92.3%)	2 (14.3%)	0 (0.0%)	14 (82.4%)
Linezolid	0 (0.0%)	11 (78.6%)	0 (0.0%)	0 (0.0%)
Gentamicin	5 (38.5%)	1 (7.1%)	3 (18.8%)	5 (29.4%)
Ciprofloxacin	5 (38.5%)	0 (0.0%)	1 (6.3%)	9 (52.9%)
Colistin	0 (0.0%)	1 (7.1%)	(81.3%)	0 (0.0%)
Teicoplanin	2 (15.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ceftazidime	0 (0.0%)	0 (0.0%)	1 (6.3%)	2 (11.8%)
Cefazolin	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (17.6%)
Meropenem	0 (0.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)
Ampicillin	0 (0.0%)	1 (7.1%)	1 (6.3%)	0 (0.0%)

Despite an increasing prevalence of Gram-positive pathogens in some regions, the surge in antibiotic-resistant strains among Gram-negative bacteria poses a greater threat, particularly within the *Enterobacteriaceae* family, where rising resistance has complicated management and increased complication rates (11). Mikulska et al., in a multicenter study across 39 sites in 18 countries, documented a global shift in bacteremia etiology among adult cancer patients, from Gram-positive to Gram-negative predominance (5), a finding echoed across multiple regions (6, 12-14). However, our results diverge from this trend, with Gram-positive bacteria still representing the leading cause of bacteremia in our study.

This regional difference may reflect variability in local epidemiology, patient case-mix, infection control practices, and antimicrobial exposure patterns. In particular, the higher frequency of Gram-positive pathogens in our study may be related to the predominance of central-line–associated infections and skin flora translocation in hematology patients. Such differences underscore that bacteremia epidemiology is strongly influenced by local healthcare settings and cannot be generalized across institutions.

Comparable studies worldwide illustrate striking geographic variation. Choi et al. in Korea reported Gram-negative dominance, with *E. coli* as the most common pathogen and high rates of vancomycin resistance in *E. faecium* (15). In Palestine, nearly half of the isolates were Gram-negative, led by *Pseudomonas aeruginosa* and *E. coli*, while all *S. epidermidis* strains were resistant to oxacillin and cephalosporins (16). A large Japanese cohort similarly identified *E. coli* as the leading pathogen, with fluoroquinolone resistance as the major concern (15). In Lebanon, Gram-negative bacteria accounted for 65% of BSIs, with 80% of *E. coli* strains producing ESBLs and more than 60% of isolates in neutropenic patients being multidrug resistant (17). Brazilian data showed 35.5% Gram-negative prevalence, of which 17.3% were carbapenem-resistant (3). By contrast, Rezvani et al. in Iran reported Gram-negative bacteria as the predominant cause (45.3%), followed by Gram-positive pathogens and fungi (5), whereas our study identified *S. aureus* as the most frequent isolate, reinforcing regional differences in epidemiology.

The widespread use of fluoroquinolones and cotrimoxazole as prophylaxis in hematology patients has been implicated in rising resistance rates (3, 4).

The rising resistance to fluoroquinolones and cotrimoxazole, observed in our study, aligns with findings from other regional studies, most notably the work by Rezvani et al. in Shiraz. While Rezvani et al. reported significantly high resistance rates in their 2016–2017 cohort (15). However, these comparisons highlight critical variations in local epidemiology. For instance, while Rezvani et al. identified *E. coli* (20.9%) and *Non-albicans Candida* (20.9%) as the predominant pathogens in their population, our study observed a distinct distribution, with *S. aureus* (15.9%) and *Acinetobacter* spp. (15%) being the most frequent isolates. This shift towards a Gram-positive dominance in our center, compared to the Gram-negative prevalence reported in the Shiraz study, may reflect differences in local antibiotic stewardship programs, varying institutional prophylactic protocols, or distinct patient admission profiles.

Furthermore, the high resistance rates observed in both studies suggest that the widespread empirical use of fluoroquinolones as prophylaxis in hematology-oncology wards is reaching a threshold of diminishing clinical utility, necessitating an urgent re-evaluation of local antimicrobial guidelines.

Mortality in our study was higher than the 13.2–25.5% reported from European and American centers (11, 18-20). This discrepancy may be due to differences in patient populations, healthcare resources, or bacterial virulence factors and merits further study.

This study has several limitations that should be acknowledged. Primarily, being a single-center study, the findings might reflect institution-specific practices, thus limiting their broader generalizability. A significant constraint was the absence of molecular typing and specific assays for ESBL or carbapenemase detection; consequently, our resistance profiles are limited to phenotypic data, preventing the identification of clonal spread or precise resistance mechanisms.

Furthermore, the lack of systematic data on prior antibiotic exposure and total blood culture volume restricts our ability to correlate treatment patterns with resistance emergence or to definitively calculate BSI incidence. Regarding blood culture interpretation, our analysis did not specifically differentiate between clinically significant coagulase-negative staphylococci (CoNS) and potential contaminants, which may have led to an overestimation of CoNS-related bacteremia. Additionally, the categorization of some bacilli as ‘unidentified’ and the limitation of our susceptibility testing panel may have resulted in an underrepresentation of certain pathogens or resistance patterns. While these constraints reflect the challenges of retrospective real-world data, they highlight the need for more robust, prospective designs in future research to incorporate molecular diagnostics and comprehensive clinical data tracking.

Taken together, the evidence indicates a growing global threat from ESBL-producing Enterobacteriaceae, carbapenem-resistant Gram-negative bacilli, and vancomycin-resistant enterococci. These findings highlight the urgency of region-specific surveillance and antimicrobial stewardship. Effective strategies should include robust monitoring of bloodstream infections, timely intervention with appropriate therapy, and rational antibiotic selection guided by susceptibility profiles. Such measures are essential to improve patient outcomes, reduce complications, and ultimately lower mortality in hematology patients.

Conclusion

In conclusion, our study reveals a distinct epidemiological profile of bloodstream infections in hematology patients in Northeastern Iran, characterized by the predominance of Gram-positive pathogens—a finding that diverges from global trends toward Gram-negative dominance. Given the high resistance rates observed, we recommend that empirical antibiotic regimens in our setting be tailored to favor agents with robust activity against local Staphylococcal strains while maintaining coverage for resistant Gram-negative organisms. Furthermore, the substantial resistance to fluoroquinolones observed suggests an urgent need to re-evaluate the utility of universal fluoroquinolone prophylaxis in this population, potentially shifting toward targeted strategies. Finally, implementing continuous, high-fidelity local surveillance and formal antimicrobial stewardship programs is critical to track emerging resistance and guide evidence-based adjustments to institutional guidelines. These measures are essential to optimize clinical outcomes and mitigate the impact of antimicrobial resistance in this vulnerable study.

Data acquisition and ethical considerations

This study was conducted in full accordance with the ethical principles of the Declaration of Helsinki. The present study was approved by the Ethics committee of Mashhad University of Medical Sciences (Code: IR.MUMS.REC.1401.223).

Conflict of interest

The authors declare no potential conflicts of interests.

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Data availability statement

Data available on request from the authors.

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Author′s contribution

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Declaration of Generative AI and AI-assisted Technologies in the Writing Process

In the development and composition of this document, generative AI was not utilized beyond the scope of fundamental grammar, spelling, and reference verification tools.

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