

## Research Article

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## Serial Blood Cultures in Neutropenic Children with Persistent Fever After Conventional Chemotherapy in Bangladesh: Their Usefulness

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### ABSTRACT

When the initial blood culture reveals no bacterial growth, the primary goal of the study is to ascertain the prevalence of bacteremia in patients admitted with febrile neutropenia and to assess patient risk factors for this occurrence. A prospective cross-sectional study was conducted. 90 children with febrile neutropenia who are being treated at Bangabandhu's Paediatrics, Hemato-Oncology Department will participate in the trial. Medical Sheikh Mujib Medical University, during the period of July'22 to December'22. Data will be collected in a questionnaire with informed written consent. Data will be presented in graph and probability values of <0.05 will be considered as statistically significant for all results. Admitted patients were selected with purposive sampling technique the primary end point was to assess the blood bacterial isolates in patients with febrile neutropenia. The mean age was found  $6.9 \pm 3.1$  years with range from 2.5 years to 15 years. About the diagnosis, more than half of the patients had ALL diagnosis followed by AML and then NHL diagnosis ( $p = 0.043$ ). The mean duration of neutropenia was found  $10.8 \pm 6.67$  days with range from 3 to 30 days. The 2 times mean number of episode fever was found  $1.2 \pm 0.4$  time varied from Regarding the blood culture isolates, growth was not found in 2nd sample and 3rd sample.

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**Received:** May 25, 2023; **Accepted:** May 31, 2023; **Published:** June 10, 2023

**Keywords:** Neutropenia, Blood culture, Paediatric, Cancer, Chemotherapy

### Introduction

One of the most dangerous side effects for individuals with haematological malignancies and severe neutropenia after cytotoxic therapy is bloodstream infections (BSIs). Among microbiological illnesses, bloodstream infections (BSIs) are the most often reported cases [1]. Almost 57 Bloodstream infections (BSIs) are linked to serious side effects include multiorgan failure and septic shock, which can be fatal, especially in immunocompromised hosts. Blood cultures (BCs) are typically taken at the onset of fever, which is the clinical hallmark of bloodstream infections (BSIs) in immune-competent hosts [2-4]. However, fever may not appear after intensive chemotherapy or haematopoietic stem cell transplantation (HSCT) due to the immune system's anergic state. Immediate empirical broad-spectrum antibiotic medication at the start was shown in several clinical trials to improve survival.

Immediate empirical broad-spectrum antimicrobial medication at the onset of fever, which has since become standard practice, was shown in several clinical trials to improve survival. Bloodstream infections (BSIs) in neutropenic individuals frequently result in high morbidity and death despite such a prompt treatment. Bloodstream infections (BSIs) with microbes resistant to broad-spectrum antibiotics, which are surfacing in many centres, are

partially responsible for the increased mortality [5-8]. As a result, antimicrobial therapy may be optimized through earlier identification and susceptibility testing of microorganisms causing bloodstream infections (BSIs). Pilot studies and demonstrated that surveillance using blood cultures (BCs) is practical in neutropenic patients and aids in the early identification of severe bloodstream infection (BSIS)-causing bacteria [9,10].

The mortality rate has fallen from more than 20.0% to 0.7-3.0% with hospital admission and the use of wide spectrum antibiotics [11,12]. At the same time, the prevalence of bacteremia has decreased from over 50% of febrile neutropenic patients to 10.0% to 20% of patients. The mortality rate from bacteremia is still high despite improvements in supportive care and antibiotic therapy [13]. One explanation for this could be related to the number of bacteria in the blood, as mortality has been found to be higher in individuals with higher levels of circulating bacteria in two independent studies [14,15]. When it occurs in a patient who has compromised host defences due to immunosuppression, this issue has even greater significance. Another issue was found in the study by Gerald and Bodey, which included two very different groups of patients [16]. One set of patients had fevers of unclear origin that persisted after 4 days of antibiotic treatment. Patients with known bacterial illnesses who experienced recurrent fever following an initial response to antibacterial therapy made up the second group. Because they had more extended neutropenia and

more prolonged antibiotic therapy both significant predisposing factors—this latter group of patients was made up of individuals who were more likely to have had a fungal infection. A risk factor for fungal infection is previous bacterial infection.

A prior history of bacteremia was a risk factor for having an initial negative blood culture with a subsequent positive blood culture. The rate of detectable bacteremia in individuals with febrile neutropenia was shown to be higher for the initial blood culture than for subsequent blood cultures obtained when the initial blood culture shows no bacterial growth [17]. The major goal is to figure out the rate of bacteremia in admitted patients with haematological malignancies like acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), non-Hodgkin lymphoma (NHL) who received standard chemotherapy and having persistent fever with neutropenia with age between 1 to 15 years of both gender when the initial blood culture shows no bacterial growth and to evaluate patient risk factors for this occurrence.

## Materials and Methods

### Episode Determination

Oncology patients who were admitted by the Pediatric Hematology/Oncology service with diagnoses associated to febrile neutropenia were searched for in the patient database from July 2022 to December 2022. No matter their age, all paediatric patients admitted with haematological malignancies who received chemotherapy were considered eligible for this study. Patients undergoing stem cell transplants and who had initial positive blood culture were excluded from this investigation. To verify the oncologic diagnosis and the occurrence of a febrile neutropenia episode during that admission, all records were carefully checked. For analytical purposes, each episode of febrile neutropenia ended when one of the following outcomes: Underlying disease, duration of neutropenia, episodes of fever, blood culture isolates. Age, gender, diagnosis, average body weight, body temperature range, and neutrophil count were among the patient information gathered in Table 1.

### Study Design

In accordance with recommendations from the Department of Paediatric, Hemato-Oncology, Bangabandhu Sheikh Mujib Medical University, Dhaka, ambulatory patients who presented with an episode of febrile neutropenia were admitted to the hospital. Number of patients was selected by student's t-test method. According to the t-test, total 90 patients were considered for observing bacterial growth.

**Table 1: Demographic and Baseline Characteristics of Study Participants**

| Factor           | Group                |
|------------------|----------------------|
| Age (years)      | 6.9±3.1              |
| Weight (kg)      | 8.6±4.1              |
| Height (cm)      | 97.20 ± 9.29         |
| Fever(average)   | 38.9-39.4 °C         |
| Neutrophil count | <500/mm <sup>3</sup> |

## Blood Cultures and Antimicrobial Treatment

During the whole study period, the standard empirical antibiotic therapy in the ward consisted of either third- generation cephalosporin (ceftazidime, cefotaxim or ceftizoxim) or piperacillin combined with an aminoglycoside (usually tobramycin). Febrile episodes were regarded as separate instances if the axillary temperature was 38.9-39.4°C > 3 days with clearly decreasing C-reactive protein (CRP) values between fever periods. From 1992 onwards an automated continuous- monitoring blood culture screening system (BacT/Alert, Organon Teknika, Durham, NC, USA) has been used [18]. Venous blood samples of 10 ml/bottle were taken into standard aerobic and anaerobic BacT/ Alert blood-culture bottles and incubated at 35°C in the analyzer for up to 7 days, to determine any bacterial growth.

## Statistical Evaluation

The SPSS software v 20.0 for Windows (IBM Corp., Armonk, NY, USA) was used to analyse the data. For categorical variables, statistical comparisons were done using the chi-square test, and for selecting volunteers, the student's t-test was used. P values of 0.05 or less were regarded as significant.

## Ethical Consideration and Consent Form

We obtained Hospital Authority & gradian's permission before taking required information from these patients. They were made aware of all of the ethical considerations (ref no. CPS No.355), primary enrolment no P-07-39-000638) and were given assurances regarding the confidentiality of their data in the process. The study was exempted from the written informed consent as we did not use name, address or any personal identification information.

## Results

The male to female ratio was 1.7:1, with the mean age being 6.9 ±3.1 years and the range being 1-15 years. Here, according to chi-square p value was shown below 0.05 indicating the significance of observed data in Table 2.

**Table 2: Distribution chart of patient according to the age and gender with chi-square method**

|                     | Observed value | Percentage (%) | P value |
|---------------------|----------------|----------------|---------|
| Observed age (year) |                |                |         |
| 1-5                 | 33             | 36.70          | 0.001   |
| 6-10                | 45             | 50.30          |         |
| 11-15               | 12             | 13.30          |         |
| Gender              |                |                |         |
| Male                | 57             | 63.30          | 0.002   |
| Female              | 33             | 36.60          |         |

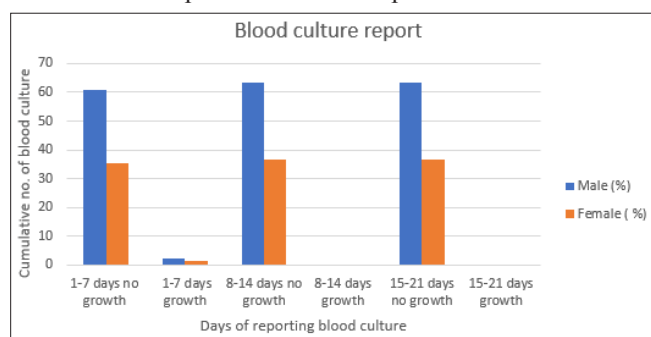
In table 3, The majority of patients both male (66.67%) and female (39.41%) had ALL as their primary diagnosis, followed by AML for male (17.54%), NHL for male (15.78%), but surprisingly for female both AML and NHL are almost same (30.30%). According to the duration of Neutropenia, both male (52.63%) and female (63.63%) observed highest percentage in <10 days which indicating that levels of Neutrophil drop immediately return to normal, an average day for duration was found 10.80±6.67 days from the calculation of Table 3 ranging from 3 to 30 days.

**Table 3: Analysis of risk factors for detection of Bacterial growth**

|                              | Male,(%)   | Female,(%) | P value |
|------------------------------|------------|------------|---------|
| Duration of neutropenia days |            |            |         |
| < 10                         | 30,(52.63) | 21,(63.63) | 0.023   |
| 11-20                        | 24,(42.10) | 06,(18.18) |         |
| 21<                          | 03,(05.26) | 06,(18.18) |         |
| Number of episode fever      |            |            |         |
| One time                     | 48,(84.21) | 24,(72.72) | 0.030   |
| Two time                     | 12,(21.05) | 06,(18.18) |         |
| Diagnosis*                   |            |            |         |
| ALL                          | 38,(66.67) | 13,(39.41) | 0.043   |
| NHL                          | 09,(15.78) | 10,(30.30) |         |
| AML                          | 10,(17.54) | 10,(30.30) |         |

\*Here, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), non-Hodgkin lymphoma (NHL)

According to the Figure 1, Regarding the blood culture isolates, growth was not discovered in the second or third samples. The mean number of episode fever was reported to be 1.20.4 times.



**Figure 1:** Results of blood cultures obtained by day of febrile neutropenia

## Discussion

Throughout the past three decades, there has been a significant improvement in the treatment of fever in neutropenic individuals. Although 60% to 80% of these febrile episodes respond to early antibiotic therapy, according to data from, 50% to 60% of them have no infectious etiology [16,19]. The treatment of individuals who do not improve after receiving antimicrobial medication continues to be a challenging issue. Although there are numerous probable reasons of these recurrent fevers, it is generally agreed that an undiagnosed fungus infection is the most likely culprit. The most frequent fungi infections in neutropenic patients are aspergillosis and diffuse candidiasis [20]. Although aspergillosis might manifest only as a fever, local signs and symptoms typically appear 3 to 5 days after the fever first appears. The most frequent fungi infections in neutropenic patients are aspergillosis and diffuse candidiasis. On the other hand, disseminated candidiasis is frequently challenging to diagnose since neutropenic patients may experience prolonged fever without any additional symptoms or indications to support the diagnosis. In our study, duration of neutropenic fever lasting withing 10 days with maximum percentage of patients. One time episode fever was highest percentage for both male (84.71%) and female (72.72%), but in two time, it was reduced to 21.05% and 18.18% for male and female respectively. Some species like Candida may not be isolated from repeated blood culture specimens, even when using

specialized techniques for culturing blood specimens, such as lysis-centrifugation. More than 25% of cases of disseminated candidiasis that were autopsy-proven did not have a Candida species isolated from premortem blood culture specimens, according to one study. This prospective observational study sought to assess the blood bacterial count in haematologically neutropenic patients, identify the range of bacteraemic microorganisms isolated during episodes of netutropenic fever (NF), as well as the susceptibility profiles of these organisms to various antibiotics, as well as assess the effectiveness of serial blood cultures (BCs) to identify bloodstream infections (BSIs) and the frequency of bacteremia in adolescent patients with haematological malignancies who received standard chemotherapy and having febrile neutropenia when the initial blood culture shows first bacterial growth at a rate of 2.33% for male and 1.54% for female of 7 days culture, there would be some patient risk factors for the totalnumber of 90 admittd patients with febrile neutropenia in department of Paediatric, Hemato-Oncology, Bangabandhu Sheikh Mujib Medical University, Dhaka. During hospital period, third-generation cephalosporin (ceftazidime, cefotaxim or ceftizoxim) or piperacillin combined with an aminoglycoside (usually tobramycin) was applied to the patient. After observing first culture, no potential bacterial growth was found for second and third culture. From this, we should confirm that antibiotic monitoring and proper uses of antibiotic stewardship with infection control department must be mandatory in every cancer patient with chemotherapy. In the current study, it was found that male patients were found with higher than that of female with the ratio of male to female individuals was 1.7:1, which suggests that female subjects had febrile neutropenia more frequently. This study's findings are in agreement with those of Serody et al., who found febrile neutropenia in 75.0% of majority have negative results compared to 46.00% neutropenic patients [21]. Surprisingly, in diagnosis, it was observed in this current series that majority of female patients had NHL and AML diagnosis compared than of male.

The results of the studies I just described are equivalent to those of this one. Even though other host response symptoms may be changed or absent, neutropenic patients nonetheless experience fever, which is a common host response to infection. Neutropenia is accompanied by fever in 90% of patients, however an infectious cause has only been identified in 60% to 65% of cases. Although though bacteremia is only found in 19–24% of cases, fever is frequently the first and only symptom of sepsis in these patients. Nonetheless, the mortality rate linked to bacteremia is thought to range between 10 and 40%. Hence, it is crucial to identify bacteremic infections as soon as possible so that the appropriate care may be provided. It has been proposed that the current method of rapidly administering antibiotics may conceal the bacterial etiology and that chemotherapy may have an impact on bacteria by inhibiting their ability to proliferate in microbiological culture systems. Unfortunately, nothing is known about the value of blood culture systems in general for spotting bacterial development. In this study, it was shown that the majority of patients (84.21.0% and 72.72%) had a single bout of fever, as shown by the number of episodes of fever they experienced. The agents that cause bacteremia and sepsis should be understood for therapy and empirical antibiotic use due to high mortality. Due to various therapeutic, medical, and antibiotic policies, the etiological agents and their antibiotic susceptibilities vary over time and between hospitals. Close and at least yearly monitoring of the agents responsible for the infection is necessary at every center because timely administration of the right antibiotics is essential for the successful management of infections.

## Conclusions and Implications

The fact that the outcomes of children with severe neutropenia and those of comparable individuals with moderate neutropenia do not appear to differ much supports the notion that there is a minor risk of serious bacterial infection (SBI) in otherwise healthy, physically attractive patients with both types of neutropenia. If the results of initial tests, such as urinalysis and chest radiography, are normal, such individuals might not need to be treated immediately with antibiotics. We think that such patients can be safely followed up on in an outpatient setting without the requirement for hospitalization. For such individuals, close patient monitoring is advised along with periodic peripheral blood ANC assessment to track bone marrow recovery. To adopt this recommendation into common practice, prospective studies would be required. Any child who has a fever and recently discovered neutropenia and who otherwise seems poorly should be treated with parenteral antibiotics in the hospital as they are likely to develop SBI.

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