ORIGINAL ARTICLE

The burden, risk factors, causative pathogens, and outcome of bloodstream infections in hematopoietic stem cell transplant recipients; single center experience from Pakistan

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ABSTRACT

Background: Hematopoietic stem cell transplant (HSCT) is an effective therapeutic option for various metabolic, immunologic, and hematologic disorders and has shown promising results in patients with various hematological malignancies over the years. However, bloodstream infections (BSI) are still one of the leading causes of morbidity and mortality in patients undergoing HSCT. The objective of this study is to evaluate the causative pathogen, risk factors, and outcome of bloodstream infections in HSCT patients.

Material and Methods: A retrospective cohort analysis from January 2019 to July 2021 was carried out on 116 patients who underwent HSCT at the National Institute of Blood Disease and Bone Marrow Transplantation.

Results: Among the 116 patients, 63.8% (n=74) were males and 38.2% (n=42) were females. The median age of the patients was 11 years (range, 0.7 to 62; IQR, 4.7 to 21 years). The incidence of bloodstream infections (BSI) was 37.9% (n=44) at 30 days, 25.0% (n=29) at 60 days, and 19.8% (n=23) at 90 days. A total of one hundred and fifty-five pathogens were detected in 116 patients; among which 103 (66.5%) were Gram-negative and 52 (33.5%) were Gram-positive organisms. Out of the 116 patients, 89.7% (n=104) were successfully treated and the overall mortality rate was 10.3% (n=12) in this study.

Conclusion: Gram-negative bacteria were the most frequently occurring pathogens in BSIs, followed by Gram-positive bacteria. The mortality associated with BSIs can be substantially reduced with the judicious use of empirical antibiotics and the implementation of appropriate infection control measures in transplant care.

Keywords: Hematopoietic stem cell transplant, bloodstream infections, Gram-positive and Gram-Negative organism, immunosuppression

BACKGROUND

Hematopoietic stem cell transplant (HSCT) is an effective therapeutic option for various metabolic, immunologic, and hematologic disorders and has shown promising results in patients with various hematological malignancies over the years.[1] However, bloodstream infections (BSI) are still one of the leading causes of morbidity and mortality in patients undergoing HSCT.[2] The epidemiology of BSIs has been altered over the past few years and has shown key shift from gram negative organisms to gram positive isolates. During the febrile neutropenic phase, Gram-negative BSIs were formerly considered the primary cause of bacteremia in the 1960s and 1970s. However, the etiology of BSIs in this patient population has evolved over the last 2 decades and became predominantly gram-positive; especially the *Viridans group streptococci* and coagulase-negative *staphylococci* were frequently isolated in blood cultures.[3] The principal reason for this shift appears to be the augmented use of prophylactic antibiotics, particularly the fluoroquinolone group against the gram-negative bacteria and an increasing trend towards the use of central venous catheters during the post-transplant period.[4]

There is an upsurge of gram-negative organism isolation observed yet again in HSCT recipients worldwide.[5] In addition to this insurgence, there is a steep elevation in resistance and more resistant microorganisms are now recognized giving rise to the BSIs.[6] The evolution of fluoroquinolone-resistant bacteria, nosocomial

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methicillin-resistant *Staphylococcus aureus* infections, and extended-spectrum beta-lactamase (ESBL) producers, carbapenem-resistant Enterobacteriaceae has led to rise in infection-related mortality or morbidity in neutropenic patients globally.[7] Due to the diversity of pathogens causing BSIs in patients with HSCT and their susceptibility pattern, continuous surveillance of BSIs is imperative to initiate effective empiric antibiotic treatment, a parameter that is closely associated with survival in bacteremic patients.[8] Furthermore, mortality is also high in BSI caused by gram-negative rods compared to gram-positive organisms.[9]

The incidence of bloodstream infections is highest during the pre-engraftment period. [10] The most common risk factors for BSI in the pre-engraftment phase as reported in various studies are mucositis, absolute neutropenia, and the presence of central venous catheters. Underlying hematological disorders, severe acute GvHD, and use of corticosteroids are additional risk factors attributable to serious post-transplant infections.[10]

As a lower-middle-income country, Pakistan faces significant socio-economic challenges related to its healthcare system. Nearly two-thirds of the patient population seeking stem cell transplantation comes from the backland where poor literacy and unfamiliarity among patients and families regarding hygiene and infection control practices makes it quite challenging for transplant physicians to achieve optimal infection control in this group of patients. Keeping in view the lack of data related to bacterial infections and their impact on the outcome of transplant in our setup, the present study aimed to explore the frequency of bacterial infections with respective antibiotic sensitivity patterns and risk factors for BSIs and their association with the clinical characteristics of patients so that judicious empiric antibiotic treatment could be instigated to minimize the infection-related mortality in the HSCT recipients.

MATERIAL AND METHODS

A retrospective cohort analysis from January 2019 to July 2021 was carried out on 116 patients who underwent HSCT at the National Institute of Blood Disease and Bone Marrow Transplantation. Pre-specified clinical variables were retrieved from the medical record and the BMT database. Research involving a human participant's data in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the National Institute of Blood Diseases and Bone Marrow Transplantation (NIBD/IRB-221/14-2021).[11] Informed consent for participants below the age of 16 was obtained from their parents and/or their legal guardians Since the majority of participants lacked literacy, parental legal guardian's informed consent was sought for each participant.

For antimicrobial prophylaxis, ciprofloxacin, fluconazole or voriconazole, and acyclovir were used as antibacterial, anti-fungal, and antiviral agents respectively in all patients until engraftment. Anti-viral prophylaxis continued till the cessation of immunosuppressive therapy. Trimethoprim-sulfamethoxazole was prescribed from day+30 onwards for Pneumocystis carinii prophylaxis till one-year post-HSCT.[12]

Bloodstream infection was defined as the isolation of bacteria not normally known to colonize the skin, such as certain pathogens like *E. coli, Klebsiella* species, and *Staphylococcus aureus* from at least one blood culture.[13] For bacteria that typically colonize the skin, such as coagulase-negative *Staphylococcus, Corynebacterium viridans group of Streptococcus***,** two consecutive positive blood cultures i.e. two positive blood cultures were drawn within 72 hours, or one positive blood culture and one positive intravascular catheter culture within 72 hours constituted a BSI.[14]Neutropenia, defined as an absolute neutrophil count < 500 cells/mm3 within 3 days before or after the positive blood culture All blood cultures were obtained after meeting the criteria of infection, largely fever.[15]

Blood culture isolates were flagged positive and detected using BACTEC 9240 system. Microbiological identification of Gram-positive and negative organisms was performed by conventional biochemical tests and rapid identification of non-fermenter gram-negative rods (IDNF) [16] Antimicrobial susceptibility testing was conducted in accordance with CLSI 2020-21, furthermore, minimal inhibitory concentration (MIC) had also been performed in accordance with CLSI 2020. Statistical analysis was conducted by using the SPSS version 24.0. Continuous variables were expressed as median, range, and interquartile range (non-parametric) and frequency and percentages were computed for categorical variables. The univariate analysis used a

Pearson Chi-square test and Fisher's exact test (both 2-sided) for the comparison of categorical variables, while logistic regression was also applied for multivariate analysis. Factors found to be significant ($P < 0.05$) or marginally significant ($P < 0.25$) in univariate analysis were included in the multivariate analysis using a forward stepwise method to explore the independent effects of different variables on the frequency of BSI. A p-value < 0.05 was considered statistically significant.

RESULTS

The baseline characteristics of the patients are shown in Table-I. Among the 116 patients, 63.8% (n=74) were males and 38.2% (n=42) were females. The median age of the patients was 11 years (range, 0.7 to 62; IQR, 4.7 to 21 years). The age was further stratified into two groups for analysis. Sixty-nine percent (n=81) patients were < 18 years of age while 31% (n=35) patients were ≥ 18 years of age. Forty-five percent (n=53) of patients received gender-matched donor transplants.

Out of the 116 HSCTs, 75.9% (n=88) transplants were done for benign while 24.1% (n=28) for malignant diseases and the indications were mainly β-thalassemia major (BTM) 36.2% (n=42), aplastic anemia (AA), 28.4% (n=33) and acute myeloid leukemia (AML) 8.6% (n=10). Among the donor types, 87.2% (n=78) transplants were matched-related, 18.1% (n=21) transplants were haploidentical, and 14.7% (n=17) were autologous transplants. Around 64.5% (n=75) patients received myeloablative (MAC) conditioning regimens, 30.2% (n=35) received non-myeloablative regimens (NMA), and 5.2% (n=6) received reduced intensity conditioning (RIC) regimens.

The graft source was mainly peripheral blood (PBSC) in 62.1% (n=72), and bone marrow (BM) in 32.8% (n=38) cases, whereas both PBSC and BM in 5.2% (n=6) cases. GvHD prophylaxis was given to all recipients of allogenic HSCT with a calcineurin inhibitor and a short course of methotrexate or mycophenolate mofetil. The median time to neutrophil engraftment was 12 days (range, 8 to 25; IQR, 11 to 15 days), and the median time to platelet engraftment was 12.5 days (range, 9 to 38; IQR, 12 to 15 days).

The incidence of bloodstream infections (BSI) was 37.9% (n=44) at 30 days, 25.0% (n=29) at 60 days, and 19.8% (n=23) at 90 days.

Febrile neutropenia was categorized into two groups; 58.6% (n=68) patients had their first episode within the first 14 days Post-transplant, 4.3% (n=5) patients had their first episode after 14 days of transplant and 37.1% (n=43) patients had missing information regarding the onset of febrile episodes.

Table-II presents an overview of diverse microorganisms obtained in various cultures received from our patient population. A total of one hundred and fifty-five pathogens were detected in 116 patients; among which 103 (66.5%) were Gram-negative and 52 (33.5%) were Gram-positive organisms. Gram-negative organisms accounted for most of the BSIs and the most commonly grown organisms were *Klebsiella pneumoniae* (11.6%) and *Escherichia coli* (11.6%) followed by *Pseudomonas aeruginosa (*9.03%).

Moreover, the data analysis reveals the antibiotic resistance pattern of the main gram-negative rod isolates against major antibiotics as illustrated in Table-III. The most surprising aspect of the data was detecting Carbapenem resistance in *Klebsiella* species and *Escherichia coli.* Ten percent of *Klebsiella* isolates were resistant to Meropenem [MIC >16] while 5% of *Escherichia coli* were resistant to Meropenem. No resistance was found to Fosfomycin in both *Klebsiella* and *E. coli*, whereas only one isolate of *Klebsiella* was resistant to Colistin [MIC >2]. Moreover, the susceptibility pattern revealed variable sensitivity to Amikacin (41.3%) and Ceftriaxone (20.6%) in *Klebsiella* species. Likewise, 55.5 % of E. coli was sensitive to Pip-Tazobactam, 61 % to Amikacin, and only 11.1 % were susceptible to ceftriaxone.

Table-IV explains the sensitivity pattern of the main gram-positive isolates. Interestingly, no resistance was found in *Staphylococcus aureus* to Vancomycin and Linezolid antibiotics, whereas 60% of *Enterococcus* species isolated from blood cultures were found resistant to Vancomycin. Variable resistance patterns to clindamycin, erythromycin, and ciprofloxacin were reported in *Staphylococcus species* and *Staphylococcus aureus* organisms.

Univariate and multivariate analyses were performed for the risk factors associated with bloodstream infections. Univariate analysis demonstrated that the incidence of BSI at 30 days (n=44) was significantly associated with the disease category (p=0.039), conditioning regimen (p<0.001), primary graft failure

(p=0.047), and relapse (p=0.047), Covariates with P < 0.25 in univariate analysis were considered for multivariate analysis. The multivariate analysis demonstrated that the NMA conditioning regimen (OR=12.54, 95% CI: 3.40–46.24; p<0.001), RIC (OR=13.29, 95% CI: 1.12–157.59; p=0.040) compared to MAC, BM (OR=10.12, 95% CI: 1.66–61.92; p=0.012) and both BM and PBSC graft sources (OR=6.17, 95% CI: 1.50–25.27; p=0.011) and relapse (OR=23.62, 95% CI: 1.50–370.36; p=0.024) were statistically significant for BSI at 30 days after HSCT. There was no significant association of any risk factors with BSI at 60- and 90-days Post-transplant in both univariate and multivariate analysis. The univariate and multivariate logistic regression analyses for risk factors affecting BSI at 30, 60, and 90 days are shown in Table-V.

Primary graft failure occurred in 4.3% (n=5) patients, whereas secondary graft failure was observed in 2.6% (n=3) patients. The primary disease was relapsed in 4.3% (n=5) patients. Out of the 116 patients, 89.7% (n=104) were successfully treated and the overall mortality rate was 10.3% (n=12) in this study. The most common cause of death was bacterial infection and sepsis. The significant p value has been noted for graft source and conditioning regimen association with BSI as shown in Table-V.

Overall mortality in this study was 10.3% (12/ 116) due to various causes. Infection-related mortality occurred in 41.6% (5/12) of patients. Closer evaluation of these patients revealed that 2 patients had Gram-negative bacterial sepsis, whereas another two had mixed Gram-negative and Gram-positive bacterial sepsis. One patient died due to a fungal infection documented on chest CT. The causes of death in the remaining 7 patients were severe acute GvHD and relapse of the primary disease.

Table-I: Baseline characteristics of study population (n=116).

		n (%)
Age in years, median (range, IQR)		11 (0.7 to 62; 4.7 to 21)
Implantation time of neutrophils in days (n=96), median (range, IQR)		12 (8 to 25; 11 to 15)
Time of platelet engraftment in days (n=60), median (range, IQR)		12.5 (9 to 38; 12 to 15)
Time of febrile in days (n=77), median (range, IQR)		7 (1 to 29; 5 to 9)
Age groups (years)		
	< 18 years	81 (69.8)
	≥ 18 years	35 (30.2)
Gender		
	Male	74 (63.8)
	Female	42 (38.2)
Gender Matched Donor		
	Female to Male	45 (38.8)
	Same Gender	53 (45.7)
Blood Strem Infection at 30 days		
	Yes	44 (37.9)
	No	72 (62.1)
Blood Strem Infection at 60 days		
	Yes	29 (25.0)
	No	87 (75.0)
Blood Strem Infection at 90 days		
	Yes	23 (19.8)
	No	93 (80.2)
Disease Category		
	Benign	88 (75.9)
	Malignant	28 (24.1)
Conditioning Regimen		
	NM	35 (30.2)
	MAC	75(64.45)
	RIC	6 (5.2)
HSCT Indication		

	Full match	78 (87.2)
	HAPLO	21 (18.1)
	Autologous	17 (14.7)
Graft Source		
	BM	38 (32.8)
	PB	72 (62.1%)
	Both	6 (5.2%)
Antifungal Prophylaxis		
	Fluconazole	107 (92.2)
	Voriconazole	6 (5.2)
Antibacterial Prophylaxis	116 (100)	
GVHD Prophylaxis (Steroids)		
	Yes	55 (47.4)
	No	61 (52.6)
Acute GVHD		
	Yes	16 (13.8)
	No	100 (86.2)
Disease		
	BTM	42 (36.2)
	AA	33 (28.4)
	AML	10 (8.6)
	Hodgkin Lymphoma	5 (4.3)
	Hurler Syndrome	5 (4.3)
	Multiple Myeloma	8 (6.9)
	Fanconi Anemia	2 (1.7)
	Other	11 (9.5)

Table-II: Isolation of Gram Positive and Gram-Negative Organisms from Blood Cultures from Hematopoietic stem cell transplant (HSCT) patients.

Gram positive organisms	**Frequency**	**Percentage** (%)
Coagulase negative Staphylococci	24	15.5
Staphylococcus aureus	18	11.6
Streptococcus species (milleri group)	2	1.29
Enterococcus species	5	3.22
Micrococcus species	3	1.93
Total	**52**	**33.5**
Gram negative organisms	**Frequency**	**Percentage** (%)
Klebsiella pneumoniae	18	11.6
Klebsiella species	11	7.09
Escherichia coli	18	11.61
Enterobacter species	1	0.64
Pseudomonas aeruginosa	14	9.03
Pseudomonas species	33	21.29
Burkholderia cepacia	5	3.22
Alcaligenes xyloxidans	1	0.64
Commamonas species	1	0.64
Flavobacterium species	1	0.64
Total	**103**	**66.5**
Fungi (Candida species)	-	

Table-III: Antimicrobial Resistance Pattern of Major Gram-negative organisms isolated from blood cultures from HSC transplant patients.

Organisms	***Klebsiella species* (29)**		***Escherichia coli* (18)**		***Pseudomonas aeruginosa* (14)**		***Pseudomonas species* (33)**	
Antibiotics	**Frequencies**	**Percentages**	**Frequencies**	**Percentages**	**Frequencies**	**Percentages**	**Frequencies**	**Percentages**
Ampicillin	-	-	16	88.8	-	-	-	-
Amoxicillin/clavulanic acid	20	69	12	67	-	-	31	94
Ceftazidime	-	-	-	-	0	0	5	15
Piperacillin/tazobactam	9	31	8	44.5	1	7	15	45
Ceftriaxone	22	80	4	77.7	-	-	26	79
Cefepime	11	38	6	33.3	2	14	13	39
Meropenem	3	10	1	5	1	7	7	24
Amikacin	17	58.6	8	39	2	14	11	33.3
Tigecycline	9	31	9	50			6	18.1
Ciprofloxacin	15	51.2	13	73	4	39	12	37
Trimethoprim/ sulfamethoxazole	20	69%	13	72	-	-	15	45

Table-IV: Antimicrobial Resistance Pattern of Major Gram-Positive organisms isolated from blood cultures from HSC transplant patients.

	Coagulase-negative Staphylococcus species		***Staphylococcus aureus***		***Enterococcus species***	
Antibiotics	**Number**	**Percentage %**	**Number**	**Percentage %**	**Number**	**Percentage %**
Ampicillin	2	92	0	0	4	80
Cefoxitin/ Methicillin	17	71	10	56		0
Ciprofloxacin	16	67	12	67	0	0
Clindamycin	10	42	12	67	0	0
Erythromycin	12	50	14	77.7	0	0
Linezolid	24	100	18	100	5	100
Vancomycin	24	100	18	100	3	60

Table-V: Univariate and multivariate analysis of risk factors for the blood stream infection after hematopoietic stem cell transplant (HSCT).

		BSI at 30 days (n=44)				**BSI at 60 days (n=29)**				**BSI at 90 days(n=23)**			
		Univariate analysis		**Multivariate analysis**		**Univariate analysis**		**Multivariate analysis**		**Univariate analysis**		**Multivariate analysis**	
	n=116	**n (%)**	**p-value**	**OR (95% CI)**	**p-value**	**n (%)**	**p-value**	**OR (95% CI)**	**p-value**	**n (%)**	**p-value**	**OR (95% CI)**	**p-value**
Age groups (years)													
< 18 years	81	33 (40.7)	0.343			24 (29.6)	0.080	1		15 (18.5)	0.591		
≥ 18 years	35	11 (31.4)				5 (14.3)		0.57 (0.12-2.73)	0.490	8 (22.9)			
Disease Category													
Benign	88	38 (43.2)	0.039*	1		23 (26.1)	0.816			18 (20.5)	0.764		
Malignant	28	6 (21.4)		1.15 (0.18-7.12)	0.875	6 (21.4)				5 (17.9)			
Conditioning Regimen													

M	59	14 (23.7)	<0.001	1		17 (28.8)	0.268			13 (22.0)	0.517	
NM	35	22 (62.9)		12.54 (3.40-46.24)	<0.001*	6 (17.1)				8 (22.9)		
BEAM	16	4 (25.0)		0.91 (0.09-8.52)	0.940	3 (18.8)				1 (6.2)		
RIC	6	4 (66.7)		13.29 (1.12-157.59)	0.040*	3 (50.0)				1 (16.7)		
Graft Source												
PB	22	4 (18.2)	0.068	1		5 (22.7)	0.790			6 (27.3)	0.622	
BM	38	14 (36.8)		10.12 (1.66-61.92)	0.012*	11 (28.9)				7 (18.4)		
Both	56	26 (46.4)		6.17 (1.50-25.27)	0.011*	13 (23.2)				10 (17.9)		
GVHD Prophylaxsis (Steroids)												
No	61	22 (36.1)				12 (19.7)		1		14 (23.0)		
Yes	55	22 (40.0)	0.663			17 (30.9)	0.163	1.55 (0.44-5.51)	0.491	9 (16.4)	0.374	
Acute GVHD												
Yes	16	4 (25.0)	0.251			5 (31.2)	0.542			5 (31.2)	0.307	
No	100	40 (40.0)				24 (24.0)				18 (18.0)		
Primary Graft Failure												
No	111	40 (36.0)	0.047*	1		26 (23.4)		1		22 (19.8)		
Yes	5	4 (80.0)		7.41 (0.64-86.05)	0.109	3 (60.0)	0.099	1.68 (0.15-18.88)	0.670	1 (20.0)	1.000	
Secondary Graft Failure												
Yes	3	2 (66.7)	0.558			1 (33.3)	1.000			1 (33.3)	0.488	0.317
No	113	42 (37.2)				28 (24.8)				22 (19.5)		
Relapse												
Yes	5	4 (80.0)	0.047*	1		1 (20.0)	1.000			0	NA	
No	111	40 (36.0)		23.62 (1.50-370.36)	0.024*	28 (25.2)				23 (20.7)		
Patient Status												
Alive	104	40 (38.5)	1.000			26 (25.0)	1.000			19 (18.3)	0.251	
Expired	12	4 (33.3)				3 (25.0)				4 (33.3)		

DISCUSSION

There is an increased predisposition of bloodstream infections in hematopoietic transplant recipients owing to the exposure to chemotherapeutic agents and continuing immunosuppressive therapy during the pre- and post-engraftment phases to secure the graft.[17] This study assessed the burden of BSIs, the various causative pathogens and their sensitivity patterns in blood culture, the risk factors, and the impact of BSI on the overall outcome of the transplant.

The frequency of culture-proven BSIs in the present study was 37.9% at 30 days, which is higher than the other studies.[18] A Chinese study by Han T *et al* stated a 17.0% incidence of bloodstream infections in post-transplant patients with febrile neutropenia.[19] An Italian study reported a 12% cumulative incidence of BSI (95% confidence interval, 8-16%) in 269 consecutive HSCT recipients. [20] Infection-related deaths in our center were 41.6%, which correlates with previously published data from European countries.[21] Stoma I and his colleagues reported a lack of sufficient empirical antibiotic treatment and isolation of carbapenem-resistant gram-negative rods (*Acinetobacter baumannii* and *Pseudomonas aeruginosa*) as the chief causes of infection-related mortality in a study of 135 adult patients with microbiologically proven BSI after HSCT. [21] Overall prevalence of gram-negative rods isolation in cultures in this study was higher than the gram-positive organisms, and this finding is also supported by Chinese transplant centers showing gram-negative bacteria as the main cause of BSIs after HSCT. [22,23] In this study, *Klebsiella pneumoniae* and *Escherichia coli* were the most commonly isolated organisms. The source of *klebsiella species* was mainly central venous catheters and person-to-person contact, whereas *E. coli* was either acquired from environmental exposure, thru healthcare workers, or medical equipment. Weijie Cao *et al* from China reported a similar finding in a clinical analysis of BSI in HSCT recipients.[24] Around 50% of these organisms show sensitivity against Piperacillin Tazobactam which favors the continuation of it as the first-line antibiotics in the febrile neutropenia setting. Unlike other studies demonstrating high rates of carbapenem resistance, in our study, it was witnessed in only 10% *of Klebsiella species* and 5% of *E. coli*, strongly suggesting the use of carbapenem drugs as empiric therapy. For carbapenem-resistant strains, a combination of drugs like Ceftazidime-avibactam, tigecycline, and colistin can be used with substantial efficiency.[25] To further prevent the rise in ESBL resistance, strategies infection control practices and antimicrobial stewardship guidelines should be implemented for management of infections and patients in BMT units.[26]

The decline in gram-positive bacterial isolation among HSCT recipients is largely ascribable to improved central venous catheter care. The addition of chlorhexidine in standard infection control practices along with upgraded dressing techniques and careful selection of insertion sites have radically declined the central-line associated infections, eventually reducing the gram-positive bacterial isolates.[27] In the present study, no resistance was observed in ***Staphylococcus aureus*** isolates to vancomycin or linezolid signifying the use of these drugs in the upfront management of gram-positive isolates. However, 60% of ***Enterococcus*** species were found resistant to vancomycin, which makes it challenging to treat. Most of the ***Enterococcus*** species were isolated from blood cultures and central lines. Good stewardship combined with aggressive treatment with linezolid, aminoglycosides, or beta-lactam drugs depending upon the antibiotic sensitivity pattern can help to encounter vancomycin-resistant enterococci.[28]

The univariate and multivariate analysis for the risk factors revealed primary disease, conditioning therapy, primary graft failure, and relapse of the disease as risk factors for BSIs during the first 30 days post-transplant. BM graft source is known to cause relatively delayed engraftment and prolonged neutropenia, which may explain the increased risk of BSIs.[29,30] In this study, MAC was the most commonly used conditioning regimen which might be one of the factors leading to increased BSIs as myeloablative conditioning is an established risk factor for BSIs globally.[31]

Overall mortality in this study was 10.3% (12/116) which is comparable to other studies conducted worldwide.[32] Infection-related mortality occurred in 41.6% (5/12) of patients while remaining 7 patients died due to severe Graft versus host disease and relapse of primary disease

CONCLUSION

We found that BSIs significantly contributed to transplant-related mortality in our study. Gram-negative

bacteria were the most frequently occurring pathogens in BSIs, followed by Gram-positive bacteria. We found an acceptable rate of carbapenem resistance to Gram-negative organisms; however, the resistance against ***Enterococci*** was relatively high. The mortality associated with BSIs can be substantially reduced with the judicious use of empirical antibiotics and the implementation of appropriate infection control measures in transplant care. There are some limitations in this study with assimilation of some clinical history details. We need to conduct further comprehensive studies covering the clinical history and outcome to improve management of infections in this highly vulnerable population.

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CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Faiza Rezwan: Idealized and conceptualized the study, manuscript writing, final approval, agreement to be accountable for all aspects of the work

Shafaq Abdul Samad: Subsequently critically reviewed and revised, final approval, agreement to be accountable for all aspects of the work

Mushkbar Fatima: Statistical analysis, final approval, agreement to be accountable for all aspects of the work

Zainab Sharif: Critical revisions, final approval, agreement to be accountable for all aspects of the work

Aisha Jamal: Subsequently critically reviewed, final approval, agreement to be accountable for all aspects of the work

Uzma Zaidi: Data collection, proofread, final approval, agreement to be accountable for all aspects of the work

REFERENCES

1. Barriga F, Ramirez P, Wietstruck A, Rojas N. Hematopoietic stem cell transplantation: Clinical use and perspectives. Biol Res. 2012; 45 (3): 307–16. DOI: https://doi.org/10.4067/s0716-97602012000300012
2. Zhang R, Xiong Y, Zhang L, Liu L. Epidemiology, microbiology, and risk factors of bacterial bloodstream infections in patients after allogeneic hematopoietic stem cell transplantation. Infect Drug Resist. 2024; 17: 1561-9. DOI: https://doi.org/10.2147/idr.s451781
3. Puerta-Alcalde P, Cardozo C, Marco F, Suárez-Lledó M, Moreno E, Morata L, *et al*. Changing epidemiology of bloodstream infection in a 25-years hematopoietic stem cell transplant program: Current challenges and pitfalls on empiric antibiotic treatment impacting outcomes. Bone Marrow Transplant. 2020; 55 (3): 603–12. DOI: https://doi.org/10.1038/s41409-019-0701-3
4. Weisser M, Theilacker C, Sutter TS, Babikir R, Bertz H, Götting T, *et al*. Secular trends of bloodstream infections during neutropenia in 15181 haematopoietic stem cell transplants: 13-year results from a European multicentre surveillance study (ONKO-KISS). Clin Microbiol Infect. 2017; 23(11): 854–9. DOI: https://doi.org/10.1016/j.cmi.2017.03.020
5. Jia Y, Li Y, Liu Y, Yang Z, Chen X, Liu Y. Epidemiology, antimicrobial resistance, and mortality risk factors of carbapenem resistant gram-negative bacteria in hematopoietic stem cell transplantation recipients. Front Cell Infect Microbiol.2023; 12: 1098856. DOI: https://doi.org/10.3389/fcimb.2022.1098856
6. Mikulska M, Del Bono V, Raiola AM, Bruno B, Gualandi F, Occhini D, *et al*. Blood stream infections in allogeneic hematopoietic stem cell transplant recipients: Reemergence of Gram-negative rods and increasing antibiotic resistance. Biol Blood Marrow Transplant. 2009; 15: 47-53. DOI: https://doi.org/10.1016/j.bbmt.2008.10.024
7. Zeng Q, Xiang B, Liu Z. Profile and antibiotic pattern of blood stream infections of patients receiving hematopoietic stem cell transplants in Southwest China. Infect Drug Resist. 2022; 15: 2045-54. DOI: https://doi.org/10.2147/idr.s358926
8. Castagnola E, Bagnasco F, Mesini A, Agyeman PKA, Ammann RA, Carlesse F, *et al*. Antibiotic resistant bloodstream infections in pediatric patients receiving chemotherapy or hematopoietic stem cell transplant: Factors associated with development of resistance, intensive care admission and mortality. Antibiotics. 2021; 10(3): 266. DOI: https://doi.org/10.3390/antibiotics10030266
9. Youssef A, Hafez H, Madney Y, Elanany M, Hassanain O, Lehmann LE, *et al*. Incidence, risk factors, and outcome of blood stream infections during the first 100 days post-pediatric allogeneic and autologous hematopoietic stem cell transplantations. Pediatr Transplant. 2020; 24(1): e13610. DOI: https://doi.org/10.1111/petr.13610
10. Mikulska M, Raiola AM, Galaverna F, Balletto E, Borghesi ML, Varaldo R, *et al*. Pre-engraftment bloodstream infections after allogeneic hematopoietic Cell transplantation: Impact of T cell-replete transplantation from a haploidentical donor. Biol Blood Marrow Transplant. 2018; 24(1): 109-18. DOI: https://doi.org/10.1016/j.bbmt.2017.08.024
11. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013; 310(20): 2191-4. DOI: https://doi.org/10.1001/jama.2013.281053
12. Maertens J, Cesaro S, Maschmeyer G, Einsele H, Donnelly JP, Alanio A, *et al.* ECIL guidelines for preventing Pneumocystis jirovecii pneumonia in patients with haematological malignancies and stem cell transplant

recipients. J Antimicrob Chemother. 2016; 71(9): 2397–404. DOI: https://doi.org/10.1093/jac/dkw157
13. Lebey AL. Diagnosis of catheter-related bloodstream infection: Differential-time-to-positivity cultures and catheter tip cultures. In Clinical Microbiology Procedures Handbook. 2016 DOI: https://doi.org/10.1128/9781555818814.ch3.6
14. Sikka G, Farooq S, Patel B, Prada RA. Strategies to prevent central line-associated bloodstream infections (CLABSIS). In: Ellsworth, M., Ostrosky-Zeichner, L. (eds) Infection Prevention in the Intensive Care Setting. Springer, Cham. DOI: https://doi.org/10.1007/978-3-031-67062-6_3
15. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, *et al*. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2011; 52(4): e56-93. DOI: https://doi.org/10.1093/cid/cir073
16. Procop GW, Koneman EW, Hall GS, Janda WM, Koneman EW, Schrekenberger PC. Koneman's Color Atlas and Textbook of Diagnostic Microbiology. 7th ed. Wolters Kluwer. 2017. p. 1980.
17. Kikuchi M, Akahoshi Y, Nakano H, Ugai T, Wada H, Yamasaki R, *et al*. Risk factors for pre- and post-engraftment bloodstream infections after allogeneic hematopoietic stem cell transplantation. Transpl Infect Dis. 2015; 17(1): 56-65. DOI: https://doi.org/10.1111/tid.12345
18. Gudiol C, Arnan M, Patiño B, Duarte R, Carratalà J, Garcia-Vidal C, *et al*. Etiology, clinical features and outcomes of pre-engraftment and post-engraftment bloodstream infection in hematopoietic SCT recipients. Bone Marrow Transpl. 2014 ;49: 824–30. DOI: https://doi.org/10.1038/bmt.2014.37
19. Cao W, Guan L, Li X, Zhang R, Li L, Zhang S, *et al*. Clinical analysis of bloodstream infections during agranulocytosis after allogeneic hematopoietic stem cell transplantation. Infect Drug Resist. 2021; 14: 185-192. DOI: https://doi.org/10.2147/idr.s280869
20. Eryilmaz-Eren E, Izci F, Ture Z, Sagiroglu P, Kaynar L, Ulu-Kilic A. Bacteremia in hematopoietic stem cell recipients receiving fluoroquinolone prophylaxis: Incidence, resistance, and risk factors. Infect Chemother. 2022; 54(3): 446-455. DOI: https://doi.org/10.3947/ic.2022.0005
21. Stoma I, Karpov I, Milanovich N, Uss A, Iskrov I. Risk factors for mortality in patients with bloodstream infections during the pre-engraftment period after hematopoietic stem cell transplantation. Blood Res. 2016; 51(2): 102–6. DOI: https://doi.org/10.5045/br.2016.51.2.102
22. Liu CY, Lai YC, Huang LJ, *et al*. Impact of bloodstream infections on outcome and the influence of prophylactic oral antibiotic regimens in allogeneic hematopoietic SCT recipients. Bone Marrow Transplant. 2020; 55(3):1231–9. DOI: https://doi.org/10.1038/bmt.2010.286
23. Rabagliati R, Salazar G, Pérez-Lazo G, Iturrieta MP, Portillo D, Soria-Segarra C, *et al*. An Emergent change in epidemiologic and microbiological characteristics of bloodstream infections in adults with febrile neutropenia resulting from chemotherapy for acute leukemia and lymphoma at reference centers in Chile, Ecuador, and Peru. Open Forum Infect Dis. 2024; 11(3): ofae052. DOI: https://doi.org/10.1093/ofid/ofae052
24. Cao1 W, Guan L, Li X, Zhang R, Li L. Zhang S, *et al*. Clinical analysis of bloodstream infections during agranulocytosis after allogeneic hematopoietic stem cell transplantation. Infect Drug Resist. 2021; 14: 185-92. DOI: https://doi.org/10.2147/idr.s280869
25. Tamma PD, Heil EL, Justo JA, Mathers AJ, Satlin MJ, Bonomo RA. Infectious Diseases Society of America 2024 guidance on the treatment of Antimicrobial-Resistant gram-negative infections. Clin Infect Dis. 2024; ciae403. DOI: https://doi.org/10.1093/cid/ciae403
26. Böll B, Schalk E, Buchheidt D, Hasenkamp J, Kiehl M, Kiderlen TR, *et al*. Central venous catheter–related infections in hematology and oncology: 2020 updated guidelines on diagnosis, management, and prevention by the infectious diseases working party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO). Ann Hematol. 2020; 100(1); 239-59. DOI: https://doi.org/10.1007/s00277-020-04286-x
27. Ding LM, Song XL, Wang XG, Peng Y, Chen YR, Jin L, *et al*. Analysing pathogenic bacterial spectrum and drug resistance of bloodstream infection in patients with allogeneic hematopoietic stem cell transplantation. Zhonghua Xue Ye Xue Za Zhi. 2021; 42(10): 807-13 DOI: https://doi.org/10.3760/cma.j.issn.0253-2727.2021.10.003
28. Papanicolaou GA, Ustun C, Young JH, Chen M, Kim S, Woo Ahn K, *et al*. Bloodstream infection due to vancomycin-resistant *enterococcus* is associated with increased mortality after hematopoietic cell transplantation for acute leukemia and myelodysplastic syndrome: A multicenter, retrospective cohort study. Clin Infect Dis. 2019; 69(10): 1771-9. DOI: https://doi.org/10.1093/cid/ciz031
29. Ge J, Yang T, Zhang L, Zhang X, Zhu X, Tang B, *et al*. The incidence, risk factors and outcomes of early bloodstream infection in patients with malignant hematologic disease after unrelated cord blood transplantation: A retrospective study. BMC Infect Dis. 2018; 18(1): 654. DOI: https://doi.org/10.1186/s12879-018-3575-x
30. Puerta-Alcalde P, Chumbita M, Charry P, Castaño-Díez S, Cardozo C, Moreno-García E, *et al*. Risk factors for mortality in hematopoietic stem cell transplantation recipients with bloodstream infection: Points to be addressed by future guidelines. Transplant Cell Ther. 2021; 27(6): 501.e1-501.e6. DOI: https://doi.org/10.1016/j.jtct.2021.03.017
31. Garcia-Vidal C, Cardozo-Espinola C, Puerta-Alcalde P, Marco F, Tellez A, Agü Ero D, *et al*. Risk factors for mortality in patients with acute leukemia and bloodstream infections in the era of multiresistance. PLoS One. 2018; 13 (6): e0199531. DOI: https://doi.org/10.1371/journal.pone.0199531
32. Bhatia S, Dai C, Landier W, Hageman L, Wu J, Schlichting E, *et al*. Trends in late mortality and life expectancy after autologous blood or marrow transplantation over three decades: A BMTSS report. J Clin Oncol. 2022; 40(18): 1991-2003. DOI: https://doi.org/10.1200/jco.21.02372