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# AN OBSERVATIONAL STUDY TO DETERMINE BLOODSTREAM INFECTIONS IN FEBRILE NEUTROPENIC PAEDIATRIC CANCER PATIENTS AND THEIR CORRELATION WITH BLOOD PROCALCITONIN LEVELS

Medical Microbiology

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| **Dr. Tanya Pandey** | Senior Resident, Department of Microbiology, King George's Medical University (KGMU), Lucknow |
| **Prof. R.K. Kalyan** | Professor, Department of Microbiology, KGMU, Lucknow |
| **Dr. Nishant Verma** | Additional Professor, Department of Paediatrics, KGMU, Lucknow |
| **Prof. Vimala Venkatesh** | Professor, Department of Microbiology, KGMU, Lucknow |
| **Prof. Prashant Gupta** | Professor, Department of Microbiology, KGMU, Lucknow |
| **Dr. Sheetal Verma** | Additional Professor, Department of Microbiology, KGMU, Lucknow |

## ABSTRACT

**Background:** Febrile neutropenia is a common and critical complication in paediatric cancer patients undergoing chemotherapy, significantly increasing their susceptibility to severe infections, including bloodstream infections Reliable biomarker for early diagnosis is essential for improving patient outcomes. This study was planned to observe correlation between blood stream infections and a biomarker procalcitonin (PCT) levels in paediatric cancer patients. **Materials and Methods:** This prospective observational study was conducted at a tertiary care hospital in northern India. A total of 106 paediatric patients under 18 years , undergoing treatment for various cancers and experiencing chemotherapy-induced neutropenia, were enrolled. Procalcitonin levels and blood cultures were done to check the septicemia and infections.**Results:** Among enrolled 106 children, the mean age was 6.42 ± 2.68 years, with a range from 2.67 to 15 years. The majority of children were male (81.2%). Elevated procalcitonin levels were detected predominantly in children with Gram-negative bacterial infections, showing higher levels ($p< 0.01$), than in patients suffering from Gram positive bacterial infection. Out of the 106 patients, 32 (30.2%) showed positive blood cultures. The most frequently isolated organisms were Gram-negative bacteria, *with Escherichia coli being* a significant contributor. Among Gram-positive bacteria, Coagulase-negative staphylococci were the most common. Additionally, one fungal isolate, *Candida auris*, was isolated. **Conclusion:** Our findings establishes a statistically significant between elevated procalcitonin levels and blood stream infections in febrile neutropenic chidren suffering form cancer. Monitoring procalcitonin levels can serve as a valuable diagnostic tool for early diagnosis of blood stream infections guiding for timely and targeted therapeutic interventions.

## KEYWORDS

Paediatric cancer patients, Febrile neutropenia, Procalcitonin, Blood stream infections, Septicaemia, Neutropenia

## INTRODUCTION

Infection is a critical threat to cancer patients undergoing chemotherapy-induced neutropenia, despite progress in treatment of febrile neutropenia (FN) with better antibiotics, antifungals and granulocyte colony-stimulating factors. However, blood stream infections whether with or without a primary site, remain the most severe bacterial complications.[1,2] Mortality rates in patients from febrile neutropenia (FN) range from 5% to 20%. Mortality rates can exceed 50% in patients with severe infections, such as septic shock or pneumonia, despite timely antibiotic treatment.

Existing research primarily focused on patients with bacteremia during febrile neutropenia, particularly those with hematological malignancies undergoing hematopoietic stem cell transplantation.[45] The risk of bacteremia in febrile neutropenia increases with prolonged neutropenia, hematologic malignancies, intensive chemotherapy, mucosal barrier injury, central venous catheters, and exposure to multidrug-resistant hospital-acquired infections.[6] Bacteraemia is still a major issue in trials for empirical treatments of febrile neutropenia with 29% of FN episodes linked to bacteraemia.[7] Viscoli. C et al, study reported that Gram positive and Gram negative bacteria were equally causative agents for these infections.[8] *Escherichia coli, Klebsiella spp., and Pseudomonas aeruginosa* are the main Gram-negative bacteria causing bacteraemia. Coagulase-negative staphylococci are the predominant Gram- positive bacteria, alongside several other less frequently isolated Gram-positive bacteria.[8,9]

A reliable marker for timely diagnosis of life-threatening infections with high specificity and sensitivity is needed. Blood cultures are the gold standard for diagnosing septicaemia but time taking and sometimes ineffective.[10] Serological biomarkers C-Reactive Protein (CRP) and procalcitonin can help in rapid diagnosis of septicaemia. PCT in particular rises early in bacterial infections and correlates with infection severity, making it useful in sepsis evaluation.[11,12,13,14,15] Quick diagnosis and appropriate empirical antibiotic treatment based on clinical status and microbial susceptibility improve prognosis of febrile neutropenia patients suffering from bacterial infections.

## MATERIAL AND METHODS

Study design: This is a prospective ,hospital based observational study

Sample Size: V. Radhakrishnan et al

n= Z2P(1-P)/D2
Confidence level-95%
Z=1.96
D=5%, Prevalence=7.5%
Sample size= 106

This study was conducted in department of microbiology in association with Paediatric department of Gandhi memorial and associated hospital of King George's Medical University Lucknow Uttar Pradesh a tertiary care hospital in northern India , a prospective hospital- based observational study focused on paediatric cancer patients experiencing febrile neutropenia. The study spanned from August 2023 to July 2024. In this study we have enrolled paediatric cancer patients under 18 years who developed febrile neutropenia during treatment . Data were collected from patients fulfilled the inclusion criteria of confirmed haematological and/or oncological disease with febrile neutropenia. Blood sample collection was focused on patients with defined neutropenia, with an Absolute Neutrophil Count(ANC) below 500 per microlitre or between 500-1000/µl expected to decrease to below 500/ µl in 48 hours. Ethical approval was taken from the institutional ethics committee (IEC) of King George's Medical University, Lucknow.

### Sample Processing

Serial Procalcitonin levels were measured in all collected blood samples as standard operational protocol of manufacturer, using the minividas automated immunoassay system of bioMérieux..Two sets of blood for culture were collected. Each blood sample was inoculated into BacT/ALERT bottles in recommended volumes. A blood culture was considered positive if one or more samples indicated the presence of an organism. An exception was made for *Coagulate-negative Staphylococci* (CoNS), where two separate positive blood cultures were required to confirm the presence of a true infection. Subculture on

blood agar, Chocolate agar and MacConkey solid agar plates from the positive BacT/ALERT culture bottles. Identification of bacteria were confirmed using MALDI TOF MS, and antimicrobial susceptibility testing followed by CLSI guidelines 2023.

**The primary outcomes** include the identification of bacterial and fungal isolates from bloodstream infections during the febrile neutropenic period, the correlation between procalcitonin levels and bloodstream infections, and the antimicrobial susceptibility patterns of all isolated strains.

**The secondary outcomes** include to know the risk factors and their correlation with bloodstream infections

**Inclusion Criteria:** All pediatrics patients with confirmed hematological or oncological disease with febrile neutropenia, fever (single oral temperature ≥ 38.3ºC or ≥ 38.ºC sustained for >1hour or that occur twice within 24 hour period, defined neutropenia ( Absolute neutrophil count < 500 µl or 1000 µl expected to decrease 500 over the subsequent 48 hours.

**Exclusion criteria:** Patients taken antibiotic treatment prior to admission to our hospital, not ready to give consent.

**Statistical Analysis:** Data was analysed using SPPS software. Association of blood stream infections with procalcitonin in febrile neutropenic pediatrics patients was assessed as mean ± standard deviation. Chi square and Fischer's exact test was used to analysed categorical variables while continuous variable were analysed using student's t- test.

**Ethic:** This study was approved by the Institutional Ethics Committee of King George's Medical University Uttar Pradesh.

## RESULTS

In this study , Procalcitonin levels were found to be lower in patients with sterile cultures (0.05-7.34ng/ml) , followed by those with Gram-positive culture findings (0.10-9.4 ng/ml). The highest procalcitonin (0.10-34.20ng/ml ) levels were observed in patients infected with Gram-negative bacteria. Among the 106 blood samples collected, 74 (69.8%) ) were found to be sterile. Gram-negative bacteria were detected in 20 cases (18.9%), and Gram-positive were observed in 11 cases (10.4%) only. Additionally, one specimen (0.9%) tested positive for a fungus (*Candida auris*). The demographic and clinical characteristics of the patients are mentioned in table 1.

**Table 1: Demographic Profile and clinical characteristics of Study Population (N=105)**

| | | Statistics | |
|---|---|---|---|
| | | No. | % |
| 1- | **Age Group** | | |
| | <5 yrs | 39 | 37.1 |
| | 5-10 yrs | 53 | 50.5 |
| | >10 yrs | 13 | 12.4 |
| 2- | **Gender** | | |
| | Female | 20 | 19.0 |
| | Male | 85 | 81.0 |
| 3- | **Underlying Cancer (Diagnosis)** | | |
| | Acute lymphoblastic leukemia | 82 | 78.1 |
| | Acute myeloid leukemia | 5 | 4.8 |
| | Burkitt lymphoma | 1 | 1.0 |
| | Chronic myeloid leukemia | 1 | 1.0 |
| | Diffuse large B cell lymphoma | 5 | 4.8 |
| | Hodgkin's lymphoma | 7 | 6.7 |
| | Non-Hodgkin's lymphoma | 2 | 1.9 |
| | T-lymphoblastic lymphoma | 2 | 1.9 |

Among isolated Gram negative bacteria *Escherichia coli* (30%) was most, followed by *Klebsiella pneumoniae* and *Acinetobacter baumanii* (25% each). Pseudomonas aeruginosa comprised 15%, while Acinetobacter schindleri was less prevalent 5%. Coagulase-negative staphylococci (CoNS) was common among gram-positive isolates (54.6%), followed by Enterococcus spp (36.3%) and Staphylococcus aureus (9.1%). table 2 shows the details of the isolated organisms.

**Table 2: Type of microbial isolates from Study population ( N = 106)**

| | ***Microbial growth observed N=32*** | ***No.*** | ***%*** |
|---|---|---|---|
| ***SN*** | ***Gram negative isolates*** | *20* | *18.9* |
| *1-* | *Escherichia coli* | *6* | *30* |
| *2-* | *Acinetobacter baumaani* | *5* | *25* |
| *3-* | *Klebsiella pneumoniae* | *5* | *25* |
| *4-* | *Pseudomonas aeruginosa* | *3* | *15* |
| *5-* | *Acinetobacter schindieri* | *1* | *5* |
| ***SN*** | ***Gram positive isolates*** | *11* | *10.4* |
| ***1-*** | ***CONS( Coagulase negative Staphylococcus )*** | *6* | *54.6* |
| 1a- | *Staphylococcus hominis* | *3* | *27.2* |
| 1b- | *Staphylococcus haemolyticus* | *2* | *18.3* |
| 1c- | *Staphylococcus arlettae* | *1* | *9.1* |
| 2- | *Enterococcus faecium* | *3* | *27.2* |
| 3- | *Enterococcus faecalis* | *1* | *9.1* |
| 4- | *Staphylococcus aureus* | *1* | *9.1* |
| ***SN*** | ***Fungal isolates*** | *1* | *0.9* |
| 1- | *Candida auris* | *1* | *1* |

We observed many risk factors associated with blood stream infection in these children included the using of central line venous catheters in one-third of gram-negative cases, but none in patients infected with gram-positive bacteria . All patients receiving chemotherapy had longer duration neutropenia (≥7 days) significantly more common in gram-negative infection (61.9%) than in gram-positive ones (9.1%). Hospital stays of 3-14 days and over 14 days were significantly more frequent in gram-negative infections. The most common risk factors were neutropenia duration ≥7 days (17.1%) and hospital stay ≥48 hours. Gram- negative infections were predominantly in the induction phase (76.2%), while gram-positive infections were more in the consolidation or maintenance phase (64.6%). Table 3 shows association of risk factors with isolated organism in study population.

**Table 3: Association of Risk factors with isolated organism in study population (Microbial growth N= 32)**

| **Risk factors** | **Total (N=32)** | **Gram Positive(N=21)** | | **Gram Negative (N=11)** | |
|---|---|---|---|---|---|
| | | **No.** | **%** | **No.** | **%** |
| ESBL | 2 | 2 | 9.5 | 0 | 0.0 |
| Central line venous catheter | 7 | 7 | 33.3 | 0 | 0.0 |
| Urine catheter | 2 | 1 | 4.8 | 0 | 0.0 |
| Hosp. stay | | | | | |
| <3 days | 10 | 2 | 9.5 | 8 | 72.7 |
| 3-14 days | 13 | 10 | 47.6 | 3 | 27.3 |
| >14 days | 9 | 9 | 42.9 | 0 | 0.0 |
| Duration of neutropenia | | | | | |
| <7 days | 18 | 8 | 38.1 | 10 | 90.9 |
| ≥7 days | 14 | 13 | 61.9 | 1 | 9.1 |
| Chemo Phase | | | | | |
| Induction | 20 | 16 | 76.2 | 4 | 36.4 |
| Consolidation | 9 | 5 | 23.8 | 4 | 36.4 |
| Maintenance | 3 | 0 | 0.0 | 3 | 27.3 |
| Antibiotic usage | 26 | 20 | 95.2 | 6 | 54.5 |

In Vitro Sensitivity Testing: Among Gram-negative isolates, Pseudomonas spp. demonstrated 66.7% sensitivity to aminoglycosides and carbapenems, while Escherichia coli showed lower sensitivity, with 50% and 33.3% susceptibility, respectively. Klebsiella spp. exhibited 60% sensitivity to both aminoglycosides and carbapenems. Colistin sensitivity was observed in 100% of Klebsiella spp. and Pseudomonas spp., whereas Escherichia coli showed 83.3% sensitivity, with 16.7% demonstrating resistance to colistin. A significant level of resistance was noted against beta-lactam and beta-lactamase inhibitor antibiotics, except for ceftazidime, which retained high sensitivity in Pseudomonas spp. (100%) and Escherichia coli (83.3%). Among Gram-negative isolates, 45% were resistant to carbapenems and classified as multidrug-resistant (MDR) pathogens. The highest rates of carbapenem resistance were observed in Escherichia coli (66.7%), Klebsiella pneumoniae (60%), and Acinetobacter baumannii (40%). Pseudomonas aeruginosa and Acinetobacter schindleri did not show carbapenem resistance. All Gram-positive bacteria were sensitive to vancomycin and linezolid. However, one isolate of Staphylococcus aureus was found to be methicillin-resistant (MRSA). No vancomycin-resistant Enterococcus (VRE) isolates were detected. Notably, high resistance (>50%) to

ciprofloxacin and erythromycin was observed among Staphylococcus species. Serial procalcitonin (PCT) monitoring played a crucial role in guiding antibiotic duration, particularly in patients with high initial levels. Infections caused by Gram-positive bacteria, such as Staphylococcus aureus and Enterococcus faecium, showed a rapid decline in PCT levels within five days, allowing for a shorter antibiotic course of 5–7 days. In contrast, infections with Escherichia coli and Klebsiella pneumoniae exhibited a moderate decline over 7–10 days, requiring a longer treatment period. Persistent elevation of PCT levels beyond 10 days was observed in patients with Acinetobacter baumannii and Pseudomonas aeruginosa infections, necessitating extended antibiotic therapy of 14 days or more. PCT-guided therapy helped optimize antibiotic use, facilitating early discontinuation in patients with a rapid decline while ensuring prolonged treatment in those with persistent infection.

## DISCUSSION

Febrile neutropenia poses a significant threat to morbidity and mortality among children with cancer. Approximately a quarter of these patients experience febrile neutropenia as a result of bacteraemia.

In this study , we found a predominant age group of 5-10 years with average age 6.42 years and a male-to-female ratio of 4:1.Similarly Lima MAF et al (2023) reported an average age of 7.3 years, with males comprising 54.7%..[16] Al-Mulla NA et al. (2014) found an average age of 6.4 years with nearly equal gender distribution[17] . Our study found acute lymphoblastic leukemia in 78.1% of cases, Hodgkin's lymphoma in 6.7%, AML and diffuse large B-cell lymphoma each in 4.8% and other cancers less prevalent. Comparatively, Lima MAF et al. noted 64.8% leukemia and 6.6% lymphomas[16.] Al-Mulla NA et al. reported 47.8% leukemia, while T Amrita et al.[9] found 82.2% leukemia and 5.1% lymphomas, with other cancers like Ewing's sarcoma, neuroblastoma, and soft tissue sarcoma each at 2.2%.[9]

In our study, 69.7% blood culture samples were sterile, 18.9% Gram-negative isolates with Escherichia coli (30%) being the most common organism, 10.4% Gram-positive isolates with Coagulase-negative staphylococci (54.6%) being the most common, and 1% containing fungal isolate i.e Candida auris. Comparatively, Kara T et al. studied 71 patients and identified 111 bloodstream infection episodes, reporting 60.5% Gram-negative with Escherichia coli being the most frequent, 35.1% Gram-positive predominantly coagulasenegative staphylococcus species, and 4.4% fungal isolates[18]. Similarly, T Amrita et al.[9] found 45 positive blood cultures, constituting 17.8% of the total samples, with 62% being Gram- negative organisms with Escherichia coli being the most common and 38% being Gram- positive organisms mainly coagulase-negative staphylococcus species[9]. Likewise, V Radhakrishnan et al. reported that among 1045 blood culture samples, 7.5% tested positive for microbial growth, with 61% Gram-negative bacteria with Klebsiella pneumoniae (32%) was the most common Gram-negative isolate, and 39% Gram-positive organisms, mainly Staphylococcus aureus[19]. In contrast, Aslan S et al. analysed 811 isolates and found 27.5% were positive in blood cultures, with 56.4% being Gram-positive cocci, with the common isolated Gram-positive bacteria from blood being coagulase-negative staphylococcus, 18.9% being Gram-negative bacilli, with Escherichia coli being the most isolated organism, and 24.7% being fungi[20].

In our study, Procalcitonin (PCT) levels were higher in patients with Gram-negative isolates (19.27±10.56 ng/ml) compared to those with Gram-positive isolates (2.57±2.35 ng/ml). Similarly, X Luo et al. reported higher median PCT values in Gram-negative bloodstream infections compared to Gram-positive infections[21] . Likewise, Yang M et al. found elevated PCT levels in Gram-negative bacterial infections compared to Gram-positive infections[22] .

In our study, hospitalizations exceeding 14 days showed a significantly higher proportion of Gram-negative bacteremia compared to Gram-positive cases. Gram-negative infections were associated with an increased requirement for central venous catheter placement and a prolonged duration of neutropenia (≥7 days). Similarly, Rosenblum et al. [23] highlighted that prolonged hospitalization (over 48 hours) significantly increased the likelihood of positive blood cultures in neutropenic patients.

Central venous catheters have been consistently identified as a critical risk factor for bloodstream infections, as demonstrated in studies by Kara S.S. et al., Rondinelli et al., and Al Omar et al. [24–26]. These findings emphasize the importance of vigilant management of central venous catheters in hospitalized patients.

Study results align with those of Freifeld et al., who reported that the risk of bacteremia in febrile neutropenic patients increases with prolonged neutropenia, hematologic malignancies, intensive chemotherapy, mucosal barrier injury, central venous catheters, and exposure to multidrug-resistant hospital-acquired infections. The increased risk associated with prolonged hospitalization and the presence of central venous catheters further underscores the necessity of strict infection control measures in this vulnerable patient population.[6]

In this study, among Gram-negative isolates, we observed varying levels of sensitivity to antibiotics. Pseudomonas spp. demonstrated sensitivity to aminoglycosides in 66.7%, carbapenems 66.7% and 100% sensitive to ceftazidime. Although Escherichia coli showed low sensitivity to aminoglycosides (50%) and carbapenems (33.3%), but 83.3% to colistin. Klebsiella pneumoniae exhibited 60% sensitivity to aminoglycosides, 60% to carbapenems, and 100% to colistin. Resistance against beta-lactam/beta-lactamase inhibitors was significant across all pathogens. In contrast, to studies T.Amrita et al. and V Radhakrishnan et al reported higher sensitivity of Pseudomonas spp. to aminoglycosides and carbapenems and lower resistance rates overall, while Babu KG et al. highlighted extensive resistance among Gram- negative isolates, particularly to cephalosporins[27].

## CONCLUSION:

Our study concludes that procalcitonin has undergone extensive research and has proven to be a valuable tool in the rapid diagnosis of bacterial infections, monitoring conditions and guiding treatment.

**Conflict of Interest:** There is no any conflict of interest in the study

**Source of Funding:** There is no any funding agency for this study

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**Summary of the research:** In my research article, I explore the impact of blood stream infections on neutropenic paediatric cancer population, I investigate a significant correlation between elevated procalcitonin levels and blood stream infections. This study reveals monitoring procalcitonin levels can serve as a valuable diagnostic tool for early identification of blood stream infections, allowing for timely and targeted therapeutic interventions, shedding light on early diagnosis of sepsis.

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