Asian Pacific Journal of Cancer Care
Vol 8 No 4 (2023), 691-695
Original Research

Bloodstream Infections in Paediatric Cancer Patients with Febrile Neutropenia in a Tertiary Cancer Centre in North-East India

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Background: The aim of the present study was to study the pattern of microbial flora, their susceptibility patterns, and clinical variables among bloodstream infections in febrile neutropenic patients with solid tumors and hematological malignancies in the paediatric age group in North-East India.
Methods: It was a retrospective and observational study done in a single tertiary care cancer centre in North-East India. The study period was from 1st January 2020 to 31st December 2021. The study population included all the patients below the age of 18 years who developed febrile neutropenia during treatment for a diagnosed cancer.
Results: A total of 378 blood culture samples were studied. Febrile neutropenia was found in 252 patients (66.7%). There were 45 positive blood cultures (17.8%) among them. Gram-negative and gram-positive organisms accounted for 62% and 38% of all positive cultures respectively. *Escherichia coli* (39%) was the most common gram-negative isolate, followed by *Klebsiella pneumoniae* (32%), *Pseudomonas aeruginosa* (18%) and *Acinetobacter baumannii* (7%). Coagulase-negative Staphylococci (CoNS) was the most common gram-positive isolate (47%). Sensitivity to beta-lactam/beta-lactamase inhibitor (BL/BLI) antibiotics like cefaperazone/sulbactam was seen in 60% of *Pseudomonas isolates*. Sensitivity to colistin was noted in 89% of *Klebsiella* and 82% of *E. coli* isolates. The incidence of methicillin resistant *staphylococcus aureus* (MRSA) was 50%.
Conclusion: The knowledge of the microbiological profile and resistance patterns among patients treated for paediatric cancer with febrile neutropenia is a key factor in deciding the antimicrobial policy.

Introduction

Febrile neutropenia is a significant cause of morbidity and mortality among cancer patients in the paediatric age group. Bacteremia is the cause of the febrile neutropenia in about one-fourth of the patients. A high mortality rate has been reported in published literature, especially in those who develop septic shock and pneumonia [1,2]. Despite the advances in treatment protocols including effective empirical broad-spectrum antibiotics, antifungals, and granulocyte colony-stimulating factors, febrile neutropenia remains a therapeutic challenge. It prolongs hospital stay, increases health-care costs, and compromises chemotherapy delivery with delays and dose reductions.

The aim of the present study was to study the pattern of microbial flora, their susceptibility patterns, and clinical variables among bloodstream infections in febrile neutropenic patients with solid tumors and hematological malignancies in the paediatric age group in North-East India.

Materials and Methods

It was a retrospective and observational study done in a single tertiary care cancer centre in North-East India. The study period was from 1st January 2020 to 31st December 2021. The study population included all the patients below the age of 18 years who developed febrile neutropenia during treatment for a diagnosed cancer. Data was collected from the patient case records, hospital electronic medical record system and the registers maintained in the Department of Microbiology. The patient's identifiable information details were de-identified upon entry into the case record forms. The study was approved by the institutional ethics committee (IEC) with waiver of consent.

Blood cultures and bacteremia

Blood cultures were done when the patient developed fever and blood investigations were checked at the same time. A blood culture was deemed positive when one or more samples showed the presence of an organism. The exception was in the case of coagulase negative *Staphylococci* (CoNS), and in such cases, two separate positive blood cultures were necessitated for representing a true result. We studied samples of peripheral blood as well as blood drawn through central venous catheters (CVCs), peripherally inserted central catheters (PICC lines) and catheter tip cultures. The BacT/ALERT system was used for studying the blood culture samples. It is a quantitative blood culture system, continuously monitoring the blood for bacteria and fungus every 10 minutes. It works on colorimetric detection of carbon dioxide (CO_2) produced by the organisms inside the blood culture bottles, which is sensed by a CO_2 sensor. Positive cultures are recognized by a computer-driven algorithm that monitors both initial and increased concentrations of CO_2.

The bacterial isolates were identified and antimicrobial susceptibility testing on isolates were performed using (bioMérieux Inc., Durham, NC, USA). It is an automated microbiology system utilizing growth-based technology.

Institutional antibiotic use policy

The institutional policy was to start all patients with febrile neutropenia on empirical antibiotic therapy with cefoperazone-sulbactam and aminoglycoside. The use of higher end antibiotics like piperacillin-tazobactum, meropenem, tigecycline, colistin, vancomycin or teicoplanin were as per the report of culture and sensitivity or when the clinical scenario deteriorated over time as per the clinician's discretion in consultation with the hospital infection control (HIC) team.

Statistical analysis

Variables studied included clinical parameters including age, co-morbidity, primary malignancy, presence of fever, number of days of intensive care unit (ICU) and hospital stays, outcomes including whether recovered or succumbed and laboratory parameters including specimen types, presence of co-infection, blood leukocytic count (DLC) and absolute neutrophil count (ANC) and antibiotic sensitivity profile. Descriptive statistics were used to elucidate the results with the use of median values, range and percentages.

Working definition of Febrile Neutropenia: Febrile neutropenia was defined as an oral temperature of ≥ 38°C on two occasions, at least one hour apart with a 12-hour period or a single temperature of > 38.5°C with an absolute neutrophil count of ≤ 0.5 × 10^9/L or ≤ 1.0 ×10^9 with a predictable decline to ≤ 0.5 × 10^9/L in 24 to 48 hours.

Results

A total of 378 blood culture samples were collected from paediatric patients less than the age of 18 years during the study period. Febrile neutropenia, as per definition, was found in 252 patients (66.7%). Thus, the denominator for interpretation of results of our study is 252. There were 45 positive blood cultures (17.8%) among them. Gram-negative and gram-positive organisms accounted for (28/45) 62% and (17/45) 38% of all positive cultures respectively. The demographic and clinical characteristics of the patients are enlisted in Table 1.

Escherichia coli (39%) was the most common gram-negative isolate

Characteristics	Number/ Value (Total number = 45)
Age	2
≤ 12 months	33
>1 year to ≤ 12 years	10
Sex	
Male	25
Female	20
Cancer type	
Acute myelocytic leukaemia (AML)	20
· Induction	15
· Consolidation	3
· Maintenance	2
Acute lymphoblastic leukaemia (ALL)	17
· Induction	6
· Consolidation	6
· Re-intensification	3
· Maintenance	2
Diffuse large B cell lymphoma	3
Lymphoblastic lymphoma	1
Burkitt lymphoma	1
Ewing’s sarcoma of bone	1
Neuroblastoma	1
Soft tissue sarcoma	1

Table 1. Demographic and Clinical Characteristics of the Patients.

, followed by *Klebsiella pneumoniae* (32%), *Pseudomonas aeruginosa* (18%) and *Acinetobacter baumannii* (7%). The other organism identified was *Burkholderia cepacia* (one isolate). Coagulase-negative *Staphylococci* (CoNS) was the most common gram-positive isolate (47%) and it was followed by *Staphylococcus aureus* (35%) and *Enterococcus faecalis* (18%). Table 2 shows the details of the microorganisms isolated in the blood cultures.

Organism	Number (Percentages)
Gram positive organisms	17/45 (38)
Coagulase-negative staphylococcus (CoNS)	08 (47)
Staphylococcus aureus	06 (35)
Enterococcus faecalis	03 (18)
Gram-negative organisms	28/45 (62)
Escherichia coli	11 (39)
Klebsiella pneumoniae	09 (32)
Pseudomonas aeuginosa	05 (18)
Acinetobacter baumannii	02 (7)

Burkholderia cepacia	01 (4)

Table 2. Organisms Isolated from Blood Cultures.

MSSA, Methicillin sensitive Staphylococcus aureus; MRSA, Methicillin resistant Staphylococcus aureus

Sensitivity to beta-lactam/beta-lactamase inhibitor (BL/BLI) antibiotics like cefaperazone/sulbactam was seen in 60% of *Pseudomonas* isolates but the sensitivity was much less in case of *Klebsiella* species (33%) and *Escherichia coli* isolates (18%) (Table 3).

Isolate	Aminoglycosides (%)	Carbapenems (%)	BL/BLI (%)	Colistin
Escherichia coli	6/11 (55)	4/11 (36)	2/11 (18)	9/11 (82)
Klebsiella pneumoniae	4/9 (44)	4/9 (44)	3/9 (33)	8/9 (89)
Pseudomonas aeruginosa	5/5 (100)	4/5 (80)	3/5 (60)	5/5 (100)
Acinetobacter baumannii*				
Burkholderia cepacian**				

Table 3. Gram-negative Isolates and Their Sensitivity Profile.

BL/BLI, Beta lactam/ Beta lactamase inhibitor; *Only two isolates and ** only one isolate and so percentages of sensitivity not included.

Sensitivity to aminoglycoside group of antibiotics was seen in all *Pseudomonas* isolates (100%) while 55% of *E. coli* and 44% of *Klebsiella* species were sensitive to them. Carbapenem sensitivity was noted in 80% of *Pseudomonas* isolates and 44% and 36% of *Klebsiella* species and *E. coli* respectively. Resistance to colistin was seen in our study. Sensitivity to colistin was noted in 89% of *Klebsiella* and 82% of *E. coli* isolates. All *pseudomonas* isolates were colistin sensitive. ESBL (Extended spectrum beta-lactamase) producer prevalence was 90% (18 out of 20 samples). This included 9 out of 11 isolates of *E. coli* and all 9 isolates of *K. pneumoniae*. The prevalence of CRE (Carbapenem-Resistant Enterobacterales) was 60% (12 out of 20 samples). This included 7 out of 11 isolates of *E. coli* and 5 out of 9 isolates of *K. pneumoniae*.

The incidence of methicillin resistant *staphylococcus aureus* (MRSA) was 50%. There was no vancomycin resistant *enterococcus* (VRE) in our study (Table 4).

Organism	ERYC	CIP	MET	GENT	VANCO	TEC	LIN
Staphylococcus aureus (n=6)	2 (33.33)	4 (66.66)	3 (50)	5 (83)	6 (100)	6 (100)	6 (100)
CoNS (n=8)	3 (37.5)	5 (62.5)	2 (25)	8 (100)	8 (100)	8 (100)	8 (100)
Enterococcus species. (n=3)	1 (33.33)	2 (66.66)	-	2 (85.71)	2 (100)	2 (100)	2 (100)

Table 4. Antibiotic Sensitivity Pattern in (%) Most of the Prevalent Gram-positive Bacteria Sensitivity (%).

*Results are expressed as a percentage of the number of isolates in each group. ERYC – Erythromycin; CIP – Ciprofloxacin; MET – Methicillin; GENT – Gentamicin; TEC – Teicoplanin; LIN – Linezolid; CoNS – Coagulase-negative Staphylococci

The use of high-end antibiotics including colistin, vancomycin, tigecycline and teicoplanin was seen

in five patients (11.1%) based on culture and sensitivity profile of the organisms.

The mortality rate seen in our study was 15.5% (7 patients). Out of them, five were patients with acute myeloid leukaemia, all in induction phase of treatment. The pathogens recovered in their blood cultures were *Klebsiella pneumoniae* (2 patients), *Escherichia coli* (1 patient), *Enterococcus spp.* (1 patient), *Staphylococcus aureus* (1 patient). The other two patients who died were on treatment for diffuse large B-cell lymphoma and B cell acute lymphoblastic leukaemia (ALL) on induction phase and both had *Escherichia coli* recovered from their blood samples.

All the patients with febrile neutropenia and positive blood culture were receiving anti-cancer drugs for their underlying malignancy and this complication resulted in treatment interruption in all of them. The use of granulocyte-monocyte colony stimulating factor (GM- CSF) is universal in patients developing neutropenia due to anti-cancer treatment, including in those who develop febrile neutropenia. Neither granulocyte transfusion nor buffy coat transfusion was done in our patients.

Discussion

We have taken the United Kingdom (UK) National Institute of Health and Care (NICE) definition of febrile neutropenia as the working definition of the condition to do our study [3]. Febrile neutropenia is one of the common complications of treatment of cancer in the paediatric age group. The incidence of this condition has been variously reported to be between 2 to 21%. It is usually seen when myelosuppressive drugs are used for the treatment of haematological or solid cancers. The contributory factors to the development of febrile neutropenia include decreased blood cell counts, marrow replacement, qualitative defects of humoral and cellular immunity, catheter-related infections and mucositis. Chemotherapy-induced mucositis compromises the gastrointestinal mucosal barrier and causes translocation of gut organisms into the bloodstream. This accounts for the gram-negative pathogens isolated in this condition [4,5,6].

The prevalence and spectrum of bloodstream infections is varied for different geographical regions [7,8,9]. The developed countries usually report a higher incidence of gram-positive organisms in blood. However, the trend seen in our region of the World is still predominantly gram-negative bacteremia. The lower use of long-term central venous catheters in developing nations compared to developed ones may be one of the reasons [10,11]. The reverse may also be true. A study was done in El Salvador, which is a developing country, comprising of 85 patients of paediatric age group who had febrile neutropenia in the study period of one year. The authors reported a higher incidence of gram-positive bacteremia (60.9%) compared to gram-negative infections (47.8%) [12]. This highlights the need of local database of the prevalent microbiological profile. In our study, we found 62% and 38% of gram-negative organisms and gram-positive organisms in the blood of the patients with febrile neutropenia with documented bloodstream infection. In a study from a tertiary care cancer centre in South India, out of 1045 blood culture samples in patients with febrile neutropenia, only 82 (7.5%) were positive. The same study showed 61% and 39% of gram-negative and gram-positive bacteremia respectively [13]. In another study from a different oncology centre in South India over a two-year period, out of 300 patients with febrile neutropenia, 15% blood culture samples had isolates and gram-negative and gram-positive organisms were identified in 58% and 40% cases respectively with 2% being fungi [14]. To the best of our knowledge, our report is the first about the microbiological profile of bloodstream infections in febrile neutropenia among cancer patients from North-East India.

A high degree of resistance was seen against beta- lactam/beta-lactamase inhibitor (BL/BLI) antibiotics (cefaperazone-sulbactam) in our study. This is often the first-line treatment for febrile neutropenia at our institute as well as in many other centres in India and the world. Sensitivity of aminoglycosides to *E. coli* and *Klebsiella* species was very less in our study and these are two very important pathogens. Hence, the knowledge of these resistance patterns is very important to the

clinicians in deciding antimicrobial treatment correlating with the clinical course of the disease. Even colistin resistance was seen in 11% and 18% of *Klebsiella* and *E. coli* isolates respectively. The incidence of MRSA was very high (50%) in our study and this is another alarming finding. In a study from a tertiary cancer centre in Western India, out of 484 isolates that represented bloodstream infections, an 18% incidence of oxacillin resistance was noted among the *Staphylococcus aureus* isolates [15]. Fortunately, our study did not reveal any isolate of vancomycin resistant *enterococcus* (VRE).

One limitation of our study is that we did not correlate the presence or absence of malnutrition with the clinical outcomes. Studies have shown that the presence of protein-energy malnutrition (PEM) significantly increases the adverse outcomes in patients with febrile neutropenia with almost doubling of mortality rate [16]

We believe that the results of our study will add to the existing data on the epidemiology of infections in paediatric cancer patients while being treated in various cancer centres in India.

In conclusion, the knowledge of the microbiological profile and resistance patterns among patients treated for paediatric cancer with febrile neutropenia is a key factor in deciding the antimicrobial policy, preventing antibiotic resistance and counteracting adverse clinical outcomes.

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