



A STUDY ON THE INCIDENCE OF SEPSIS AND ITS CORRELATION WITH ABSOLUTE NEUTROPHIL COUNT IN PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES IN A TERTIARY CARE HOSPITAL.

Microbiology

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ABSTRACT

Bacterial infections are a major cause of morbidity and mortality in patients with haematological malignancies due to their immunocompromised state. Sepsis in patients with neutropenia is a medical emergency.

AIMS AND OBJECTIVES To identify the bacterial isolates and its antibiotic susceptibility pattern causing sepsis in patients with neutropenia following chemotherapy for Haematological malignancies and to correlate the Absolute Neutrophil Count (ANC) with febrile episodes in neutropenic patients.

MATERIALS AND METHODS This prospective study was carried out over a period of 1 year in a tertiary care hospital in 94 patients with a total of 115 episodes of febrile neutropenia. Blood culture was done for patients with febrile episodes, as per the standard Microbiological technique. Antimicrobial susceptibility testing was done by Kirby-Bauer Disk Diffusion method. Absolute neutrophil count was measured by Automated Cell Counter.

RESULTS In this study, patients suffered 1.22 episodes of infection per patient per year. Bacteraemia was observed in 16.5% of febrile episodes. Gram positive organisms were the predominant cause of infections in febrile neutropenia. 53% of blood stream infections were found in patients with ANC of less than 500 cells/mm³.

CONCLUSION: Therapy induced neutropenia is the most important risk factor for complications due to infections and sepsis in patients with haematological malignancy. Multidrug resistant bacteria were predominant cause of persistent infection in these patients.

KEYWORDS

Febrile neutropenia, Hematological malignancies, Blood stream infections

INTRODUCTION

Haematological malignancies compromise all aspects of the immunity, as a result of the underlying malignancy or due to the therapeutic interventions employed to manage the disease. Neutropenia resulting from cytotoxic chemotherapy, is the most common risk factor for severe bacterial infection in haematological malignancies. The incidence of serious infection significantly increases, when the Absolute Neutrophil Count (ANC) falls, below 1500 cells / mm³. The duration of neutropenia also contributes significantly to the risk of serious infection. All the patients with ANC <100 cells/mm³ for 3 weeks or more, develop documented infection.

¹Blood stream infections (BSI) in neutropenic patients is significantly associated with prolonged hospital stay, extra costs, and excess mortality. Severe sepsis and septic shock are closely correlated with adverse outcome.²

AIMS AND OBJECTIVES

- To identify the bacterial isolates causing sepsis and its antibiotic susceptibility pattern in patients with neutropenia following chemotherapy for Haematological malignancies.
- To correlate the Absolute Neutrophil Count (ANC) with febrile episodes in neutropenic patients.
- To monitor the emergence of resistant strain.

INCLUSION CRITERIA: Patients having episodes of fever 38.4°C (100°F) and above with or without any systemic complaints and those patients on chemotherapy for hematological malignancies.

EXCLUSION CRITERIA: Patients with febrile episodes due to non-infectious cause of fever such as administration of blood / blood products, pyrogenic drugs, cytotoxic therapy (Amphotericin B)

MATERIALS AND METHODS

This prospective study was carried out over a period of 1 year in a tertiary care hospital in 94 patients with a total of 115 episodes of febrile neutropenia.

Under appropriate sterile precautions, 10ml of venous blood samples were collected for culture from two different sites and inoculated into 50 ml of Brain Heart Infusion (BHI) broth and incubated at 37°C. The

samples were processed and the isolates were identified by standard microbiological techniques.

Antimicrobial susceptibility testing was done on Mueller Hinton Agar plate (MHA) by Kirby - Bauer disk diffusion method. Absolute neutrophil count was measured by Automated Cell Counter. The screening of MDR-phenotypes including MRSA, ESBL production, and carbapenemase production was conducted according to CLSI recommendations. Extended spectrum betalactamase (ESBL) production was identified by Phenotypic Screening for ESBL detection.

Operational definitions:

Neutropenia is defined as a neutrophil count <500 cells / mm³ or < 1000 cells / mm³ with expected decrease to < 500 cells / mm³ within 48 hours. **Microbiologically Documented Infection (MDI)** consists of bloodstream infections and may be either primary or secondary to a proven focus of infection (eg. pneumonia, cellulitis, catheter related infection, UTI).

OBSERVATION AND RESULTS

Table 1: Distribution of Haematological malignancies in the study population (n=94)

S.No.	Type of Haematological malignancy	Number of Patients (%)
1	Acute Myeloid Leukemia	47 (50)
2	Acute Lymphatic Leukemia	21 (22)
3	Chronic Myeloid Leukemia	4 (4)
4	Chronic Lymphocytic Leukemia	1 (1)
5	Lymphoma	6 (7)
6	Haematological disorders	15 (16)
	Total	94

Table 2: Bacterial profile of Blood Stream Infections in Haematological malignancies

Bacterial Isolates	Number of Isolates (%)
<i>Staphylococcus aureus</i>	6 (31.6)
<i>Staphylococcus epidermidis</i>	5 (26.3)
<i>Diphtheroids</i>	1 (5.3)
<i>Escherichia coli</i>	2 (10.5)

<i>Klebsiellapneumonia</i>	1 (5.3)
<i>Pseudomonas aeruginosa</i>	2 (10.5)
<i>Acinetobacter spp.</i>	2 (10.5)
Total	19

Blood culture was positive in 16.5% of patients. Predominant isolate was *Staphylococcus spp.*

Table 3: Comparative Analysis of Absolute Neutrophil count (ANC) vs Number of Febrile episodes vs Number of Positive Blood Cultures

Absolute Neutrophil Count (ANC)	Number of Febrile Episodes	Blood Culture Positive (%)
500 cells/mm ³	30	10(53)
500 – 1000 cells/mm ³	12	3(16)
1000 – 2000 cells/mm ³	14	2(10)
>2000 cells/mm ³	59	4(21)
Total	115	19

Isolation rate was found to be higher in patients with ANC less than 500/mm³ of blood

DISCUSSION

This study was undertaken in a tertiary care hospital in 94 patients with haematological malignancies. The primary aim of this study was to understand the current pattern of BSI in patients with febrile neutropenia undergoing treatment for hematological malignancies. The most frequent sites of infection in neutropenic cancer patients with haematological malignancies by decreasing order of frequency was found as the blood stream, the oral cavity and nasopharynx, the skin, soft tissue, the respiratory tract, the gastrointestinal tract, and the urinary tract.

Among the haematological malignancies, Acute Myeloid Leukemia (AML) was the most common diagnosis (50%), followed by Acute Lymphatic Leukemia (Table 1). This correlates with a study by Jacob *et al.*³

In this study, majority of the patients were in the age group of 21-30yrs. There was a male preponderance constituting nearly three fifth of the total study population. Total of 94 patients suffered from 115 episodes of infection. This works out to 1.22 episodes of infection per patient per year. Robert B. Jerknes *et al* quotes an overall incidence of 0.25 – 0.50 episodes per patient per year increasing up to 1.8 episodes per year in patients who have advanced disease.⁴

Fever was the main presenting symptom in 73% of patients in this study, which correlates well with the study by Khan M.A *et al.* who reported that 86% of the patients presented with fever in his study.⁵

In this study, bacteraemia was observed in 16.5% of febrile episodes which correlates well with Lakshmaiah K C *et al.*⁶ During the course of study, 78 patients suffered from a single episode of fever, 12 patients suffered two such episodes and 3 patients had three episodes and one patient had four episodes of fever.

In blood culture, Gram positive organisms were the predominant cause of infections in febrile neutropenia accounting for 63% while Gram negative organism accounts for 37%. This correlates well with the study of Jagarlamudi R. *et al.*⁷

Staphylococcus aureus was isolated in 31.6% and *Staphylococcus epidermidis* was isolated in 26.3% of all bacteraemias. (Table 2). This correlates with the increasing incidence of CONS bacteraemia in many centres.^{8,9} The most prevalent species of CONS was *S. epidermidis*.¹⁰

The spectrum of Gram negative isolates includes *Escherichia coli* (2), *Pseudomonas aeruginosa* (2), *K. pneumoniae* (1), *Acinetobacter spp.*, (2) (Table 2). This correlates well with the study of Cordonnier C. *et al.*,¹⁵ and Kumar. L. *et al.*¹⁶

Absolute Neutrophil Counts have been found to be the most useful prognostic indicator for the development of infection. 53% of BSI were found in patients with ANC of less than 500 cells/mm³ (Table 3) Giamarellou and Antoniadou regard neutrophil counts less than 100 / mm³ as having high risk of infections and mortality.¹¹ D. Hiwase, A. Mukhopadhyaya *et al* reported an increased risk of infection at counts <1000 /mm³ with life threatening infection at levels of 100 /mm³.¹²

Since increased duration of neutropenia leads to risk of infection, it is a universal practice to start the patients on prophylactic empirical antibiotic therapy. In the antibiotic susceptibility test performed for the 19 bacterial isolates from blood culture from patients with febrile neutropenia, 66% of isolates of *Staphylococcus aureus* and 50% of *S. epidermidis* isolates were found to be Methicillin Resistant. This is in accordance with the findings of Kirby JT *et al.*¹³

Amikacin was found to be the most effective antibiotic with 93% sensitivity for all the isolates. All the Gram positive organisms including Methicillin resistant isolates were sensitive to Vancomycin.¹⁴ This finding was found to be statistically significant with p value 0.003. Only 37% of all isolates were sensitive to cefotaxime.

Three isolates of *Klebsiella pneumoniae* and one isolate of *E. coli* were found to be multidrug resistant and all of them were found to be ESBL producers (57%). All the Gram negative organisms including ESBL producers were sensitive to Imipenem and Piperacillin-Tazobactam combination. This was found to be statistically significant with p value of 0.01. These organisms were resistant to all Cephalosporins and exhibit decreased sensitivity to Ciprofloxacin (50%). Cefepime-sulbactam and Ofloxacin were found to be the other effective antibiotics. This points out to the emergence of ESBL producing organisms as an important cause of infection in these patients. This also highlights the importance of using antibiotics that are capable of neutralising the β -lactamase produced by these organisms and incorporating them into newer empirical antibiotic combinations.

CONCLUSION

Bacterial profile in patients with Haematological malignancies among febrile neutropenic patients, appears to be shifting towards Gram positive microorganisms. Therapy induced neutropenia is the most important risk factor for infectious complications in patients with haematological malignancy. Appropriate antibiotic policy should be implemented. Antibiotics should be started only after collecting appropriate samples for culture and de-escalation of antibiotics should be done according to the antibiotic susceptibility report.

REFERENCES

- Hematology Am. Soc. Hematol Educ. Program 2003; 438-72.
- Bodey GP, Buckley M, Sathe Y. S. *et al.* Quantitative relationships between circulating leukocytes and infections in patients with acute leukemia. *Ann Intern Med* 1966; 64(2): 328-40.
- Vijay L A, Lakshmaiah K C, Govindbabu K, Suresh T M, Lokanatha D, Sinha M, Vijaykumar B R, Sumathi B G, Jayashree R S. Clinical and microbiological profile of febrile neutropenia in solid tumors and hematological malignancies at a tertiary cancer care center in South India. *Indian J Cancer* 2014; 51: 464-8.
- Robert B. Jerknes Oystein Bruserud and clans O. Solberg Hematologic indigence.
- Khan M.A., Siddiqui BK, Shamim A. Emerging bacterial resistance pattern in febrile neutropenic patients - experience at a tertiary care hospital in Pakistan 2002. *J PMA* 2004. Vol. 54, No. 7: 357-360.
- Lakshmaiah KC, Malabagi AS, Govindbabu, Shetty R, Sinha M, Jayashree RS. Febrile neutropenia in hematological malignancies: Clinical and microbiological profile and outcome in high risk patients. *J Lab Physicians* 2015; 7: 116-20.
- Jagarlamudi R, Kumar L, Kochupillai V, Kapil A. Infections in acute leukemia: an analysis of 240 febrile episodes. *Annals of Oncology* 2006 (5): 763-768.
- Bodey GP, Unusual presentations of infections in neutropenic patients. *Int J Antimicrob Agents* 2000 Oct; 16 (2): 93-5.
- Rolston K.V, Yadegarynia D. The spectrum of gram positive blood stream infections in patients with hematologic malignancies and the in vitro activity of various quinolones. *Int J Infect Dis* 2006 May; 10(3): 223-30.
- Persson L, Strid H. Phenotypic and genotypic characterization of CONS isolated in blood cultures from patients with haematological malignancies. *Eur J clin microbiol infect Dis* 2006 May; 25(5): 229-309.
- Helen Giamarellou and Anastasia Antoniadou Infectious complication of febrile leucopenia. *Journal of North America* Vol 15; No 2 June 2001.
- Meunier, D.K. Hiwase, A. Mukhopadhyaya *et al.* Indian Society of Haematology and Transfusion medicine.
- Kirby JT, Fritsche TR, Jones RN. Influence of patient age on the frequency of occurrence and antimicrobial resistance pattern of isolates from hematology patients. *Diagn Microbiol Infect Dis* (2006) Sep; 56(1): 75-82.
- Falcone M, Micozzi A, Pompeo ME. Methicillin resistant staphylococcal bacteremia in patient with hematologic malignancies. *J Chemother* 2004 Dec; 16(6): 540-8.
- Venditti M, Falcone M, Micozzi A. *Staphylococcus aureus* bacteremia in patients with hematologic malignancies, a retrospective case – control study. *Haematologica* 2004 Apr; 89(4): EL To6.
- Kumar L, Kochupillai V, Bhujwala RA. Infection in Acute Myeloid leukemia – Study of 184 febrile episodes. *Journal of Medical Oncology* 2002 19: 4: 267 Page 267-272.