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### Causes of Fever in patients with neutropenia : Hospital based clinical study

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#### A B S T R A C T

Fever in neutropenic patients is a common problem encountered in clinical settings like leukemias, plasma cell dyscrasias, multiple myeloma, patients undergoing organ or bone marrow transplantation, those with bone marrow failure and in certain infections like Enteric fever and HIV infection. The objective of this study was to study the clinical and microbiological profile of fever in neutropenic patients. This study included 110 patients, who had episodes of fever and neutropenia and were studied during a period of one year. In this study we concluded that the majority of the patients were middle aged and elderly. Fatigability is a common presentation of febrile neutropenic patients in this study. Large number of patients presented with clinical signs and symptoms suggestive of respiratory system involvement. Most of the febrile episodes are from unknown sources. Gram positive infections especially Staphylococci species were a common cause of febrile neutropenia.

### Introduction

Fever in neutropenic patients is a common problem encountered in clinical settings like leukemias [commonly AML, ALL, CML] and plasma cell dyscrasias, multiple myeloma, patients undergoing organ or bone marrow transplantation, those with bone marrow failure and in certain infections like enteric fever and HIV infection. Causes can be infectious and non-infectious. Non-infectious causes include drugs like chemotherapeutic agents (for example cyclophosphamide,

methotrexate), chloramphenicol, penicillins, sulphonamides, carbamazepine, clozapine etc, certain cancers themselves such as Hodgkin's disease and lymphoma, vasculitis, transfusion reactions and graft versus host disease. Among infectious causes, primary infections related to central venous catheters and secondary infections related to respiratory tract [like pneumonia], surgical sites, genitourinary tract, intra-abdominal cavity and non

surgical skin abscesses are common. Different organisms isolated in these patients include gram positive organisms, gram negative organisms, invasive mycoses, mycobacteriae and viruses. Gram positive bacteriae like *Staphylococcus aureus*, Coagulase-negative *Staphylococci* and *Streptococcal* species e.g. alpha-hemolytic *Streptococci* were isolated in these patients. Gram negative aerobic bacteriae like *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* have been isolated in these patients. Gram negative anaerobic organisms such as *Leptotrichia buccalis*, *Clostridium septicum*, *C.tertium* and *C.difficile* have been identified in neutropenic patients. Invasive mycoses like species of *Candida* and *Aspergillus* are isolated in these patients. Mycobacteriae such as *Mycobacterium chelonae* and *M.fortuitum*, herpes viruses especially *Herpes simplex virus*, *Varicella zoster virus* and *Cytomegalovirus* have also been identified in these patients<sup>1</sup>.

Infections are a major cause of morbidity and mortality in cancer patients. The risk of infections is principally related to the intensity and duration of the immune suppressive chemotherapy. In the 1980's there was a shift in the relative prevalence of specific pathogens afflicting patients with cancer. Whereas in the 1960's and 1970's Gram negative bacterial pathogens [*Enterobacteriaceae* and *pseudomonas aeruginosa*] were the principal cause of bacteremia, in 1980's and 1990's Gram positive bacterial pathogens became predominant<sup>2</sup>.

The spectrum of invasive fungal infections has dramatically increased in patients with prolonged neutropenia. Examples of such emerging pathogens include *Fusarium*, *Acremonium* & *Scedosporium*. Most

infections occur about 12-14 days after the 1st day of chemotherapy<sup>3</sup>. Although the precise reasons for the changing patterns of bacterial pathogens are unknown, the use of intensive chemotherapeutic regimens ( with associated immune suppression and mucositis)<sup>4</sup>, antibacterial prophylaxis targeted against gram negative bacilli, selective gut decontamination, invasive procedures/catheters have all been cited as possible contributing factors.

Antibiotic resistant bacteria tend to be more prevalent in neutropenic patients because they are exposed to prolonged courses of broad spectrum antimicrobials e.g. *Enterobacteriaceae* expressing extended spectrum  $\beta$  lactamases (ESBL); fluroquinolone resistant *E. coli*, methicillin resistant *staphylococci* & vancomycin resistant *enterococci*. An early increase in infections attributable to *viridians streptococci* is also a common; these infections can result in severe complications [ARDS, Shock] in neutropenic patients<sup>5</sup>. There are many studies regarding empirical use of broad spectrum antibiotics in this group of patients. Systematic study of the etiological profile of these fevers would help to formulate antibiotic policy as well as effective infection control measures. There are only a few Indian studies in the literature addressing similar issues. Our study will attempt to establish the infectious as well as non infectious causes of febrile neutropenia in a local setting.

### **Methodology**

The study material was collected from the wards and ICUs of the hospitals of Medical College. Totally 110 patients, who had episodes of fever and neutropenia on admission or anytime during hospital stay, were studied during a period of one year from June 2013 to June 2014. A detailed

history was taken and physical examination was done in all patients. They were subjected to appropriate investigations to find out the cause of fever. These included complete blood counts, urine microscopy, chest x-ray & blood smear for malarial parasites. Blood – sputum - stool - urine and access device cultures done if clinically indicated. Cultures from any other suspicious/focal lesions were taken. CT scan of the chest, abdomen & pelvis were done if clinically indicated. Elisa for HIV was done if considered relevant

### **Result and Discussion**

Among 110 patients, 60% were males and 40% were females. More than 80% of patients were aged more than 40 years and all the patients had fever >101<sup>0</sup>F and ANC <500/micL.

In this study we observed 20.27% of febrile episodes were true-positive cultures. Gram positive microorganisms predominantly staphylococcal species were isolated in this study.

Similar to other infections, the incidence of febrile episodes increases with age and is influenced by a variety of physiological factors. However, in this study, 60.81% of the episodes occurred among patients above 38 years of age, which may be related to the large number of acute leukemias and use of CVC in this age-group. The majorities of our patients were admitted to the hematology service and were exposed to intensive chemotherapy & had severe neutropenia. Intravascular devices are considered the main source of febrile episodes. Our data showed that only 04.05% of FN episodes were considered CVC-related, although 40.54% of our patients had CVC.

In a study done by I. Hann, C. Viscoli et al<sup>6</sup> there was no significant difference in overall rates of bacteria in children less than 18 years and adults. The present study shows largest numbers of infections were seen middle and elderly age groups.

Children under 18 years developed more streptococcal infections where as adults developed more staphylococcal infections, in a study done by I. Hann, C.Viscoli et al. In this study, in all cases of gram positive bacteremia, staphylococcus was the predominant organism isolated. An Indian study by RR Dutta et al in New Delhi showed the common foci of infections to be pneumonia, perianal abscess, thrombophlebitis, furuncle and oral mucositis. The organisms isolated were Coagulase negative *Staphylococcus aureus*, *Streptococcus pyogenes*, *E-coli*, *Pseudomonas aeruginosa*, *Proteus vulgaris* and *Klebsiella pneumoniae*. They concluded that gram-positive infections especially staphylococcal infections were common<sup>7</sup>.

A shift in the bacteriological spectrum was shown in a study by Stephen H. Zinner, in this showed that there has been a clear shift in infecting organisms, such that 60 -70% of bacteremias with single organisms are due to gram positive organisms compared to the spectrum two decades earlier. In this study gram negative organisms were still the most common infectious organisms making 52.94% of total cases where causative organism was isolated.

In a study by Stephen H.Zinner some of the causes of shift towards gram positive infections include oral mucositis as a result of increase in use of potent chemotherapeutic regimens, profound and prolonged neutropenia, increasing use of long dwelling intravascular catheters, use of antacids and H2 blockers.

**Table.1** Clinical presentation of patients

Clinical presentation	Frequency	Percentage
Pallor	74	67.2%
Lymphadenopathy	14	12.7%
Crepitations	10	09.0%
Oral mucositis	08	07.2%
Tender abdomen	06	05.4%
Infected chemoport	06	05.4%
Hemorregic bullae over tongue	04	03.6%
Hepatomegaly	04	03.6%
Splenomegaly	04	03.6%
Icterus	02	01.8%

Among total study subjects, 56% had a source of infection and 44% did not have any source of infection.

**Table.2** Diagnosis

Diagnosis	Frequency	Percentage
Haematological malignancies	61	55.4%
Solid tumours	42	37.8%
Metastasis of unknown origin	04	03.6%
Sepsis	01	09.1%
Pancreatitis	01	09.1%
HIV	01	09.1%
Total	110	100%

In this study the use of chemotherapeutic agents and profound neutropenia were shown to be associated with increased frequency of infections. Long dwelling intravascular and urinary catheters were found to be associated with gram negative infections.

In the study by Vicki A. Morrison<sup>8</sup> both gram positive and gram negative organisms were isolated from respiratory tract in which staphylococcus aureus and pseudomonas were predominant. In this study gram positive organism streptococcus pneumonia and acinetobacter species organisms isolated from respiratory tract.

A study by Eduardo Velasco et al<sup>9</sup> showed a predominance of primary infections with a

high frequency of episodes of unknown origin. This significant finding can be attributed to the prompt institution of broad-spectrum antibiotics for febrile cancer patients. In our study also episodes of unknown origin were common.

In a study done by Philip A.Pizzo, neutropenia itself (less than 500 polymorphs/cubic millimeters) is the single most important risk factor for the infections. Other factors which can alter the risk of infections are degree of neutropenia (patient with less than 100 neutrophils/cubic mm highest risk of infections) and alterations in physical defence barriers (e.g. due to mucositis, presence of indwelling catheters). In this study, patients who had ANC less than 500 cubic mm were at risk of getting

infections. Other factors such as mucositis associated with ongoing chemotherapy and presence of indwelling catheters also appeared to play a role. In a study Philip A.Pizzo<sup>10</sup>, monotherapy with some 3rd generation cephalosporins which have bacterial activity against enterobacteriaceae, *P.aeruginosa* and many gram positive

### **Conclusion**

Majority of patients were middle and elderly aged and a large number of patients presented with symptoms suggestive of Respiratory system. Malignancies were the main cause of neutropenia.

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