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Microbiological Profile of Blood Stream Infections in Febrile Neutropenic Patients at a Tertiary Care Teaching Hospital in Rishikesh, Uttarakhand

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Abstract

Context Febrile neutropenia is a serious complication of chemotherapy affecting patients with both hematological and solid malignancies, respectively. To the best of our knowledge, there is paucity of literature from Uttarakhand, India on microbiological profile of blood stream infections (BSIs) in febrile neutropenic patients.

Aims The study aims to generate preliminary data on microbiological profile and antibiotic resistance pattern of BSIs in febrile neutropenic patients.

Settings and Design The design involved cross-sectional study from January 1, 2019 to July 31, 2019.

Methods and Materials Data of nonrepetitive paired peripheral blood samples obtained from 306 consecutive febrile neutropenic cancer patients of all age groups and both sexes, for culture and sensitivity testing, were retrospectively analyzed. All blood samples were subjected to aerobic culture using BACT/ALERT three-dimensional microbial detection system. Growth obtained in culture was identified by conventional biochemical methods. Antibiotic susceptibility testing of bacterial isolates was performed using modified Kirby Bauer disk diffusion method.

Statistical Analysis Used Fisher's exact test was used for the analysis.

Results Mean age ± SD of the study population was 32.39 ± 10.56 years with a male to female ratio of 1.55:1. 74.18% of the blood samples were received from patients suffering from hematological malignancies. Microbiologically confirmed BSIs were observed in 27.1% patients. Gram-negative bacilli were predominantly isolated in culture with *Klebsiella spp*. being the most common. Percentage resistance values of gram-negative bacilli to aminoglycosides, β-lactam/β-lactamase inhibitor combinations, fluoroquinolones, cephalosporins, carbapenems, chloramphenicol, ampicillin, co-trimoxazole, and doxycycline were 26.6 to 91.7%, 8.3 to 86.6%, 10 to 66.7%, 13.3 to 73.3%, 8.3 to 73.3%, 80 to 93.3%, 13.3 to 20%, 16.7 to 66.6%, and 13.3 to 16.7%, respectively.

Conclusion Implementation of antimicrobial stewardship program along with hospital infection control practices is needed for preventing BSIs due to MDR organisms.

Keywords
- febrile neutropenia
- BSIs
- hematological malignancies
- gram-negative bacilli

Introduction

Febrile neutropenia (FN) or neutropenic fever is defined as a single oral temperature of ≥38.3°C (101°F) or temperature of ≥38.0°C (100.4°F) sustained over a 1-hour period along with an absolute neutrophil count (ANC) of <500 cells/mm^3, or an ANC that is expected to decrease to <500 cells/mm^3 during the next 48 hours.[1] It is a serious complication of chemotherapy affecting 80% and 10 to 50% of those with hematological and solid malignancies, respectively.[1,2] Despite major advances in medical management, FN is associated with prolonged hospital stays, increased health care costs, compromised efficacy

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of chemotherapy, increased morbidity, and mortality rates, respectively.[3]

The possibility of blood stream infections (BSIs) is a major cause of concern in these patients. BSIs are responsible for 10 to 25% of all febrile episodes in neutropenic patients, with an incidence as high as 13 to 60% in hematopoietic stem cell transplantation recipients. Severe sepsis and septic shock have been, respectively estimated to occur in 20 to 30% and 5 to 10% of FN patients.[1,4-7] Crude mortality rates reaching 40% have been reported in FN patients with underlying hematological malignancies.[8] Although, there has been a substantial reduction in mortality rates in neutropenic patients with BSIs from 25% in late 1970s to 6% in the recent years, increased prevalence of multidrug-resistant (MDR) bacterial infections may hamper this progress, as has been highlighted by several authors.[9-12]

There has been a paradigm shift in the spectrum of microorganisms isolated from FN patients over the last 40 years. Until mid-1980s, *Escherichia coli*, *Klebsiella spp.*, and *Pseudomonas aeruginosa* among gram-negative bacilli and *Staphylococcus aureus* among gram-positive cocci, respectively, were the most frequently isolated organisms from this group of patients. These organisms have gradually been replaced by coagulase-negative staphylococci (CoNS) and viridans group of streptococci ever since.[3] In the late 1970s and early 1980s, gram-negative bacilli were the predominant cause of BSIs in neutropenic patients which were gradually replaced by gram-positive cocci in the 1990s.[13] Several studies published in the recent years have reported a shift in prevalence from gram-positive to gram-negative bacteremia with an accompanying rise and successful dissemination of MDR gram-negative bacterial infections.[8,14]

Keeping in mind the ever-changing microbiological profile of BSIs in FN patients, it is imperative that data about the locally prevalent pathogens and their antimicrobial resistance patterns should be generated and analyzed to decide appropriate empirical therapy. The present study was conducted with the aim of generating preliminary data on microbiological profile and antibiotic resistance pattern of BSIs in FN cancer patients. To the best of our knowledge, this study is the first of its kind from the state of Uttarakhand, India. The findings of this study will be of immense help to treating physicians in this part of the country, in instituting timely and appropriate antimicrobial therapy in this group of patients.

Subjects and Methods

A cross-sectional study was conducted at a tertiary care teaching hospital located in Rishikesh, Uttarakhand, for a time period of 7 months from January 1, 2019 to July 31, 2019. Data of nonrepetitive paired peripheral blood samples obtained from 306 consecutive FN cancer patients of all age-groups and both sexes, for culture and sensitivity testing, were retrospectively analyzed. This study was approved by Institutional Ethics Committee vide letter number AIIMS/IEC/19/1275 dated December 31, 2019. A total of 306 episodes of FN (one per patient) were studied. Each incident of FN was treated as a separate episode. An episode of bacteremia was defined as greater than or equal to one blood culture yielding a pathogen, with the exception of CoNS, for which isolation from two blood culture samples was considered significant.

All blood samples had been subjected to aerobic culture using BACT/ALERT 3D microbial detection system (bioMerieux India Private Limited). The blood culture bottles which beeped positive were subjected to preliminary microscopic examination of gram-stained smears of their contents and the concerned treating physicians were informed telephonically. Subcultures were also performed from these bottles on blood and MacConkey agar plates, respectively, which were incubated aerobically at 37°C overnight. Growth obtained on culture plates was studied on the following day and subjected to further identification by conventional (manual) biochemical methods.[15] Antibiotic susceptibility testing of bacterial isolates was performed using modified Kirby Bauer disk diffusion method, the results of which were interpreted as per Clinical and Laboratory Standards Institute guidelines 2019.[15,16] American Type Culture Collection control strains were used to ensure the quality of each procedure.

Categorical variables were presented as proportions while continuous variables were presented as mean with standard deviation. Comparison of categorical variables was done by Fisher's exact test. All statistical tools were two-tailed and a significant level $p < 0.05$ was used. All statistical tests were performed using InStat software (GraphPad Software, San Diego, California, United States).

Results

(1) *Baseline characteristics*: During the study period, 60.8% (186/306) and 39.2% (120/306) of the paired peripheral blood samples were from male and female patients, respectively, with a male to female ratio of 1.55:1. Mean age ± S.D. of these patients was 32.39 ± 10.56 years, with maximum number of cases occurring in 0 to 10 [62/306 (20.2%)] followed by 21 to 30 [61/306 (19.9%)] years of age groups, respectively. One hundred and fifty-four (50.3%), 121 (39.5%), and 31 (10.1%) of these samples were received from Haemato-Oncology, Medical Oncology, and Surgical Oncology wards, respectively.

(2) *Clinical diagnosis*: Most of the blood samples were received from patients suffering from hematological malignancies (227/306 [74.18%]), with acute leukemia being the most common diagnosis (185/306 [60.46%]). Overall frequency distribution of FN patients with respect to clinical diagnosis has been depicted in ►**Fig. 1**. ►**Tables 1** and **2**, respectively summarize the frequency distribution of FN among different types of hematological and nonhematological malignancies.

(3) *Microbiological* profile: While 66.6% (204/306) of the paired blood samples were sterile, laboratory contaminants were grown in culture from 18.6% (19/102) of the remaining samples. Growth of microorganisms with potential clinical significance, was obtained in culture from 81.3% (83/102) of the samples, which included 54 gram-negative bacilli, 21 gram-positive cocci, and eight fungal isolates, respectively, as enumerated in ►**Table 3**.

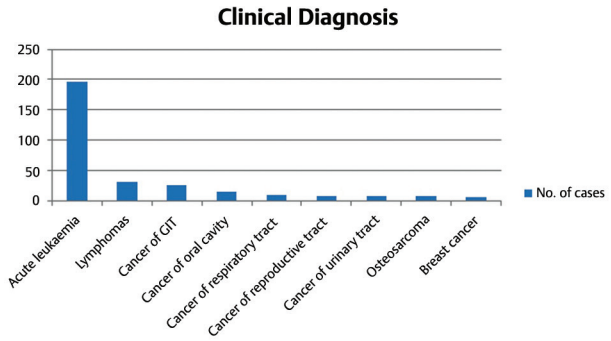

Fig. 1 Overall frequency distribution of febrile neutropenic patients with respect to clinical diagnosis.

Table 1 Frequency distribution of febrile neutropenia among patients with different types of hematological malignancies (N = 227)

Type of hematological malignancy	Febrile neutropenic patients *n* (%)
ALL	79 (34.80)
B-cell ALL	62 (27.31)
AML	32 (14.09)
T-cell ALL	12 (5.28)
NHL	10 (4.4)
DLBCL	9 (3.96)
CML	9 (3.96)
HL	4 (1.76)
Burkitt's lymphoma	4 (1.76)
HGBCL	3 (1.32)
T-cell LBL	2 (0.88)
Splenic lymphoma	1 (0.44)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; DLBCL, diffuse large B-cell lymphoma; HGBCL, LBL-lymphoblastic lymphoma; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma.

No statistically significant difference was observed between patients with hematological and nonhematological malignancies with respect to growth of potentially pathogenic microorganisms obtained in culture (*p*-value:0.077; confidence interval [CI]: –0.004 to 0.21), type of microbial isolates obtained in culture (bacterial vs. fungal [*p*-value: 0.34; CI: could not be calculated]; gram-negative bacilli vs. gram-positive cocci [*p*-value: 0.33; CI: –0.082 to 0.32]), and gender (*p*-value: 0.44; CI: 0.65–0.17), respectively.

(4) *Antibiotic susceptibility*: ►**Tables 4** and **5**, respectively summarize the percentage antibiotic resistance pattern of predominant gram-negative bacilli (*Klebsiella spp.*, *E. coli*, and *Acinetobacter spp.*) and gram-positive cocci (Coagulase negative *Staphylococcus spp.*).

Among the less frequently isolated bacterial isolates were *Enterobacter spp.* (3), *P. aeruginosa* (2), *Citrobacter spp.* (2), and *Enterococcus spp.* (1), respectively. Hundred percent in vitro resistance to ampicillin (*Enterobacter spp.* and *Citrobacter spp.*), fluoroquinolones (*Citrobacter spp.*), and co-trimoxazole (*Citrobacter spp.*), respectively was observed. Among the two *P. aeruginosa* isolates, one was pan sensitive and the other was resistant to aztreonam and gentamicin, respectively. *Enterococcus* species exhibited in vitro susceptibility to tigecycline, linezolid, chloramphenicol, and resistant to high level gentamicin (120 µg), respectively. In vitro tigecycline susceptibility test results were interpreted as per European Committee on Antimicrobial Susceptibility Testing Guidelines (EUCAST) 2019.[17]

Table 2 Frequency distribution of febrile neutropenia among patients with different types of nonhematological malignancies (N = 79)

Type of nonhematological malignancy	Febrile neutropenic patients *n* (%)
Ca gallbladder	19 (24.05)
Ca oral cavity	10 (12.65)
Ca urinary bladder	7 (8.86)
Ca lung	7 (8.86)
Ca breast	5 (6.33)
Osteosarcoma	4 (5.06)
Ca endometrium	4 (5.06)
Ca ovary	3 (3.79)
Ca stomach	3 (3.79)
Ca pancreas	2 (2.53)
Ca rectum	2 (2.53)
Ca lower lip	2 (2.53)
Ca larynx	2 (2.53)
Ewing sarcoma	2 (2.53)
Metastatic synovial sarcoma	2 (2.53)
Ca tongue	2 (2.53)
Ca buccal mucosa	1 (1.26)
Nasopharyngeal carcinoma	1 (1.26)

Abbreviation: Ca, cancer.

Discussion

Patients with underlying malignancies receiving cytotoxic antineoplastic therapy sufficient to adversely affect myelopoiesis and the developmental integrity of the gastrointestinal mucosa, are at risk for invasive infection due to microorganisms that translocate across intestinal mucosal surfaces. Fever may be the earliest and only sign of infection in neutropenic patients owing to muted neutrophil-mediated inflammatory response. Early recognition of neutropenic fever is critical for prompt initiation of empiric systemic antibacterial therapy to avoid progression to a sepsis syndrome and possibly death.[18]

Chemotherapy-induced mucositis occurs throughout the alimentary system. Seeding of the bloodstream with endogenous gastrointestinal tract flora is believed to cause the majority of episodes of FN. Also, administration of

Table 3 Frequency distribution of microorganisms isolated from paired peripheral blood samples of febrile neutropenic patients (*N* = 83)

Organisms isolated	Type of malignancy		Total
	Hematological malignancies *n* (%)	Nonhematological malignancies *n* (%)	
Klebsiella spp.	18 (21.7)	2 (2.4)	20
Escherichia coli	11 (13.2)	4 (4.8)	15
Acinetobacter spp.	11 (13.2)	1 (1.2)	12
Citrobacter spp.	2 (2.4)	0 (0)	2
Enterobacter spp.	1 (1.2)	2 (2.4)	3
Pseudomonas aeruginosa	2 (2.4)	0 (0)	2
Coagulase negative *Staphylococcus spp*.	14 (13.2)	6 (1.2)	20
Enterococcus spp.	1 (1.2)	0 (0)	1
Candida spp.	7 (10.3)	0 (0)	7
Trichosporon spp.	1 (1.2)	0 (0)	1
Total	68 (81.9)	15 (18.1)	83

chemotherapy not only decreases the number of neutrophils but also results in chemotactic and phagocytic defects. Immune defects related to underlying hematologic disorders, in addition to the immunosuppressive effects of chemotherapy, also place patients at higher risk for infection.[18,19]

In the present study, microbiologically confirmed BSIs were more commonly observed in male patients. Similar findings have been reported by various authors from different parts of the world.[3,20-28] However, there is no specific explanation for this finding. The most common age group of patients in this study was 0 to 10 years which is in agreement with the study conducted by Kamonrattana et al.[28]

More number of FN patients in our study, had underlying hematological as compared with nonhematological malignancies (solid tumors). These observations are in agreement with those of studies conducted by various authors.[3,20,23,24,28,29] It is a well-established fact that FN is more commonly observed in patients with hematological malignancies probably due to bone marrow dysfunction induced by underlying disease and chemotherapy.

Microbiologically confirmed BSIs were observed in 83 out of 306 patients (27.1%). Similar observations were made by Mandal et al[30] The prevalence of microbiologically confirmed BSIs in FN patients with hematological and nonhematological malignancies was 22.2% (68/306) and 4.9% (15/306), respectively. The reported prevalence of BSIs in patients with hematological malignancies ranges from 11 to 38%.[8] Low culture positivity rates in these patients may be explained in general by insufficient sample volume, prior administration of antibiotics, and provision of inappropriate culture conditions not suitable for growth of anaerobes and fastidious microorganisms, respectively. In the present study, all paired peripheral blood samples were subjected to aerobic culture only. Also, 22 out of 306 patients were on antibiotic therapy and blood cultures of 18 of these patients were sterile.

In this study, gram-negative bacilli were predominantly isolated in culture with *Klebsiella spp*. being the most common. Similar results were obtained in studies conducted by El-Mahallawy et al, Esbenshade et al, and Kokkayil et al.[23-25,31] Among gram-positive bacteria, coagulase-negative staphylococci were the predominant isolates obtained in culture. Similar trend has also been reported by several other studies.[23-25,27,32]

Varying resistance to different antibiotics was observed among gram-negative and positive bacteria, respectively. Among gram-negative bacilli, percentage resistance to aminoglycosides, β-lactam/β-lactamase inhibitor combinations, fluoroquinolones, cephalosporins, carbapenems, chloramphenicol, ampicillin, co-trimoxazole, and doxycycline was 26.6 to 91.7%, 8.3 to 86.6%, 10 to 66.7%,13.3 to 73.3%, 8.3 to 73.3%, 80 to 93.3%, 13.3 to 20%, 16.7 to 66.6%, and 13.3 to 16.7%, respectively. In case of CoNS, percentage resistance to aminoglycosides, macrolides, fluoroquinolones, ampicillin, clindamycin, linezolid, doxycycline, chloramphenicol, and co-trimoxazole was 40%, 35 to 50%, 60 to 65%, 90%, 45%, 30%, 40%, 40%, and 55%, respectively. These findings are in concordance with the studies conducted by various authors.[23,27,29,31,33-35] Blood stream infections due to antibiotic-resistant bacterial strains are on the rise in patients with neutropenic fever. The irrational use of broad-spectrum antibiotics as well as prolonged hospitalization may both add to the risk of acquiring infections with antibiotic-resistant bacteria. These pathogens are usually endogenous. Broad

Table 4 Percentage antibiotic resistance pattern of predominant gram-negative bacterial isolates (*N*1 = 20, *N*2 = 15, *N*3 = 12)

Antibiotics	*Klebsiella spp.* *n* (%)	*Escherichia coli* *n* (%)	*Acinetobacter spp.* *n* (%)
Aminoglycosides			
Amikacin	6 (30)	4 (26.6)	7 (58.3)
Gentamicin	8 (40)	8 (53.3)	11 (91.7)
β-lactam/β-lactamase inhibitors combinations			
Amoxicillin-clavulanate	7 (35)	13 (86.6)	NA
Piperacillin-tazobactam	6 (30)	5 (33.3)	4 (33.3)
Ampicillin-sulbactam	5 (25)	10 (66.6)	1 (8.3)
Fluoroquinolones			
Ciprofloxacin	2 (10)	2 (13.3)	8 (66.7)
Ofloxacin	2 (10)	2 (13.3)	NA
Penicillins			
Ampicillin	16 (80)	14 (93.3)	NA
Cephalosporins			
Cefuroxime	11 (55)	8 (53.3)	NA
Cefotaxime	13 (65)	11 (73.3)	5 (41.6)
Ceftriaxone	10 (50)	10 (66.6)	2 (16.6)
Cefixime	3 (15)	2 (13.3)	NA
Cefepime	5 (25)	5 (33.3)	2 (16.6)
Carbapenems			
Imipenem	7 (35)	11 (73.3)	4 (33.3)
Meropenem	4 (20)	5 (33.3)	3 (25)
Ertapenem	5 (25)	4 (26.6)	NA
Doripenem	5 (25)	2 (13.3)	1 (8.3)
Phenicols			
Chloramphenicol	4 (20)	2 (13.3)	NA
Folate pathway inhibitors			
Co-trimoxazole	12 (60)	10 (66.6)	2 (16.7)
Tetracyclines			
Doxycycline	3 (15)	2 (13.3)	2 (16.7)

Abbreviations: NA, not applicable; *n*, number of resistant isolates; *N*1, *N*2, *N*3, total number of isolates of *Klebsiella spp*., *Escherichia coli* and *Acinetobacter spp*., respectively

spectrum antibiotics given as treatment or prophylaxis exert selection pressure leading to the survival of resistant strains of bacteria, particularly in the gut.[36]

Some of the limitations of this study were as follows: (1) Speciation of microbial isolates could not be performed as conventional methods of microbial identification were used. (2) Anaerobic blood culture was not done owing to infrastructure-related issues. (3) Special growth conditions for fastidious organisms could not be provided owing to non-availability of special media. (4) Specific resistance categories like methicillin resistance, vancomycin resistance, extended-spectrum beta-lactamases, metallo-β-lactamases, etc., were not looked into. (5) Antifungal susceptibility testing could not be performed. (6) Treatment outcomes of the patients were not analyzed.

It is evident from the results of this study that BSIs due to antibiotic-resistant bacteria are prevalent in FN patients receiving treatment at our center. BSIs with MDR pathogens in FN patients can lead dire complications and high mortality rates. Implementation of antimicrobial stewardship program along with evidence-based hospital infection control practices is the need of the hour.

Table 5 Percentage antibiotic resistance pattern of coagulase negative Staphylococci (N = 20)

Antibiotics	Coagulase negative *Staphylococcus spp. n* (%)
Aminoglycosides	
Amikacin	NA
Tobramycin	NA
Gentamicin	8 (40)
Macrolides	
Azithromycin	7 (35)
Erythromycin	10 (50)
Fluoroquinolones	
Ciprofloxacin	12 (60)
Ofloxacin	13 (65)
Penicillins	
Ampicillin	18 (90)
Lincosamides	
Clindamycin	9 (45)
Oxazolidinones	
Linezolid	6 (30)
Tetracyclines	
Doxycycline	8 (40)
Phenicols	
Chloramphenicol	8 (40)
Folate pathway inhibitors	
Co-trimoxazole	11 (55)

Abbreviations: NA, not applicable; *n*, number of resistant isolates; *N*, total number of isolates.

Source(s) of Support
None.

Conflict of Interest
None.

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