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Pathogenic Menace of MDR Bacteria in Stool and Throat Swab Surveillance Cultures of Hematopoietic Stem Cell Recipients and Evaluation of Post-Transplant Bloodstream Infections: A Cross-Sectional Study from A Tertiary Care Teaching Hospital of Kolkata, India

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ABSTRACT

Background: Surveillance culture of stool and throat swabs may guide antibiotic therapy in hematopoietic stem cell transplant recipients where MDRO poses a threat. We have conducted this study to determine the profile of organisms isolated from stool and throat swab cultures, their susceptibility patterns, and the presence of MDRO to detect post-transplant bloodstream infections in this tertiary care teaching hospital in Kolkata.

Methods: This study was conducted over a period of one year. Pre-transplant surveillance culture of stool and throat swabs along with antibiotic susceptibility were performed on seventy patients using standard laboratory guidelines. The organisms were phenotypically screened for drug resistance and molecular confirmation was done for carbapenemase producers. Bloodstream infections in these recipients were detected by blood culture.

Results: In 70 transplant recipients stool surveillance culture yielded maximum incidence of *Escherichia coli* of which 32.8% were MDRO. Throat surveillance culture yielded *Escherichia coli* with 51.8% MDRO. bla_{NDM} was the most common carbapenemases gene detected. Post-transplant bloodstream infections seen in 32 recipients with *Acinetobacter baumannii* being the predominant.

Conclusion: Colonization with MDRO in HSCT recipients before transplant is a potential threat. Performing stool and throat surveillance cultures before transplantation can help in formulation of empirical antibiotic strategies and tailored individualized antibiotic treatment.

Key words: Bone marrow cell transplantation, Stool surveillance culture, Drug Resistance, Bacteremia

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT), which can involve the use of the patient's own hematopoietic progenitor cells (autologous HSCT) or those from a donor (allogeneic HSCT), is a promising therapeutic option with the potential to cure a range of severe cancers and non-cancerous diseases.[1] Leukemia, lymphomas, and myelodysplastic or myeloproliferative syndromes are among the most common conditions treated with allogeneic and autologous HSCT.

Administration of high-level immunosuppressants increases chances of infection (especially in neutropenic patients) and the frequent use of prophylactic antibiotics (Beta-lactams, metronidazole, vancomycin, fluoroquinolone), increases the risk of post-transplant infection.[2]

Recipients of HSCT are highly susceptible to bacteremia in the early post-transplant period due to two main factors that compromise their innate immune system. Firstly, following their conditioning regimen, patients experience prolonged neutropenia, leaving them without the key phagocytes needed to fight bacterial infections. Secondly, significant gastrointestinal mucositis can develop, further compromising the integrity of the mucosal barrier. These two key insults establish a high-risk setting for enteric-borne bacteremia and serious complications from these infections. Recipients of HSCT face a distinctive risk from the rise of multidrug-resistant organisms (MDRO), as these individuals depend on prompt initiation of effective antimicrobial treatment to manage bacterial infections. [3]

In the pre-engraftment phase, infections can be caused by bacteria, viruses, and fungi, with bacterial pathogens being responsible for over 90% of infections during the neutropenic period. Among these, Gram-negative bacteria and *Enterococcus faecalis* are the most frequently identified culprits of bacteremia during this phase.[4]

Patients may be colonized with resistant bacteria from the hospital environment consisting of extended-spectrum beta-lactamases producing *Enterobacterales*, carbapenemases-producing *Enterobacterales*, and vancomycin-resistant *Enterococcus sp.* Presence of these multiple resistant bacteria can result in increased morbidity and mortality.[4]

Antibiotic prophylaxis is commonly given to patients prior to transplantation. Insights into the gut microbiota of transplant recipients help clinicians to design targeted prophylactic antimicrobial protocols to manage infections better related to the transplant.[5] Variations of gut microbiota in transplant recipients along with the paucity of reports monitoring gut microbiota in such recipients from this part of the country create greater challenges.

This study was conducted to determine the profile of organisms isolated from stool and throat swab cultures, their susceptibility patterns, the presence of multi-drug-resistant organisms and to detect post-transplant bloodstream infections in this tertiary care teaching hospital of Kolkata, India.

MATERIALS AND METHODS

The study was conducted in a tertiary care teaching hospital in Kolkata from 1st January 2023 to 31st December 2023 in the Department of Microbiology. This is a single center hospital based cross-sectional study where surveillance, culture and sensitivity of stool and throat swabs and blood culture were done.

Data was collected from the laboratory registers where report details were available in the Department of Microbiology. Laboratory records of all the patient samples received in the Department of Microbiology who were undergoing Hematopoietic Stem Cell transplantation (HSCT) at the Department of Hematology in this study period of one-year, total enumeration was done

Data collection and interpretation: The study was approved by IEC, vide memo no NRSMC/IEC/204/2024 dated 27.06.2024 and after taking administrative permission, data collection was done using pre-designed case report form. Laboratory reports from the registers of Department of Microbiology and BHT of the patients from MRD section was the source of information.

Sample processing: Pre transplant stool and throat swab samples were received in the Department of Microbiology for surveillance and were processed following standard laboratory guidelines and organisms isolated were further processed for antibiotic susceptibility using both conventional Kirby Bauer disc diffusion method and automated method- VITEK 2© compact system, Biomerieux©, France following CLSI 2023 guidelines.[6]

Post transplant, blood cultures were sent from the recipients with suspected bloodstream infections. Blood culture was performed using BacTalert© automated system and positive flagged bottles were processed for identification and antibiotic susceptibility testing following standard methods.[6]

Surveillance for antibiotic resistance was done both phenotypically for detection of ESBL and genotypically for detection of carbapenemases genes.

ESBL producing bacteria were detected by conventional double disc synergy test (Ceftazidime/Ceftazidime-clavulanate discs & Cefotaxime/Cefotaxime-clavulanate discs).

MDROs (multidrug-resistant organisms) are defined as bacteria that exhibit resistance to at least one antibiotic from three or more different classes.[7] MDRO isolated from stool cultures were subjected to molecular characterization for carbapenemase producing genes by RT-PCR using TruPCR© Carbapenem resistance detection kit as per the manufacturer's guidelines.

Bacterial DNA was extracted using TruPCR©. Total Nucleic Acid Extraction Kit provided by the same manufacturer as per kit literature.

The TruPCR© Carbapenem Resistance Detection Kit is an in-vitro nucleic acid amplification test designed for the qualitative detection and differentiation of gene sequences associated with carbapenem resistance. This includes the *bla*$_{KPC}$ (KPC-Klebsiella pneumoniae carbapenemase), blaNDM (NDM-New Delhi Metallo-beta-lactamase), *bla*$_{VIM}$ (VIM-Verona integron-mediated metallo-beta-lactamase), *bla*$_{OXA-48}$ (OXA-48-Oxacillinase-48), and *bla*$_{IMP}$ (IMP-Imipenemase metallo-beta-lactamase) genes, all of which are linked to carbapenem non-susceptibility, using Real-Time PCR.

The primer and probe mix provided utilizes the TaqMan© principle. During PCR amplification, the forward and reverse primers bind to the target nucleic acid. A fluorogenic probe, which is labeled with a 5'-dye and a 3'-quencher, is also included in the reaction mixture. As amplification proceeds, the probe is cleaved, causing the reporter dye and quencher to separate. This separation leads to an increase in fluorescence, which is then detected using the BioRad© real-time PCR platform. An internal control was incorporated into the system to verify the amplification procedure and the possible presence of inhibitors, which may cause false negative results.

Two sample tubes were prepared to be run for a single sample.
Tube 1: *bla*$_{KPC}$ gene+ *bla*$_{NDM}$ gene + Internal control
Tube 2: *bla*$_{VIM}$ gene+ *bla*$_{OXA-48}$ gene+ *bla*$_{IMP}$ gene

The PCR master mix was prepared in two tubes:
Tube 1: Multiplex master mix (15µl) + Primer probe mix-1 (5µl)
Tube 2: Multiplex master mix (15µl) + Primer probe mix-2 (5µl

The following protocol was adopted for RT-PCR.

Step 1: Enzyme activation and initial denaturation = 94°C for 10 minutes for 1 cycle

Step 2: Denaturation at 94°C for 15 seconds then annealing at 60°C for 45 seconds followed by elongation at 72°C for 15 seconds, this will run for 38 cycles

Primer probe sequence for target genes:

IMP
F - GGAATAGAGTGGCTTAAYTCTC
R - GGTTTAAYAAAACAACCACC

VIM
F - GATGGTGTTTGGTCGCATA
R - CGAATGCGCAGCACCAG

KPC
F - TGTCACTGTATCGCCGTC
R - CTCAGTGCTCTACAGAAAACC

NDM
F - CCGTATGAGTGATTGCGGCG
R - GCCCAATATTATGCACCCGG

OXA-48
F - GCTTGATCGCCCTCGATT
R – GATTTGCTCCGTGGCCGAAA

Table 1: Target genes and associated fluorescent probes in RT-PCR detector channel

Tube No.	Detection	Detector channel
Tube 1	KPC	Green/FAM
	NDM	Yellow/HEX/VIC
	Internal Control	Orange/Texas Red/ROX
Tube 2	OXA 48	Green/FAM
	VIM	Yellow/HEX/VIC
	IMP	Orange/Texas Red/ROX

Quality control: For both VITEK2© and disc diffusion methods, ATCC strains of *Escherichia coli* 25922 and ATCC *Escherichia coli* 35218 for ESBL, *Klebsiella pneumoniae* ATCC 700603 for ESBL were used as per CLSI 2023 guidelines.[6]

Statistical methods: Recipients' demographic data and microbiological findings were represented using standard statistical methods. Collected data was compiled in MS-EXCEL sheet to form a master chart. Data was codified and summarized by estimating mean, median, standard deviation for continuous variables and proportion for categorical variables. Data displaying was done by various charts and tables.

RESULTS

Between 1st January 2023 to 31st December 2023, there were 70 HSCT recipients in this tertiary care teaching hospital of Kolkata. There was female preponderance (71%). The median age group was 31-40 years (25%) followed by 41-50 years (20.4%). The minimum age of the recipients was 1 year and the maximum was 60 years.

All the recipients were subjected to stool and throat swab culture surveillance. Stool surveillance culture yielded the following results:

Escherichia coli was the predominant isolate-38/70 (54.3%) in all the recipients in stool culture followed by *Klebsiella pneumoniae* 20/70 (28.5%), *Enterobacter cloacae* 4/70 (5.7%) and *Acinetobacter baumannii* 2/70 (2.8%). Among *Escherichia coli* isolates, 14 out of 38 (36.8%) were MDRO. *Enterococcus faecalis* was the only Gram positive isolate 6/70 (8.5%). (Figure 1)

In the throat swab culture surveillance, 27/ 70 recipients yielded growth of bacteria, predominant being *Escherichia coli*- 14/27 (51.8%) followed by *Klebsiella pneumoniae* - 10/27 (37%), rest were Coagulase negative *Staphylococcus* sp. 3/27 (12%).

There were 32 events of bloodstream infections documented in 70 recipients. Among Gram negative isolates, most commonly isolated organism was *Acinetobacter baumannii* 4/32 (12.5%) followed by *Pseudomonas aeruginosa* 2/32 (6.2%). MDR *Escherichia coli* was isolated from 1 (one) recipient in blood culture. Methicillin resistant Coagulase negative *Staphylococcus* sp. 10/32

(31.2%) isolated from concomitant blood culture was the predominant Gram positive isolates followed by BSI due to *Staphylococcus aureus* 8/32 (25%) and Methicillin resistant *Staphylococcus aureus* 3/32 (9.3%).

Escherichia coli isolates were resistant to major classes of antibiotics; fluoroquinolones were the most resistant group of antibiotics followed by co-trimoxazole. These isolates were only 43% susceptible to cefepime, 50 % susceptible to imipenem, meropenem, and 65 % susceptible to amikacin, gentamicin. Susceptibility of 35% and 39% were observed respectively against beta-lactam/beta-lactamase inhibitors such as piperacillin-tazobactam and cefoperazone-sulbactam. (Figure 2)

Among *Klebsiella pneumoniae* isolates, 71% were resistant to cefuroxime and ceftriaxone, 50% resistant to imipenem, meropenem, amikacin and gentamicin. Fifty seven percent of the isolate were resistant to the amoxicillin-clavulanate, 50% resistant to piperacillin-tazobactam and cefoperazone-sulbactam; 71% resistant to co-trimoxazole. All isolates were susceptible to ertapenem.

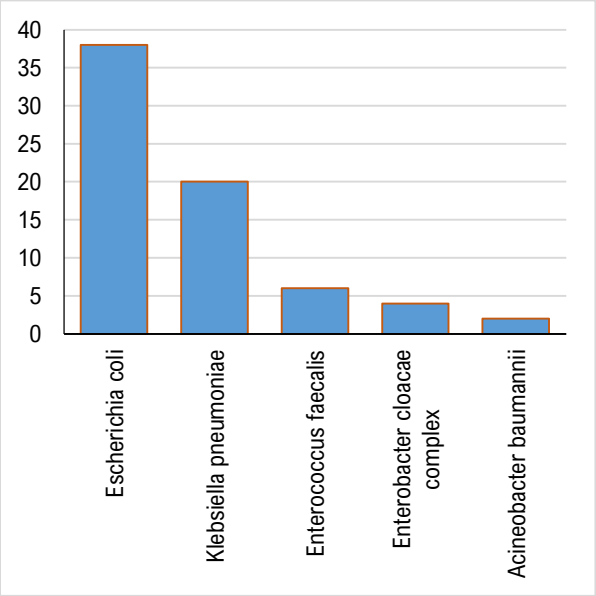

Figure 1: Organisms isolated from stool samples

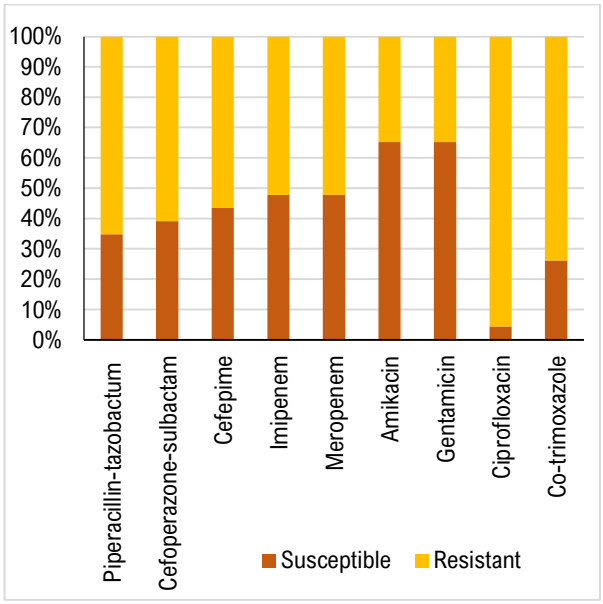

Figure 2: Antibiotic susceptibility pattern of *E. coli*

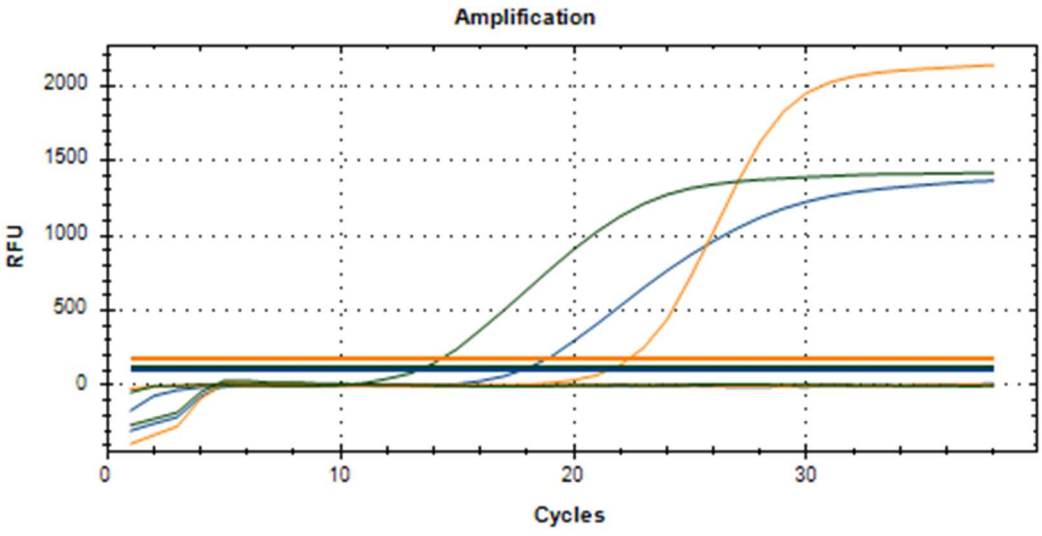

Figure 3: Sigmoid curve of blaOXA$_{-48}$ & *bla*$_{NDM}$ detected in RT-PCR

Table 2: Resistance mechanisms among isolated pathogens

Organism	Resistance phenotype	Stool surveillance	Throat swab surveillance	Positive blood culture
Escherichia coli	ESBL	11/38 (29%)	3/14 (21.42%)	1/32 (3%)
	Carbapenemases	14/38 (36.8%)	2/14 (14.28%)	0
	ESBL + CARBAPENEMASE	8/38 (21%)	0	0

There were two isolates of *Acinetobacter baumannii* that showed resistance to major classes of antibiotics. Both isolates were susceptible to amikacin and gentamicin.

All isolates of *Enterococcus faecalis* were resistant to penicillin and 50% were vancomycin resistant (VRE).

Among Gram negative organisms isolated from blood culture, 100% were resistant to cefuroxime and ceftriaxone, 87.5% resistant to ciprofloxacin, 84% resistant to piperacillin-tazobactam, 75% resistant to doripenem, 67% resistant to cefepime, 60% resistant to ticarcillin-clavulanate, 57% resistant to levofloxacin and amikacin, 50% resistant to cotrimoxazole. The isolates were 100% susceptible to minocycline, tigecycline and ertapenem while colistin was 100% intermediate susceptible among all the isolates.

Resistance gene pattern in the 14 MDR *Escherichia coli* isolates revealed bla_{NDM} and bla_{OXA48} gene in 8 out of 14 isolates (57.1%), bla_{VIM} and bla_{NDM} gene in 4 out of 14 isolates (28.4%) and bla_{NDM} gene in 2 out of 14 isolates (14.2%). (Figure 3)

Among the *Escherichia coli* isolates proportion of ESBL producers in stool surveillance culture were 29% (n=11), carbapenemases producers were 36.8% (n=14); both ESBL and carbapenemases producers were 21% (n=8).

In throat swab surveillance culture ESBL producers were 21.42% (n=3) and carbapenemases producers were 14.28% (n=2). In blood culture only one isolate of *Escherichia coli*, which was ESBL producer. (Table 2)

DISCUSSION

Data on culture surveillance is important for assessing the prevalence of infections that help prevent patient morbidity and mortality and for assessing the efficacy of infection control practices in hospital settings.

In our study, Gram-negative organisms were highly prevalent in the gut flora of patients undergoing hematopoietic stem cell transplant in stool culture surveillance. Throat swab culture surveillance yielded less growth of organisms, but the predominant organism was *Escherichia coli*. Post-transplant blood culture yielded growth of pathogens in 32 events, the most common being *Acinetobacter baumannii*.

Hematopoietic stem cell transplantation (HSCT) has become a successful and potentially curative treatment for various malignant diseases. However, it is often complicated by infections, graft rejection, and graft-versus-host disease (GVHD).[1]

The use of pre-transplant stool and throat culture surveillance helps in guiding empirical therapy that helps in better management of patients with complicated infections and leads to good outcomes in transplant recipients in the post-transplant period.

In a recent study conducted in a cancer institute in eastern India, A total of 64 patients were included in the study. Pre-transplant stool surveillance cultures revealed that 85.9% of patients were colonized with MDROs. Nearly half (48.5%) of the isolates tested positive for carbapenemase-producing genes, predominantly New Delhi metallo-beta-lactamase-1 (NDM-1) and oxacillinase-48 (OXA-48). During the peri-engraftment neutropenic phase, 28% (18/64) of patients had positive blood cultures for MDROs. A correlation between surveillance and blood cultures was observed in 61% (11/18) of these patients.[5]

In a similar study conducted in western India on 76 HSCT recipients, stool culture surveillance had a gut colonization rate of 73.75% where the most common culture isolate was *Escherichia coli*.[8]

In the same study, *Escherichia coli* was the most common MDRO in stool samples (Amp C 29.6%, ESBL 34.3%, and Carbapenemase 25%). The findings are concordant with our study where 36.8% of isolates were MDRO. In a similar study from Vellore, India, the prevalence of drug-resistant isolates in fecal culture surveillance was 57.7% with 81% being ESBL and 11.5% carbapenem-resistant.[9] In patients admitted at the Johns Hopkins Medical Centre, USA, in stool culture surveillance, MDRO was detected in 251 out of 732 cases (34.2%) and ESBL was 22.2% and carbapenemases only 4.4%.[10]

Molecular pattern of resistance in carbapenem-resistant organisms in patients undergoing HSCT in a tertiary care hospital in Mumbai, found NDM alone in 7 out of 23 (31%) and CTX-M along with NDM in 9 out of 23 (39%), CTX-M along with OXA-48 in 2 out of 23 (9%), CTX-M, OXA-48 and NDM in 4 out of 23 (17%) and NDM with OXA-48 in 4 out of 23 (4%).[11] These results are concordant with our study as a similar picture is observed in this institution. A global report has put India and its neighboring regions as the epicenter for the carbapenemase-producing Gram-negative organisms.[12]

In throat swab culture surveillance, our prevalence of ESBL and carbapenemase-producing organisms like *Escherichia coli* and *Klebsiella pneumonia*e was 20% while in the study conducted in eastern India, overall carbapenemase resistance was 48.5%.[5]

In the 32 events of bloodstream infections following transplantation, the most common isolate was Methicillin-resistant Coagulase-negative *Staphylococcus* sp. (MR-CoNS). The possibility of MR-CoNS being a contaminant was weighed down by the isolation of the same species from paired samples collected at 12 hours intervals from two venipuncture sites with different susceptibility profiles. The second most commonly isolated organism was *Acinetobacter baumannii*. In a study by Bhat VG, *et al*. who only reported Gram-negative bacterial sepsis in a cancer center in Mumbai, Maharashtra where 179 out of 5391 (30.2%) and organisms were predominantly *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Acinetobacter baumannii.* [13]

Bacterial infections are the leading cause of mortality in recipients of allogeneic stem cell transplants. These infections can arise at various stages, including during the pre-transplant, post-transplant, or neutropenic phases, after neutrophil recovery, or while the patient is on extended immunosuppressive therapy, such as steroid treatment. The wide variety of bacterial infections, coupled with the growing issue of multi-drug resistance, significantly contributes to both morbidity and mortality. In the Asian subcontinent, most documented bacterial infections are caused by Gram-negative organisms. [14,15,16] In Western populations, there has been a shift from infections caused by sensitive strains to those caused by resistant strains of *Enterobacterales.* [17,18] During stem cell transplantation, the disruption of gut microbial flora promotes the overgrowth of certain bacterial species, which can subsequently lead to bacteremia.[19] Even in developed countries the incidence of drug-resistant strains is low even in high-risk population cohorts [20] and travel to endemic areas has documented conversion to drug-resistant microbiome detected in subsequent fecal surveillance culture. [21]

Although drug resistance rates were higher, the organisms detected in blood culture and their surveillance patterns did not entirely align with those found in fecal surveillance cultures in a similar study. In the study by Korula A *et al* ESBL was present in over 80% of positive surveillance cultures but was isolated from only 3% of blood cultures. This could be due to the frequent use of carbapenems in cases of febrile neutropenia or immunosuppression, even when cultures were negative. The study observed that patients with drug-resistant organisms in blood cultures later showed different resistant strains. This may indicate a genetic predisposition to infections with resistant organisms. Mortality was also notably higher among patients with drug-resistant organisms in fecal surveillance cultures than those without.[9]

Limitations of this study are the unavailability of molecular detection of other resistant genes except carbapenemases and the inability to correlate the pre-transplant surveillance culture detected bacteria with post-transplant bloodstream infections. As follow-up could not be done in all patients, the outcome of the transplant recipients could not be determined.

CONCLUSION

Conducting active surveillance involves screening HSCT recipients for colonization with MDR Gram-negative bacteria and VRE, enabling multiple intervention opportunities. The prevalence of MDRO in stool and throat swab culture surveillance showed that there is an increased probability of adversities in post-transplant period. Conducting active surveillance involves screening HSCT recipients for colonization with MDR Gram-negative bacteria and VRE, enabling multiple intervention opportunities. First, colonized patients can be placed under contact precautions, which will reduce in-patient transmission to some extent. These colonized patients may be candidates for targeted decolonization strategies. The practice of performing pre transplant surveillance culture helps in formulating antibiotic policy and allows for rapid escalation to appropriate antibiotic when the patient is suffering from post-transplant infection. This cohort of patients could potentially have their initial antimicrobial prophylaxis to ensure coverage of MDR bacteria with which they carry a high risk of infection.

Approval of Institutional Ethical Review Board

The study was approved by IEC, vide memo no NRSMC/IEC/204/2024 dated June 27, 2024

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Individual authors contribution

SG*: Conceptualization, Methodology, Supervision, Validation, **KC**: Original draft preparation, Methodology, Writing, Software. **SD**: Original draft preparation, Data curation, **SK**: Writing, Software, Investigation, **BD**: Data curation, **TKD:** Conceptualization, Visualization, **JBD**: Supervision

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