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Original Article

Bloodstream Infections in Febrile Neutropenic Patients Post Bone Marrow Transplantation, Microbial Profile and Antimicrobial Susceptibility Patterns

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ABSTRACT

Background: Bloodstream infections remain a significant cause of morbidity and mortality in febrile neutropenic patients undergoing bone marrow transplantation.

Objective: This study aimed to identify the microbial profile and antimicrobial susceptibility patterns in bone marrow transplantation recipients with febrile neutropenia at a tertiary care center.

Methods: A retrospective analysis of blood culture results and antimicrobial susceptibility patterns was conducted from 16 febrile neutropenic patients who underwent bone marrow transplantation at Montaserieh Hospital in Mashhad, Iran. Demographic data, presence of central venous catheters, isolated microorganisms, and antibiotic susceptibility profiles were analyzed.

Results: The majority of patients were female (62.5%) and under 10 years of age (37.5%). All patients had central venous catheters. Gram-positive bacteria predominated (68.7%), with Staphylococcus epidermidis being the most common isolate (25%), followed by Enterococcus spp. (18.8%). Among Gram-negative bacteria, Klebsiella pneumoniae was most prevalent (18.8%). All infections were monomicrobial, with no polymicrobial or fungal infections detected. Gram-negative isolates showed highest resistance to levofloxacin, cefazolin, and cotrimoxazole, while remaining highly susceptible to imipenem. Gram-positive bacteria exhibited highest resistance to oxacillin, with preserved susceptibility to vancomycin, linezolid, and gentamicin.

Conclusion: Gram-positive cocci, particularly coagulase-negative staphylococci, are the predominant cause of bloodstream infections in febrile neutropenic bone marrow transplantation patients, likely associated with central venous catheter use. The observed resistance patterns have important implications for empiric antimicrobial therapy, suggesting that vancomycin or linezolid combined with carbapenems may be appropriate initial treatment for febrile neutropenia in this population. Implementing antimicrobial stewardship and improving catheter care practices are essential strategies to address these findings.

KEYWORDS: Febrile neutropenia; Bone marrow transplantation; Antimicrobial resistance; Antimicrobial Susceptibility; Microbial Profile; Central venous catheter

INTRODUCTION

Febrile neutropenia represents one of the most serious complications in patients undergoing bone marrow transplantation (BMT), with bloodstream infections (BSIs) being a leading cause of morbidity and mortality in this vulnerable population. The profound immunosuppression resulting from intensive conditioning regimens, prolonged neutropenia, and disruption of mucosal barriers significantly increases susceptibility to bacterial and fungal infections [1-3]. Additionally, the routine use of central venous catheters (CVCs) for medication administra-

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tion and blood sampling provides a potential portal of entry for pathogens [4].

The etiology of BSIs in neutropenic patients has evolved significantly over the past several decades. Historically, Gram-negative bacteria were the predominant pathogens; however, many centers have reported a shift toward Gram-positive organisms since the 1990s [5, 6]. This epidemiological transition has been attributed to multiple factors, including the widespread use of fluoroquinolone prophylaxis, increased use of indwelling vascular catheters, and intensified chemotherapeutic regimens causing severe mucositis [1, 6].

The emergence and spread of antimicrobial resistance represents another critical challenge in managing febrile neutropenia. The increasing prevalence of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, carbapenem-resistant organisms, methicillin-resistant Staphylococcus aureus (MRSA), and vancomycin-resistant enterococci (VRE) has substantially complicated the selection of appropriate empirical antimicrobial therapy [2, 6]. This situation is particularly concerning in regions with limited resources and high rates of antimicrobial resistance, where delayed or ineffective antimicrobial therapy can significantly increase mortality rates [2, 3].

The empirical management of febrile neutropenia relies heavily on knowledge of local epidemiology and antimicrobial susceptibility patterns [1]. However, data on the microbial etiology and resistance profiles of BSIs in BMT recipients from many regions, including Iran, remain limited [3]. In particular, comprehensive data from transplant centers in Mashhad, the second most populous city in Iran, are scarce. Such information is crucial for guiding empirical antibiotic choices and developing institutional protocols for the management of febrile neutropenia [4].

In this study, we aimed to characterize the microbial profile and antimicrobial susceptibility patterns of BSIs in febrile neutropenic patients undergoing BMT at a specialized transplant center in Mashhad, Iran. We hypothesized that understanding local epidemiology and resistance patterns would provide valuable insights to optimize empirical antimicrobial regimens, improve infection prevention strategies, and ultimately enhance patient outcomes.

MATERIALS AND METHODS

Study Design and Patient Population

We conducted a retrospective observational study of febrile neutropenic patients who underwent bone marrow transplantation at Montaserieh Hospital, a tertiary care center in Mashhad, Iran. The study included all BMT recipients with febrile neutropenia who had positive blood cultures between January 2020 and December 2021. During the study period, 238 patients underwent bone marrow transplantation at our center; 16 of them developed microbiologically confirmed bloodstream infections and met the inclusion criteria. Febrile neutropenia was defined as a single oral temperature of ≥38.3°C or a temperature of ≥38.0°C sustained over one hour, in a patient with an absolute neutrophil count (ANC) <500 cells/μL or expected to fall below 500 cells/μL within 48 hours [1]. Patients with incomplete medical records or with blood cultures obtained after initiation of antimicrobial therapy were excluded.

Data Collection

Patient data were extracted from medical records using a standardized form. Demographic information included age, sex, and underlying disease necessitating BMT. Clinical data comprised the presence of central venous catheters, antimicrobial prophylaxis regimens, and empirical antibiotics administered for febrile neutropenia. Microbiological data included all blood culture results obtained during febrile episodes, isolated pathogens, and their antimicrobial susceptibility profiles.

Microbiological Methods

Blood samples were collected during febrile episodes in accordance with the hospital's standard operating procedures. For each patient, at least two sets of blood cultures were

Table 1: Demographic and clinical characteristics of febrile neutropenic bone marrow transplant recipients (n= 16).

Characteristic	n (%)
Age group (years)	
<10	6 (37.5)
10–20	3 (18.8)
20–30	3 (18.8)
>30	4 (25.0)
Sex	
Female	10 (62.5)
Male	6 (37.5)
Underlying disease	
Multiple myeloma	4 (25.0)
Acute lymphoblastic leukemia	3 (18.8)
Acute myeloid leukemia	3 (18.8)
Other diseases	6 (37.5)
Central venous catheter present	16 (100.0)

obtained from different venipuncture sites or from both the central venous catheter and a peripheral vein. Blood samples were cultured using the BACTEC automated blood culture system (Becton Dickinson, USA) [7]. Positive cultures were processed for identification and antimicrobial susceptibility testing according to the Clinical and Laboratory Standards Institute (CLSI) guidelines [8, 9].

Microbial identification was performed using standard biochemical methods and confirmed by automated systems where available. Antimicrobial susceptibility testing was conducted using the disk diffusion method for a panel of antibiotics relevant to each isolate, including penicillins, cephalosporins, carbapenems, aminoglycosides, fluoroquinolones, glycopeptides, and oxazolidinones. Results were interpreted as susceptible, intermediate, or resistant according to CLSI breakpoints [8].

Ethical Considerations

The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences (Approval code: IR.MUMS.REC.1401.269). As this was a retrospective study using anonymized data, the requirement for individual informed consent was waived.

Table 2: Distribution of microorganisms isolated from blood cultures of febrile neutropenic bone marrow transplant recipients (n= 16 isolates).

Microorganism	n (%)
Gram-positive bacteria	11 (68.7)
Staphylococcus epidermidis	4 (25.0)
Enterococcus spp.	3 (18.8)
Other Gram-positive bacteria	4 (25.0)
Gram-negative bacteria	5 (31.3)
Klebsiella pneumoniae	3 (18.8)
Escherichia coli	2 (12.5)
Fungal isolates	0 (0.0)
Infection type	
Monomicrobial infections	16 (100.0)
Polymicrobial infections	0 (0.0)

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics and microbiological findings. Categorical variables were presented as frequencies and percentages, while continuous variables were expressed as means and standard deviations or medians and interquartile ranges, as appropriate. Data analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient Characteristics

A total of 16 febrile neutropenic patients who underwent BMT during the study period were included in the analysis. Patient characteristics are summarized in Table 1. The majority were female (62.5%, n=10), and 37.5% (n=6) were under 10 years of age. The most common underlying disease was multiple myeloma (25%, n=4), followed by acute lymphoblastic leukemia (18.75%, n=3), acute myeloid leukemia (18.75%, n=3), and other hematological malignancies or disorders. All patients (100%, n=16) had central venous catheters in place at the time of the febrile episode.

Microbial Profile

The distribution of microorganisms isolated from blood cultures is presented in Table 2 and Fig. 1. Gram-positive bacteria were the

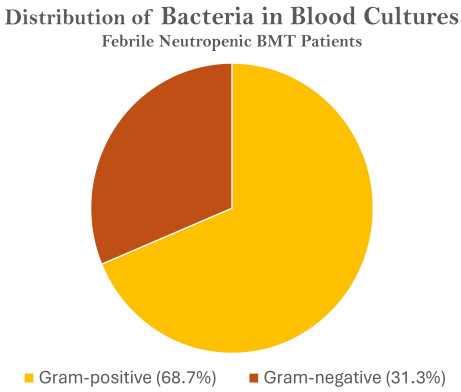

Figure 1: Distribution of Gram-positive and Gram-negative bacteria isolated from blood cultures. This pie chart shows the distribution of Gram-positive and Gram-negative bacterial isolates obtained from blood cultures of febrile neutropenic bone marrow transplant recipients (n= 16 isolates). Gram-positive bacteria accounted for 11 isolates (68.7%), while Gram-negative bacteria accounted for 5 isolates (31.3%).

predominant causative agents, accounting for 68.7% (n=11) of all isolates, while Gram-negative bacteria represented 31.3% (n=5). No fungal pathogens were isolated from any of the blood cultures.

Among Gram-positive bacteria, *coagulase-negative staphylococci*, specifically *Staphylococcus epidermidis*, were the most frequently isolated organism (25%, n=4), followed by Enterococcus species (18.8%, n=3), and *Staphylococcus aureus* (12.5%, n=2). Other Gram-positive isolates included *Streptococcus viridans* (6.25%, n=1) and *Streptococcus pneumoniae* (6.25%, n=1) (Fig. 2).

Klebsiella pneumoniae was the most prevalent Gram-negative organism (18.8%, n=3), followed by *Escherichia coli* (12.5%, n=2). No cases of *Pseudomonas aeruginosa*, Acinetobacter species, or other multidrug-resistant Gram-negative bacteria were identified in our cohort.

All infections were monomicrobial, with no polymicrobial BSIs identified in our cohort.

Antimicrobial Susceptibility Patterns

The antimicrobial susceptibility patterns of Gram-positive and Gram-negative isolates are presented in Tables 3 and 4, respectively, and visualized in Fig. 3.

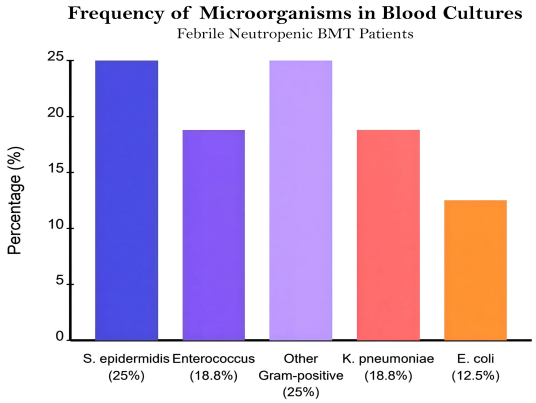

Figure 2: Frequency of different microorganisms isolated from blood cultures. This bar graph shows the distribution of bacterial species isolated from blood cultures of febrile neutropenic bone marrow transplant recipients (n= 16 isolates). Gram-positive isolates included Staphylococcus epidermidis (4 isolates, 25.0%), Enterococcus spp. (3 isolates, 18.8%), and other Gram-positive bacteria (4 isolates, 25.0%). Gram-negative isolates included Klebsiella pneumoniae (3 isolates, 18.8%) and Escherichia coli (2 isolates, 12.5%).

Gram-positive isolates showed the highest resistance to oxacillin (43.9%), followed by ciprofloxacin (37.6%), clindamycin (37.6%), and cotrimoxazole (37.6%). The highest susceptibility was observed for vancomycin (56.4%), linezolid (56.4%), and gentamicin (56.4%).

Gram-negative isolates demonstrated the highest resistance to levofloxacin (80%), cefazolin (80%), and cotrimoxazole (80%). The highest susceptibility was observed for imipenem (100%), followed by amikacin (80%) and gentamicin (60%).

DISCUSSION

This retrospective study investigated blood culture results and antimicrobial susceptibility patterns of bacteria isolated from febrile neutropenic patients undergoing bone marrow transplantation at Montaserieh Hospital in Mashhad. Our findings provide valuable insights into the local epidemiology of BSIs and antimicrobial resistance patterns in this high-risk population.

A key finding of our study was the predominance of Gram-positive bacteria (68.7%) as

Table 3: Antimicrobial susceptibility pattern of Gram-positive isolates from blood cultures of febrile neutropenic bone marrow transplant recipients (n= 11 isolates).

Antibiotic	Susceptible n (%)	Intermediate n (%)	Resistant n (%)
Vancomycin	6 (54.5)	5 (45.5)	0 (0.0)
Linezolid	6 (54.5)	5 (45.5)	0 (0.0)
Gentamicin	6 (54.5)	4 (36.4)	1 (9.1)
Oxacillin	2 (18.2)	4 (36.4)	5 (45.5)
Ciprofloxacin	3 (27.3)	4 (36.4)	4 (36.4)
Clindamycin	2 (18.2)	5 (45.5)	4 (36.4)
Cotrimoxazole	2 (18.2)	5 (45.5)	4 (36.4)

causative agents of BSIs, with *Staphylococcus epidermidis* (25%) being the most frequently isolated pathogen. This observation is consistent with trends reported in Western countries and in some Asian centers, where a shift from Gram-negative to Gram-positive infections has been documented over the past several decades [5, 10]. However, our findings contrast with some studies from the Middle East [11] and other regions of Iran that have reported Gram-negative bacteria as the predominant cause of BSIs in neutropenic patients [12].

The high prevalence of *Staphylococcus epidermidis* in our study population is noteworthy and likely reflects the universal use of central venous catheters among our patients. The second most common Gram-positive isolate in our study was *Enterococcus* species (18.8%). The increasing recognition of *enterococci* as important pathogens in neutropenic patients aligns with global trends and highlights the changing epidemiology of infections in this population [13].

All positive blood cultures in our study were monomicrobial, with no polymicrobial infections identified. This finding is consistent with some studies conducted in the Middle East, such as the study by El Omri *et al.* in Qatar, which reported 83% monomicrobial BSIs [14], and the study by Mandal *et al.* in India, which similarly found that all blood cultures were monomicrobial [15]. However, globally, the reported incidence of polymicrobial BSIs ranges from 5% to 15% and is associated with higher mortality than monomicrobial infections [16].

The absence of polymicrobial infections in our study may be attributed to methodological limitations, including the use of conventional microbial culture methods that might preferentially identify dominant microorganisms [17]. Additionally, the relatively small sample size of our study may have limited the detection of less common polymicrobial infections.

Despite the high risk of invasive fungal infections in neutropenic patients, no fungal pathogens were isolated from the blood cultures in our study. This finding is somewhat unexpected, as invasive candidiasis and aspergillosis are recognized complications in patients with prolonged neutropenia, particularly those undergoing hematopoietic stem cell transplantation [18]. Like another similar study [19], the absence of fungal BSIs in our cohort may be attributed to several factors, including effective antifungal prophylaxis practices at our institution, limited sensitivity of blood cultures for detecting fungal pathogens, or the relatively small sample size.

The antimicrobial susceptibility profiles observed in our study raise significant concerns regarding resistance patterns in our setting. Among Gram-negative bacteria, high resistance rates were observed for commonly used antibiotics including levofloxacin, cefazolin,

Table 4: Antimicrobial susceptibility pattern of Gram-negative isolates from blood cultures of febrile neutropenic bone marrow transplant recipients (n= 5 isolates).

Antibiotic	Susceptible n (%)	Intermediate n (%)	Resistant n (%)
Imipenem	5 (100.0)	0 (0.0)	0 (0.0)
Amikacin	4 (80.0)	0 (0.0)	1 (20.0)
Gentamicin	3 (60.0)	0 (0.0)	2 (40.0)
Levofloxacin	1 (20.0)	0 (0.0)	4 (80.0)
Cefazolin	1 (20.0)	0 (0.0)	4 (80.0)
Cotrimoxazole	1 (20.0)	0 (0.0)	4 (80.0)

and cotrimoxazole. These findings align with a study by Abdollahi *et al.* in Isfahan, which reported high resistance to cotrimoxazole across various microorganisms isolated from neutropenic patients [20]. Notably, imipenem demonstrated 100% efficacy against Gram-negative isolates in our study, consistent with findings from Zimmer *et al.*, who reported 96% sensitivity to carbapenems in Gram-negative bacteria isolated from febrile neutropenic patients [21]. Carbapenems remain valuable therapeutic options for serious infections caused by Gram-negative bacteria, particularly in settings with high rates of ESBL production [22]. However, the emergence of carbapenem-resistant Enterobacteriaceae (CRE) in many regions emphasizes the need for judicious use of these agents and ongoing surveillance of resistance patterns [23].

Among Gram-positive bacteria, the high oxacillin resistance rate (90.9%) is particularly concerning, as it indicates widespread methicillin resistance among *staphylococcal* isolates. All *Staphylococcus epidermidis* isolates in our study were methicillin-resistant, reflecting global trends of increasing resistance in coagulase-negative *staphylococci* [24]. The preserved susceptibility to vancomycin and linezolid indicates that these agents remain active against Gram-positive isolates for suspected Gram-positive infections in our setting. However, the emergence of vancomycin-intermediate and vancomycin-resistant *staphylococci* in some regions underscores the importance of antimicrobial stewardship and continued monitoring of resistance patterns [25].

Our findings have several important clinical implications for the management of febrile neutropenia in BMT recipients at our institution and in similar settings. First, the predominance of Gram-positive bacteria, particularly coagulase-negative *staphylococci*, suggests that empirical antimicrobial regimens should provide adequate coverage for these pathogens. Given the high rate of methicillin resistance observed, glycopeptides such as vancomycin or oxazolidinones like linezolid should be considered as part of initial therapy when Gram-positive infection is suspected, especially in patients with indwelling central venous catheters.

Second, despite the lower prevalence of Gram-negative infections in our cohort, the potential severity of these infections and the observed resistance patterns warrant careful consideration. The high sensitivity to carbapenems supports their use in empirical regimens, particularly for patients with severe sepsis or septic shock [26]. However, to preserve the effectiveness of these agents, carbapenem-sparing strategies should be implemented whenever possible, based on culture results and clinical response [27].

Third, the universal presence of central venous catheters in our patient population and the high prevalence of *Staphylococcus epidermidis* infections highlight the importance of catheter care practices. Implementation of evidence-based bundles for the insertion and maintenance of central lines, education of healthcare personnel, and adherence to strict

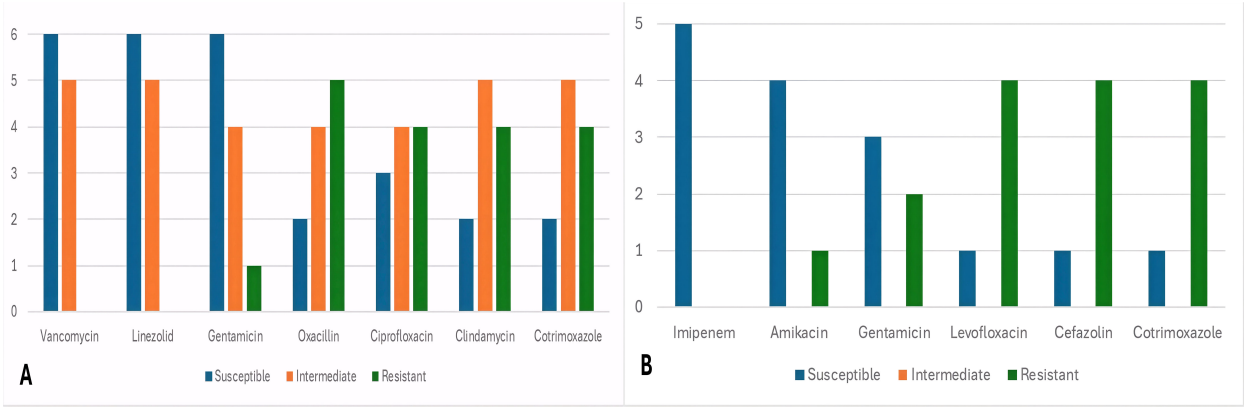

Figure 3: These bar graphs show the antimicrobial susceptibility patterns of Gram-positive bacterial isolates (n= 11 isolates) (**A**) and Gram-negative bacterial isolates (n= 5 isolates) (**B**) recovered from blood cultures of febrile neutropenic bone marrow transplant recipients. Bars represent the percentage of isolates classified as susceptible, intermediate, or resistant according to CLSI criteria.

hand hygiene protocols are essential measures to reduce the incidence of CRBSIs [28].

Finally, the absence of fungal BSIs in our study does not eliminate the need for vigilance regarding invasive fungal infections. Given the limitations of blood cultures for detecting fungi, clinicians should maintain a high index of suspicion for these infections, particularly in patients with persistent or recurrent fever despite broad-spectrum antibiotics [29]. Integration of non-culture-based diagnostic methods into clinical practice may enhance the detection of fungal pathogens and guide antifungal therapy [30].

Our study has several limitations that warrant consideration. First, the retrospective design and reliance on previously collected data may have introduced selection bias and limited access to some clinical information. Second, the relatively small sample size from a single center may limit the generalizability of our findings to other settings or patient populations. Third, the use of conventional microbiological methods without molecular typing techniques precluded more detailed characterization of the isolated pathogens and potential mechanisms of resistance. Fourth, the limited sensitivity of blood cultures for detecting certain pathogens, particularly fungi, may have led to an underestimation of their prevalence. Finally, the lack of information on prior antimicrobial exposure and the impact of prophylactic regimens on the observed microbiological patterns is another limitation. Additionally, the small number of isolates, particularly among Gram-negative bacteria, may limit the stability of susceptibility percentages and should be interpreted with caution.

In conclusion, our study demonstrates that Gram-positive bacteria, particularly *Staphylococcus epidermidis*, are the predominant cause of bloodstream infections in febrile neutropenic patients undergoing bone marrow transplantation at our center in Mashhad, Iran. This finding, likely associated with the universal use of central venous catheters, has important implications for empirical antimicrobial therapy. The observed resistance to beta-lactams among Gram-positive isolates and to various antibiotics among Gram-negative bacteria underscores the therapeutic challenges in this vulnerable population. Based on our findings, these findings may help inform empirical antimicrobial selection in our center; however, larger studies are required to confirm these observations.

Future prospective studies with larger sample sizes, multicenter designs, and more advanced microbiological methods are needed better to characterize the changing epidemiology of infections in this population and to develop evidence-based strategies for prevention and management. Implementing robust antimicro-

bial stewardship programs, enhancing infection control practices, and improving catheter care protocols are essential approaches to addressing the challenges identified in our study and improving outcomes for BMT recipients with febrile neutropenia.

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