Original Research Article

Microbiological profile and antimicrobial susceptibility patterns of blood stream infections in febrile neutropenic patients with hematological malignancies in a tertiary care hospital, Kolkata

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ABSTRACT

Background: Blood stream infection (BSI) in febrile neutropenic (FN) patients with hematological malignancy is a common manifestation with high mortality rate. To reduce mortality knowledge of pathogens causing BSI and their antimicrobial susceptibility patterns are required for timely initiation of appropriate antimicrobial therapy. This study was aimed to characterize the pathogenic spectrum and antimicrobial resistance patterns of BSI in these patients.

Materials and Methods: In this cross-sectional study patients admitted in the Hematology department over a period of one year with laboratory confirmed positive blood cultures were enrolled. Information regarding demographic profiles and microbiological profiles were recorded. Standard procedures were applied to identify the isolates and their resistance patterns in positive blood culture. Data was collected and analyzed on MS-Excel sheet with various charts and tables.

Result: During the study period of one year 198 episodes of BSI recorded in 147 FN patients. Majority of isolates were Gram-negative bacilli (GNB: n=107, 54.04%). Among GNB *Acinetobacter baumannii* (n=34, 31.77%) was most frequently isolated and in Gram-positive cocci (GPC) majority isolated was *Staphylococcus aureus* (n=37, 62.71%). *Candida auris* (n=12, 37.5%) was the commonest fungal pathogen isolated. Susceptibility to penicillin, clindamycin and quinolones were least among GPC. Among GNB higher resistance patterns were observed against ceftazidime, cefepime, cefoperazone-sulbactam, piperacillin-tazobactam and meropenem. All *C. auris* isolates were resistant to fluconazole.

Conclusion: This study revealed a significant increase in proportion of Gram-negative non-fermenting bacteria (GNNFB). These findings highlight the necessity for regular revision of institutional antimicrobial policy which will reduce mortality as well as development of resistant pathogens.

1. Introduction

Hematologic malignancies are cancers of the blood, bone marrow, and lymph nodes. India ranked next to China in all hematological malignancy categories except in Hodgkin lymphoma where it has reported the highest number of cases in Asia.[1] Reported prevalence of malignant hematological disorder in our hospital is 26%.[2] Patients develop febrile neutropenia as a consequence of bone marrow suppression either due to disease process, as result of anti-cancer therapy or combination of both events. Blood stream infection

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(BSI) is frequently reported in patients who develop febrile neutropenia with a mortality of 11%.[3] To reduce mortality in these patients, prophylactic empirical antimicrobial therapy that includes broad spectrum antibiotic with anti-*Pseudomonal* effect should be promptly initiated. Subsequently appropriate antimicrobial therapy should be adopted according to the pathogen and their susceptibility pattens.[4]

Gram-positive cocci (GPC), Gram-negative bacilli (GNB) and *Candida sp.* are frequently isolated from culture positive BSI. Recent studies suggest Gram-negative bacteremia is mostly responsible among these patients[3,5] and increased reports of multidrug resistant GNB (MDR-GNB) e.g., carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB) and difficult-to-treat resistance *Pseudomonas aeruginosa* (DTR-*P. aeruginosa*) are available.[6] Increase of non-albicans *Candida sp.* in BSI e.g., *Candida auris*, *Candida glabrata* and *Candida parapsilosis*, which are resistant to major groups of anti-fungals either intrinsically or by acquired mechanism, leads to increased mortality and enhanced treatment costs.[7,8]

Knowledge of pathogens causing BSI and their antimicrobial susceptibility patterns are crucial for timely initiation of appropriate empirical antimicrobial therapy in febrile neutropenic patients with hematological malignancies. Hence this study was undertaken to determine pathogens causing BSI and their antimicrobial susceptibility patterns in a tertiary care hospital.

2. Materials and Methods

This is a cross-sectional study conducted in the Department of Microbiology at a tertiary care hospital in Kolkata, among culture positive BSI in febrile neutropenic patients with hematological malignancy between 1st January 2023 to 31st December after obtaining Institutional Ethics Committee certificate for this study (NRSMC/IEC/57/2024 Dt. 13.04.2024).

Data was collected between 14st April 2024 and 30st April 2024 and data analysis was done between 1st May 2024 to 14th May 2024.

2.1. Definitions

Febrile neutropenia (FN) was defined by a single oral temperature of 101°F or temperature of >100.4°F for 1 hour with an absolute neutrophil count (ANC) <500/mm^3 or an ANC that was expected to decrease to <500/mm^3 during the next 48 hours.[9]

Blood stream infection (BSI) was defined by the isolation of a pathogenic organism (excluding organisms that are in the NHSN common commensal organism list) in paired blood culture sets (one set including one aerobic and one anaerobic); for diagnosing coagulase-negative *Staphylococci sp.* and *Candida sp.*, paired positive cultures were required from two different venipuncture sites 12 hours apart.[10]

Multidrug-resistant (MDR) bacteria is defined as the isolate which is non-susceptible to at least 1 agent in ≥ 3 antimicrobial categories, extensively drug-resistant (XDR) is defined as the isolate which is non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories and pan drug-resistant (PDR) bacteria is defined as non-susceptibility to all agents in all antimicrobial categories for each bacterium.[11]

The primary objective of this study was to identify organisms causing BSI in febrile neutropenic patients with hematological malignancy and their antimicrobial susceptibility patterns.

All the cases fulfilling the definition of BSI and FN during the study period of one year were included in this study. Medical records e.g., demographic profile, microbiological reports of the patients were collected from HMIS in case record form.

2.2. Microbiological analysis

Paired blood samples in aerobic and anaerobic automated blood culture bottles (from BIOMERIEUX, Paris, France) were received in the Microbiology Laboratory with detailed clinical history. Immediately blood culture bottles were incubated in automated blood culture machine BACT/ALERT® 3D (from BIOMERIEUX, Paris, France). Gram staining was done from positively flagged bottles and subculture was done in 5% Sheep Blood Agar, MacConkey agar and for yeasts on Sabouraud dextrose agar plates. Plates were incubated at 37°C for 48 hours and for yeasts up to 5 days. After incubation culture plates were examined for colony morphology and preliminary microbiological identification was done by Gram stain, motility test and standard biochemical tests.

Further identification was done by Vitek 2 Compact ® automated system (from BIOMERIEUX, Paris, France). Antimicrobial susceptibility test (AST) was performed by both Vitek 2 Compact ® and Kirby Bauer disc diffusion method following the Clinical and Laboratory Standards Institute (CLSI) 2023 guidelines as required. On Vitek 2 Compact ® For identification of Gram-positive, Gram-negative bacteria and yeasts GP, GN and YST ID cards were used. For Gram-negative bacteria AST 405, 406 and 407 cards were used and for AST of Gram-positive bacteria 628 and ST03 cards were used. Isolation of *C. auris* in Vitek 2 Compact ® was further confirmed by MALDI-TOF (Figure 8).

For AST of *Candida sp.* isolates YS09 card was used except in *C. auris* isolates where ant-fungal susceptibility testing was done by broth microdilution method using SENSITITRE YEASTONE® plates (from Thermo Fisher Scientific, Waltham, MA, USA) following manufacturers

instruction and interpretation of result was done following CDC guideline [12] (Figure 9).

Kirby Bauer disc diffusion method was performed on Mueller Hinton agar plate with discs of penicillin (10U), ampicillin (10μg), cefoxitin (30μg), oxacillin (1μg), linezolid (30μg), erythromycin (15μg), clindamycin (2μg), ciprofloxacin (5μg), levofloxacin (5μg), amikacin (10μg), gentamicin (10μg), ceftazidime (30μg), cefepime (30μg), piperacillin-tazobactam (100/10μg), cotrimoxazole (1.25/23.75μg), cefoperazone-sulbactam (75/30μg), imipenem (10μg), meropenem (10μg), minocycline (30μg). ATCC strains of *Staphylococcus aureus* (25923), *Escherichia col*i (25922) and *Pseudomonas aeruginosa* (27853) were used as controls in disc diffusion method.

Vancomycin resistance in *Enterococcus sp.* was confirmed by Vancomycin Ezy MIC^{TM} Strip (gradient diffusion AST test) (from HiMedia Laboratories Pvt. Ltd, Mumbai, India). Carbapenemase production in enterobacterales and *P. aeruginosa* was phenotypically detected by modified carbapenem inactivation method (mCIM) along with EDTA carbapenem inactivation method (eCIM) following CLSI 2023 guidelines.

All the dried culture media and antibiotic discs were commercially obtained from HiMedia Laboratories Pvt Ltd.

Data was collected in a Microsoft Excel sheet and analyzed with various charts and tables. Categorical variables e.g., gender of patient, types of organisms isolated, susceptibility patterns and resistance mechanisms were expressed in frequency counts with percentage distribution and Quantitative variable e.g., age of patient was categorized using 10-year categories and expressed using percentage.

3. Result

During the study period, total 198 episodes of BSI were recorded in 147 FN patients who fulfilled the criteria of BSI and FN according to given definition.

3.1. Patient profile

Out of 147 patients, 101 patients were male and rest were female (n=46) with a male to female was 2.19:1 (Figure 1). Majority of the patients were ≤ 10 years of age (34.69%) followed by age group of 11 – 20 years (19.73%) (Figure 2).

3.2. Microbiological profile

Among the all 198 episodes of BSI, only mono-microbial growth was detected in each episode. Among these 198 BSI episodes majority times Gram-negative bacilli (n=107, 54.04%) were isolated followed by Gram-positive cocci (n=59, 29.79%) and *Candida sp.* (n=32, 16.17%) (Figure 3).

Among Gram-positive cocci, majority was *Staphylococcus aureus* (n=37, 62.71%) followed by Coagulase negative *Staphylococci sp.* (CONS) (n= 14,

23.72%), *Enterococcus sp.* (n=6, 10.16%) and *Streptococci sp.* (n=2, 3.41%) (Figure 4).

Gram-negative non-fermenter bacilli (GNNFB) *Acinetobacter baumannii* (n=34, 31.77%) was the most frequent isolate in GNB group followed by *Klebsiella pneumoniae* (n=22, 20.56%), *Pseudomonas aeruginosa* (n=18, 16.82%), *Enterobacter sp.* (n=15, 14.01%), *Burkholderia cepacia* (n=10, 9.34%) and *Escherichia coli* (n=8, 7.5%) (Figure 5).

Among the 32 isolated *Candida sp.* majority was *C. auris* (n=12, 37.5%) followed by *C. parapsilosis* (n=8, 25%), *C. albicans* (n=5, 15.62%) and *C. glabrata* (n=5, 15.62%) (Figure 6).

Among the isolated pathogens *A. Baumannii*, *P. aeruginosa*, *Enterobacter sp.* and *Klebsiella pneumoniae* were repeatedly isolated from same patients (Figure 7).
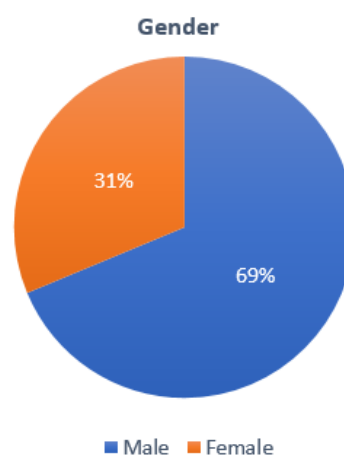

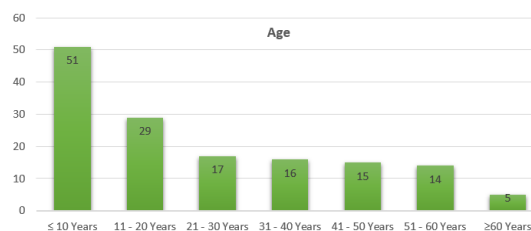**Figure 1:** Pie diagram showing gender distribution among patients.

Figure 2: Bar diagram showing distribution of ages in 10 years categories in horizontal axis and number of patients in vertical axis

Among GPC majority of *S. aureus* (n=30, 81.08%) and all CONS were methicillin resistant. Most of the *Staphylococci sp.* isolates were resistant to penicillin, clindamycin, levofloxacin and ciprofloxacin. CONS were more resistant to gentamicin and cotrimoxazole as compared to *S. aureus*. Better susceptibility was observed against linezolid, vancomycin, teicoplanin and daptomycin.
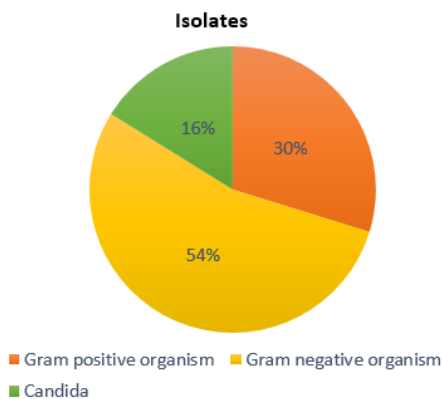
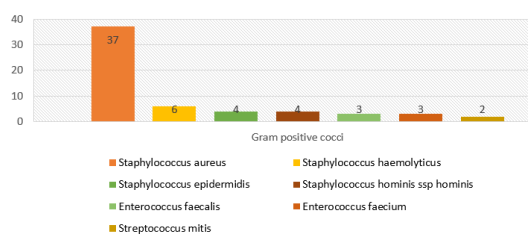**Figure 3:** Pie diagram showing distribution of isolated organisms

Figure 4: Bar diagram showing distribution of Gram-positive cocci, types of Gram-positive cocci in horizontal axis and numbers of isolated pathogens in vertical axis
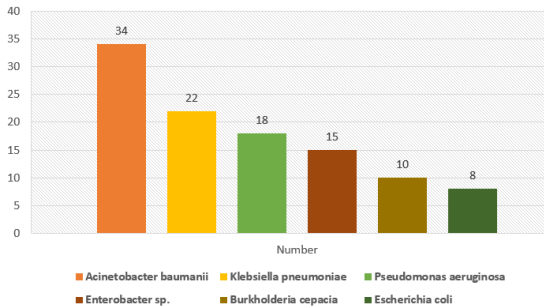

Figure 5: Bar diagram showing distribution of Gram-negative bacilli, types of isolated pathogen shown in horizontal axis and numbers of isolation shown in vertical axis
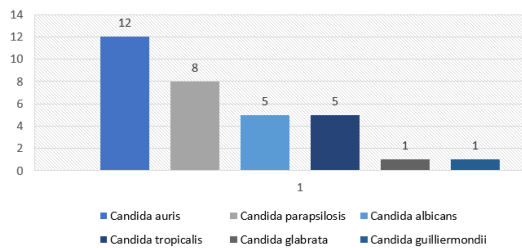

Figure 6: Bar diagram showing distribution of *Candida sp*. Types of *Candida sp*. showing in horizontal axis and numbers of isolated *Candida sp*. showing in vertical axis
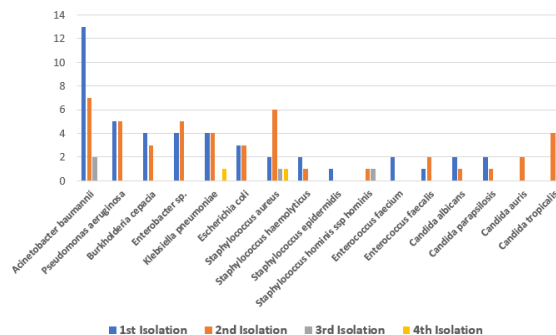

Figure 7: Bar diagram showing frequency of repeated isolation of pathogens. Type of isolated pathogens shown in horizonal axis and number of times each pathogen isolated in 1st, 2nd, 3rd and 4th isolation shown in vertical axis.

Among *Enterococcus sp*. *E. faecium* showed marked resistance as compared to *E. faecalis*. Fifty percent of *Enterococcus sp*. were resistant to Vancomycin (VRE) (Table 1 and Table 5).

GNB showed alarming resistant patterns against major classes of antibiotics. *A. baumannii* was least susceptible to ceftazidime, cefepime, meropenem, imipenem and piperacillin-tazobactam while better susceptibility was observed against aminoglycosides, quinolones, cefoperazone-sulbactam and minocycline. Similar susceptibility patterns was also noted in *K. pneumoniae* along with higher resistance patterns seen against cefoperazone-sulbactam and minocycline while ceftazidime was more susceptible. *P. aeruginosa* was resistant to aminoglycosides, ciprofloxacin, carbapenems and minocycline and susceptible to ceftazidime, cefepime, cefoperazone-sulbactam, piperacillin-tazobactam and levofloxacin. *Enterobacter sp*. had poor susceptibility pattern against cephalosporins, cefoperazone-sulbactam, piperacillin-tazobactam, amikacin, levofloxacin, carbapenems and better susceptibility was observed against gentamicin, ciprofloxacin and minocycline. In *Escherichia coli* better susceptibility was observed against meropenem only. Among Enterobacterales 71.11% was CRE and 55.88% *A. baumannii* was CRAB (Table 2 and Table 5).

In this study 70% *S. aureus* and 50 % *Enterococcus sp*. isolates were MDR. Among GNB 47.05% *A. baumannii* was MDR and among *Klebsiella pneumoniae* XDR and MDR were recorded 31.81% and 50% respectively (Table 3).

Among fungal pathogens, *C. parapsilosis*, *C. tropicalis* and *C. albicans* were susceptible to fluconazole whereas *C. glabrata* and *C. tropicalis* were susceptible to voriconazole. Caspofungin resistance was seen in *C. glabrata*. All *C. auris* isolates were resistant to fluconazole and only susceptible to caspofungin (Table 4).

Table 1: Showing antimicrobial susceptibility patterns in Gram-positive cocci, S = susceptible R = resistant

		Staphylococcus aureus (n=37)	*Staphylococcus haemolyticus* (n=6)	*Staphylococcus epidermidis* (n=4)	*Staphylococcus hominis ssp hominis* (n=4)	*Enterococcus faecalis* (n=3)	*Enterococcus faecium* (n=3)	*Streptococcus mitis* (n=2)
Penicillin	S	5.40%	0%	0%	0%	33.34%	0%	100%
	R	94.60%	100%	100%	100%	66.66%	100%	0%
Clindamycin	S	27.02%	0%	0%	0%	-	-	50%
	R	72.98%	100%	100%	100%	-	-	50%
Levofloxacin	S	18.91%	0%	0%	0%	66.66%	0%	100%
	R	81.09%	100%	100%	100%	33.34%	100%	0%
Ciprofloxacin	S	29.72%	0%	0%	0%	66.66%	0%	-
	R	70.28%	100%	100%	100%	33.34%	100%	-
Cotrimoxazole	S	59.45%	0%	25%	0%	-	-	-
	R	40.55%	100%	75%	100%	-	-	-
Teicoplanin	S	94.59%	100%	100%	100%	66.66%	100%	-
	R	5.41%	0%	0%	0%	33.34%	0%	-
Gentamicin	S	67.56%	0%	25%	50%	-	-	-
	R	32.44%	100%	75%	50%	-	-	-
Vancomycin	S	100%	100%	100%	100%	66.66%	33.34%	100%
	R	0%	0%	0%	0%	33.34%	66.66%	0%
Linezolid	S	100%	100%	100%	100%	66.66%	100%	100%
	R	0%	0%	0%	0%	33.34%	0%	0%
Daptomycin	S	100%	100%	100%	100%	33.34%	33.34%	100%
	R	0%	0%	0%	0%	66.66%	66.66%	0%

Table 2: Showing antimicrobial resistance patterns in Gram-negative bacilli

	Acinetobacter baumannii (n=34)	*Klebsiella pneumoniae* (n=22)	*Pseudomonas aeruginosa* (n=18)	*Enterobacter sp.* (n=15)	*Burkholderia cepacia* (n=10)	*Escherichia coli* (n=8)
Ceftazidime	73.52%	31.81%	50.00%	80.00%	80%	75.00%
Cefepime	73.52%	81.81%	44.44%	66.66%		75.00%
Cefoperazone-Sulbactam	41.17%	77.27%	61.11%	73.33%	100%	62.50%
Piperacillin-Tazobactam	70.58%	81.81%	50.00%	73.33%	-	62.50%
Amikacin	41.17%	40.90%	72.22%	60.00%	-	75.00%
Gentamicin	44.11%	45.45%	88.88%	20.00%	-	75.00%
Levofloxacin	44.11%	31.81%	50.00%	73.33%	100%	75.00%
Ciprofloxacin	41.17%	86.36%	72.22%	40.00%	90%	75.00%
Imipenem	61.76%	72.72%	72.22%%	73.33%	-	62.50%
Meropenem	85.29%	86.36%	72.22%	73.33%	10%	37.50%
Co-trimoxazole	64.70%	45.45%	-	73.33%	80%	62.50%
Minocycline	20.58%	81.81%	72.22%	33.33%	80%	50.00%

Table 3: Percentage distribution of MDR, XDR and PDR bacteria among Gram-positive cocci and Gram-negative bacilli

	MDR	XDR	PDR
Staphylococcus aureus (n=37)	26 (70.27%)	-	-
Enterococcus sp. (n=6)	3 (50%)	-	-
Acinetobacter baumannii complex (n=34)	16 (47.05%)	5 (14.7%)	1 (2.94%)
Klebsiella pneumoniae (n=22)	11 (50%)	7 (31.81%)	2 (9.09%%)
Pseudomonas aeruginosa (n=18)	2 (11.11%)	8 (44.44%)	-
Enterobacter cloacae complex (n=15)	6 (40%)	5 (33.33%)	-
Escherichia coli (n=8)	1 (12.5%)	5 (62.5%)	-

Table 4: Antifungal susceptibility patterns in *Candida sp.*

		Amphotericin B	Fluconazole	Voriconazole	Flucytosine	Caspofungin
Candida auris (n=12)	S	50%	0	-	-	100%
	R	50%	100%	-	-	0
Candida parapsilosis (n=8)	S	62.50%	100%	62.50%	87.50%	-
	R	37.50%	0	37.50%	12.50%	-
C. albicans (n=5)	S	40%	60%	100%	60%	100%
	R	60%	40%	0	40%	0
Candida tropicalis (n=5)	S	100%	80%	100%	80%	100%
	R	0	20%	0	20%	0
Candida guilliermondii (n=1)	S	0	0	0	0	100%
	R	100%	100%	100%	100%	0
Candida glabrata (n=1)	S	100%	-	100%	-	0
	R	0	-	0	-	100%

Table 5: Showing distribution of different resistance mechanisms among isolated microorganisms

Organism	Resistance mechanism	Number (%)
Staphylococcus aureus (n=37)	MRSA	n=30, 81.08%
Enterococcus sp. (n=6)	VRE	n= 3, 50%
Enterobacterales (n=45)	CRE	n=32, 71.11%
Acinetobacter baumannii (n=34)	CRAB	n=19, 55.88%
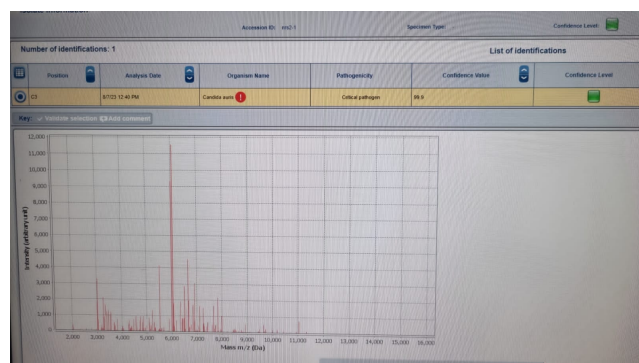
Figure 8: MALDI-TOF confirmation of *C. auris* isolates
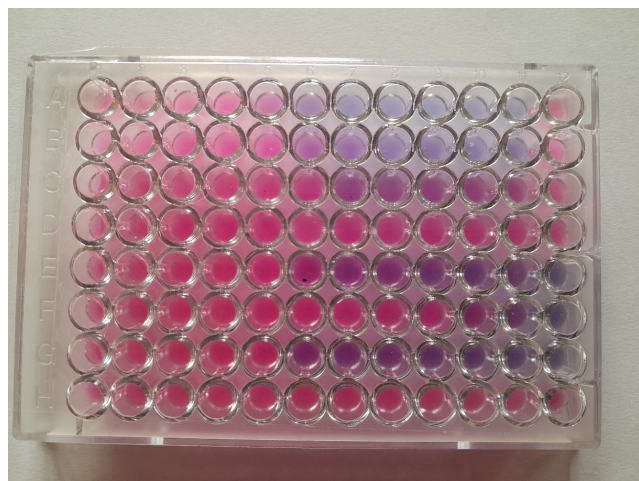
Figure 9: Antifungal susceptibility testing by broth microdilution method of *C. auris* isolates

4. Discussion

In this study we observed microbial profile and their antimicrobial susceptibility patterns among 198 episodes of BSI in 147 FN patients with hematological malignancy who were admitted in our hospital during the study period of one year. Disease process, myelo-suppressive chemotherapy and immunotherapy-induced immune-related adverse events (irAEs) are contributing factors to FN.

In our study it was found that there was a paradigm shift of causative pathogens of BSI from Enterobacterales to NFGNB. There was marked increase in MDR pathogens in all categories. An alarming numbers of *C. auris* were also isolated which is very difficult to treat because of higher resistance and easily transmitted from patient to patient in healthcare setting.

In our study majority of the patients were below 20 years of age with a male preponderance. All the BSI episodes showed mono-microbial growth where majority isolates were GNB followed by GPC and *Candida Sp*.

Previously GPC was the commonest pathogen of BSI in FN patients.[13] But in last two decades studies from India and abroad have shown Enterobacterales e.g., *Klebsiella pneumoniae* and *Escherichia coli* have become prevalent pathogens of BSI.[14–16]

In the current study among GNB non-fermenter *A. baumannii* (31.77%) was the predominant pathogen isolated followed by *Klebsiella pneumoniae* (20.56%) *A. baumannii* was also isolated repeated times from the same patient. This is an alarming scenario because GNNFBs are mostly associated with healthcare associated infections (HCAI). These pathogens are usually MDR due to intrinsic and

acquired resistance which is highly problematic in treating immunocompromised patients.

Studies done by Talukdar et al.[17] in 2023 among pediatric FN malignancy patients, showed only 7% *A. baumannii* which is far less than our study, another similar study by Babu KG et al.[3] in 2016 showed 15.62% *A. baumannii* isolation.

Among GPC majority isolates were MRSA which is easily transmitted in healthcare setting. Higher resistance pattern was observed against penicillin, macrolides, and quinolones. Though less number *Enterococcus sp.* have been isolated as compared to other similar studies[15] but fifty percent were VRE which is again very difficult to treat. Both MRSA and VRE can survive as colonizer in immunocompromised patients for a long time. A study done by Hefazi M. et al.[18] showed VRE colonization was a surrogate marker of worst outcome among post hematopoietic cell transplantation (HCT).

Antimicrobial susceptibility patterns in GNB showed, except *Escherichia coli* and *Burkholderia cepacia,* majority isolates were resistant to meropenem. *P. aeruginosa* and *Escherichia coli* were least susceptible to aminoglycosides. Most of the isolates except *A. baumannii* also were resistant to β-lactam/β-lactam inhibitor combinations, e.g., piperacillin-tazobactam. Similar study done by Kokkayil P et. al[5] showed low susceptibility to cefoperazone-sulbactam, piperacillin-tazobactam, carbapenems and aminoglycosides among GNB. *Enterobacter sp.* was resistant to all major classes of antimicrobials except ciprofloxacin and minocycline. As most of the *Enterobacter sp.* produces chromosomal AmpC β-lactamases[19], repeat blood culture of *Enterobacter sp.* showed acquired resistant to previously susceptible antibiotics in two cases. The magnitude of CRE and CRAB was found to be 71.11% and 55.88% respectively.

In our study an alarming numbers of *S. aureus* (70.27%), *A. baumannii* (47.05%), *K. pneumoniae* (50%) were MDR and *P. aeruginosa* (44.44%) were XDR. Reddy R et al.[20] in is his study showed that MDR phenotype was seen in 48%, XDR in 32% and PDR 16% of Gram-negative isolates, which similar to our study.

In our study 4 out 6 isolated *Candida sp.* belong to WHO priority pathogens' critical priority group (*C. auris, C. albicans*) and high priority group (*C. parapsilosis* and *C. tropicalis*).[21] As there are no antifungal susceptibility reference criteria present in current CLSI guideline we followed CDC cut-off values to determine susceptibility patterns of *C. auris.* All *C. auris* isolates were azole resistant and sensitive to caspofungin., these findings are quite concerning.

This microbiological profile in our study provides valuable insights into infection epidemiology of BSI in FN patients in Eastern India. Increasing isolation of NFGNB, MRSA, VRE and *C. auris* require strict adherence to existing IPC measures, identify and promote existing IPC measure where it is lacking and develop new preventive measures at the healthcare setting.

5. Limitation

There are several limitations in our study. In our study we have only determined causative pathogens of BSI and their antimicrobial susceptibility patterns but we have not followed up for the outcome of these patients. As the study period is only one year, we had a relatively small numbers of samples to process with, a larger sample size would have better understanding of the current scenario. As we have not able to perform broth microdilution AST for colistin so we did not include Vitek 2 Compact ® results of colistin in our study. We have only detected phenotypic resistance mechanisms in our isolates, genotypic detection of resistance mechanism is more accurate. We did not perform Kirby Bauer disc diffusion directly from positive blood culture bottles as advised in CLSI guidelines. Due to resource constraint, we were able to perform antifungal broth microdilution for *C. auris* isolates only.

6. Conclusion

Prompt empirical broad-spectrum antibiotic therapy is crucial in FN management which will reduce hospitalization duration, morbidity, and mortality rates. The antimicrobial resistance patterns observed in our study highlights the critical role of microbiological knowledge in decision making while treating high risk patients for improved clinical outcome as well as in shaping antimicrobial policies of the institute.

7. Ethical Approval

Institutional Ethics Committee approval was taken before this study (NRSMC/IEC/57/2024 Dt. 13.04.2024)

8. Source of Funding

This study received no funding or any kind of study grants.

9. Conflicts of Interest

The authors declare no conflicts of interest.

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