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Clinical profile of high-risk febrile neutropenia in a tertiary care hospital

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RESEARCH

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ABSTRACT

Background
Infection in the immunocompromised host has been a reason of concern in the clinical setting and a topic of debate for decades. In this study, the aim was to analyse the clinical profile of high-risk febrile neutropenic patients.

Aims
To study the clinical profile of high risk febrile neutropenia patients with the objective of identifying the most common associated malignancy, most common associated pathogen, the source of infection, to correlate the treatment and management with that of the Infectious Diseases Society of America (IDSA) 2010 guidelines and to assess the clinical outcome.

Methods
A cross-sectional time bound study was carried out and a total of 80 episodes of high-risk febrile neutropenia were recorded among patients with malignancies from September 2011 to July 2013 with each episode being taken as a new case.

Results
Non-Hodgkin's lymphoma (30 per cent) was the most common malignancy associated, commonest source of infection was due to central venous catheters, the commonest pathogens were gram negative (52 per cent) the treatment and management of each episode of high risk febrile neutropenia correlated with that of IDSA 2010 guidelines and the mortality rate was 13.75 per cent.

Conclusion
Febrile neutropenia is one of the major complications and cause of mortality in patients with malignancy and hence understanding its entire spectrum can help us reduce morbidity and mortality.

Key Words
Febrile neutropenia, gram-negative organisms, central venous catheters

What this study adds:

1. What is known about this subject?
High-risk febrile neutropenia is a major cause of morbidity and mortality in cancer patients.

2. What new information is offered in this study?
The causative pathogen is constantly changing and hence identification and empirical treatment of the same can increase the rate of survival.

3. What are the implications for research, policy, or practice?
Review of literature has not found any recent study, which makes this research useful in understanding the pattern and management in developing countries.

Background

Febrile neutropenia is the most important factor for predisposition of infection in patients with malignancies irrespective of it being haematological or solid tumours.[1] Immune defects related to underlying haematological

disorder itself plays an important role in the occurrence of febrile neutropenia.[2]

The causative pathogens have gradually changed over the past few years in febrile neutropenic patients. Gram negative organisms dominated during the 1960s and 1970s, but in the ensuing years gram-positive organisms became the major source of infection, the reason being extensive use of central and peripheral venous catheters which led to massive colonisation by skin flora which are predominantly gram-positive. In developed countries the commonest organism isolated from blood cultures are coagulase-negative staphylococci (CONS), but in developing nations gram negative organisms (e.g., *Pseudomonas*, *Escherichia coli*, and *Klebsiella*) continue to be in majority due to its inherent drug resistant properties.[2] In most of the patients with febrile neutropenia there has been no prominent source of infection and no positive blood culture yield.[3]

In major fraction of patients where blood cultures collected from central line becomes positive about two hours before the blood cultures drawn from a peripheral line, central venous catheters (CVC) is identified as the major source of infection.[4]

In any neutropenic patient who presents with fever, blood culture has to be drawn immediately and they should be started empirically on broad spectrum antibiotics within an hour of presentation. The motto behind such emergent therapy is to cover the drug resistant and virulent gram negative organisms which may prove fatal in neutropenic patients.[5]

The aim of the study was to identify the commonest associated malignancy, most common associated pathogen, the predominant source of infection, to correlate the management in accordance to the infectious disease society of America (IDSA) 2010 guidelines and to assess the clinical outcome.

Method

A cross sectional, time bound study was conducted at Kasturba medical college and hospital at medical oncology service from September 2011 to July 2013. A total of 80 episodes of high-risk febrile neutropenia were recorded among patients with malignancies after complying with the inclusion and exclusion criteria.

All patients aged above 18 years with high-risk febrile neutropenia (as per IDSA 2010 guidelines definition) were included in the study with each episode being considered as a new incident and the exclusion criteria was neutropenia due to any other cause.

Recording of temperature: Only oral temperature was recorded with standard calibrated thermometer. Axillary temperature was avoided as they do not reflect accurate core temperature, but was measured in patients with severe oral mucositis.

Haematological and biochemical parameters: All the parameters were graded as per ECOG (Eastern Cooperative Oncology Group) criteria.

Blood culture: Minimum two sets of blood cultures were procured; one set from central line and one from peripheral line. All the cultures were taken under aseptic precautions and within an hour of onset of fever.

Antibiotic sensitivity: Kirby Bauer disk diffusion method and CLSI (clinical and laboratory standards institute) guidelines were utilised to assess the antibiotic sensitivity of the organisms.

Methodology: Once the subject was identified based on the inclusion criteria the following parameters were recorded during each episode: type of underlying malignancy, presence or absence of CVC, presence or absence of mucositis, presence or absence of oral candidiasis, imaging studies, isolated organism and its antibiotic susceptibility and duration of fever and neutropenia. All patients were followed up till the absolute neutrophil count (ANC) was >500cells/cu mm or death.

Statistical analysis: All data analysis and interpretation was done using IBM SPSS statistics version 20.0 software. The data has been presented in the form of percentage, frequency distribution tables and histograms.

Results

Type of malignancy: In this study, 69 per cent had haematological malignancies and 31 per cent had solid tumours.

Spectrum of various types of malignancies: The distribution of various types of malignancies in patients with febrile neutropenia included:

Non-Hodgkin's lymphoma (NHL) in 30 per cent, acute lymphoblastic leukaemia (ALL) in 28.75 per cent, acute myeloblastic leukaemia (AML) in 3 per cent, chronic lymphocytic leukaemia (CLL) in 6.25 per cent, metastatic

squamous cell carcinoma (MET SCC) in 6.25 per cent, metastatic undifferentiated carcinoma (MUC) in 5 per cent, rhabdomyosarcoma (RMS) in 3.75 per cent, and others in 16.25 per cent, which include ovarian carcinoma, osteogenic sarcoma, metastatic anal canal carcinoma, germ cell tumour of testes, breast carcinoma, gastric carcinoma and multiple myeloma. Among them the commonest was Non- Hodgkin's lymphoma (NHL) followed by acute lymphoblastic leukaemia (ALL) (Figure 1).

Source of infection: In 16 episodes (20 per cent) of high-risk febrile neutropenia blood culture was positive (detected by BacT alert system). Among them, 12 had a central venous catheter (CVC) which was identified as the most common source of infection (Figures 2 and 3).

Most common pathogen: Majority were gram-negative organisms (52 per cent), followed by gram-positive organisms (40 per cent), and 8 per cent had fungal aetiology. The most common organism isolated was *Escherichia coli* and coagulase negative *Staphylococcal aureus* (CONS) in six episodes, ESBL *E. coli* (extended spectrum beta lactamases *Escherichia coli*) in three episodes; Methicillin resistant *Staphylococcus aureus* (MRSA), Pseudomonas, Klebsiella and Candida species in two episodes each; Proteus vulgaris and Alpha haemolytic streptococci were found in one episode each (Figure 4).

Correlation of treatment and management with IDSA 2010 guidelines:

1. Initiation of empirical antibiotic: In all 80 episodes of febrile neutropenia the patients were started empirically on IV cefepime.

2. Initiation of azoles in patients with oral candidiasis: In this study, 38 episodes had clinical evidence of oral candidiasis and they were started on oral azoles. The KOH mount of the oral swab collected from the patients with clinical evidence of oral candidiasis showed no pathogen in 28 episodes, candida species in seven episodes and filamentous fungi during one episode (Figure 5).

3. Initiation of empirical gram positive coverage: All patients with CVC were empirically started on gram positive coverage. In 45 episodes, the CVC was in situ. Among them, in 41 episodes linezolid was started on day 1, in 4 episodes teicoplanin was started on day 1; Later on, in 20 cases the antibiotic was changed to teicoplanin on the third day.

All patients with severe mucositis were empirically started on gram positive coverage. Among 45 episodes, in 39 episodes linezolid was started on day 1 and in four episodes teicoplanin was started on day 3; Later on, in 11 episodes the antibiotic was changed to teicoplanin on the third day.

This initial use of linezolid in these high risk patients for gram positive infections was due to the financial constraints (Figure 6).

In patients with fever for more than 2 days: In five episodes IV amikacin and in 2 episodes IV meropenem was started as they continued to have fever and were clinically unstable.

In patients with fever for more than 4 days: In 11 episodes, empirical antifungal therapy was initiated where fever was present beyond four days. Among them, in four episodes IV caspofungin, in four episodes IV voriconazole and in the remaining two episodes IV Amphotericin-B was initiated. This variation in the selection of antifungals was due to the difference in the pathogen and the cost of the medication (Tables 1 and 2).

Table 1: Patients with fever for more than 48–72 hours

Number of Patients	Agent Started
2	Meropenem
5	Amikacin

Table 2: Patients with fever for more than 96–120 hours

Number of Patients	Agent Started
4	Caspofungin
2	Amphotericin-B
5	Voriconazole

Outcome: The mortality rate was 13.75 per cent, which is in accordance with most of the Indian and western studies (Figure 7). Mortality rate was high in those with ANC <100cells/mm^3.

Discussion

Febrile neutropenia is considered as an emergency in medical oncology and a part of treatment complication in most of the cancer patients. Because of its increasing frequency and high fatality it leads to a negative impact on the health resources. Infectious disease society of America (IDSA) realised its importance in patient with malignancies (solid or haematological) at an early stage and hence published the very first guidelines way back in 1997, which was later updated twice in a span of two decades.

The most recent guidelines has been published in 2010 which clearly defined the population group with cancer which might benefit from empirical use of broad spectrum antibiotics (gram negative and gram positive coverage) and systemic antifungals.

In this study, among the 80 episodes recorded, 66 per cent had haematological malignancy and 34 per cent had solid tumours. In the study conducted by Klastersky et al. the incidence of febrile neutropenia was 10–50 per cent in patients with solid tumours and more than 80 per cent in patients with haematological malignancies.[6] The reasons for the occurrence of febrile neutropenia in haematological malignancies are prolonged duration of chemotherapy or immunosuppressive therapy, increased incidence of altered mucosal barrier, prolonged presence of CVC and prolonged duration of neutropenia.

In current study, the most common haematological malignancy associated with the occurrence of febrile neutropenia was Non-Hodgkin's Lymphoma (NHL) followed by Acute Lymphoblastic Leukaemia (ALL) whereas study conducted by Swati et al. showed that the incidence of febrile neutropenia was highest in patients with leukaemia (53.5 per cent) and in lymphoma patients it was 50 per cent, which is in contrast with this study.[7] The patients with lymphoma have higher incidences of infection by intracellular organisms due to immune defects of lymphoma per se and the immunosuppression caused by anticancer drugs and therefore associated with higher occurrence of febrile neutropenia.

Hubel et al. reported that immune defects in the form of impaired chemotaxis and phagocytosis by the neutrophils are usually found in patients with febrile neutropenia who are prone to severe infection by both gram-positive and gram negative organisms.[8]

In the current study blood cultures were positive in 16 episodes (20 per cent). The study by Ramphal et al. showed that in most patients with febrile neutropenia no organism/pathogen was isolated, only 20–30 per cent of the febrile neutropenic episodes displayed the presence of an identifiable organism with bacteraemia occurring in only 10–20 per cent of patients.[9]

In the present study among the 16 episodes with positive blood culture, 12 of them had a central venous catheter which was identified as the most common source of infection. Wisplinghoff et al. conducted the SCOPE (Surveillance and Control of Pathogens of Epidemiologic Importance) project in United States from 1995 to 2001, which showed that the most potential source of infection was the presence of central line which was seen in 90 per cent of neutropenic patients which is in accordance with the present study.[10] A study by Raad et al. showed that lumen of central venous line is the major site of colonisation, therefore a major source of infection and previous catheter site being an independent risk factor for the occurrence of bacteraemia.[11]

In the present study among the pathogens isolated, majority of them constituted gram-negative organisms (52 per cent), followed by gram-positive organisms (40 per cent), and 8 per cent had fungal aetiology. The most common organism isolated was *Escherichia coli* and Coagulase negative *Staphylococcal aureus* (CONS) in six episodes. According to the studies conducted in western population there has been a gradual change from gram negative organisms to gram positive organisms as the important causative factor in febrile neutropenia with CONS leading the group.[9]

In the present study, in all 80 episodes of febrile neutropenia the patients were started empirically on IV Cefepime. The study by Rolston et al. showed that the empirical use of broad spectrum antibiotics covering gram negative organisms is of utmost importance in view of their high virulence, strong association with sepsis as they cause majority of the infections outside the blood stream involving the genitourinary tract, skin, bronchial tree, hepato-biliary system and gastrointestinal system.[12] IDSA 2010 guidelines recommends use of a single drug like cefepime, piperacillin-tazobactum and meropenem as the initial drug of choice since it covers majority of the gram negative organisms including pseudomonas.[2]

In the present study, 38 episodes had clinical evidence of oral candidiasis and they were started on oral azoles. According to IDSA 2010 guidelines all high-risk patients with persistent fever are to be screened for any fungal colonisation/infection and a positive result should mandate the need for treatment with antifungal drugs.[2]

In current study all patients with CVC and severe mucositis were empirically started on gram positive coverage but the initial use of Linezolid in these high risk patients for gram positive infections was due to financial constraints. As per IDSA 2010 guidelines[2] and a study by Paul et al.[13] the indications for the use of antibiotics covering gram positive organisms are severe sepsis/septic shock, lung involvement, positive cultures, central line infection, infection involving

skin and subcutaneous tissue and extensive mucositis. Vancomycin is used most commonly with linezolid being an alternative.

In the present study, in five episodes IV amikacin and in two episodes we used IV meropenem was started as they continued to have fever and were clinically unstable. As per IDSA 2010 guidelines, the antibiotics during the initial period can be modified accordingly in patients who are at risk of infection by drug resistant pathogens, clinically unstable patients and in patients with documented infection by drug resistant organisms.[2]

In the current study there were 11 episodes where the fever was present beyond four days and they were started on empirical antifungal therapy. As per IDSA 2010 guidelines, all patients of high-risk febrile neutropenia with persistent fever, no documented aetiology/source of infection and longer duration of neutropenia (more than one week) are to be initiated on antifungal drugs after 4–7 days of fever.[2]

The mortality rate in the present study is 13.75 per cent which is in accordance with most of the Indian and western studies. The SCOPE project showed a mortality rate varying from 16 per cent to 45 per cent. A study from Tata memorial institute (Mumbai, India)[14] also showed a mortality rate of 18–42 per cent in the high risk febrile neutropenic patients. This slightly higher occurrence of mortality in above studies when compared to the present study is because they had a large number of population under study, varying type and stage of underlying malignancies, the underlying comorbidities of the febrile neutropenic patients were not included in the study, severity and duration of mucositis was not assessed; and the depth and duration of neutropenia was not considered.

Limitation of the study is that, febrile neutropenic patients at risk of infection from gram positive organisms were given IV teicoplanin whereas the IDSA guidelines recommended the use of IV vancomycin and the reason being ease of administration of teicoplanin over vancomycin.

Conclusion

According to this study we conclude that NHL is the most common malignancy associated with high risk febrile neutropenia, the most common source of infection being central venous catheters with *E. coli* being the most common isolated organism.

Overall this study helps us to look into the entire spectrum of patients with high-risk febrile neutropenia in developing countries which is quite different when compared to the developed nations and thus guides the treating physician.

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PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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None

ETHICS COMMITTEE APPROVAL

Informed consent was obtained and the study was approved by the Institutional Ethics Committee (356/2011 meeting held on 08th November 2011).

Figure 1: Spectrum of various malignancies in the study

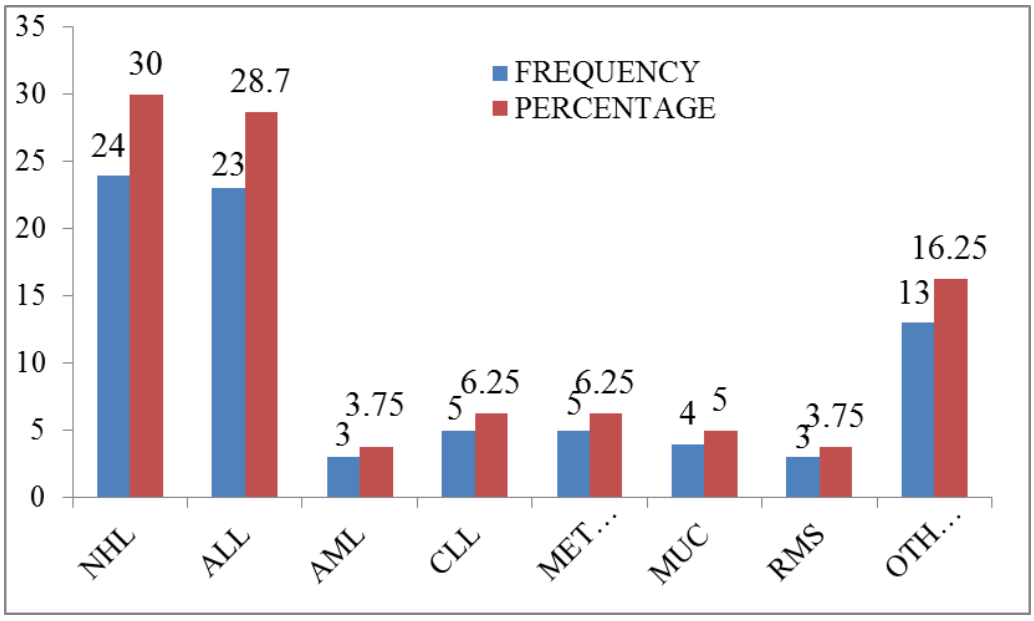


Figure 2: Blood culture positivity rate

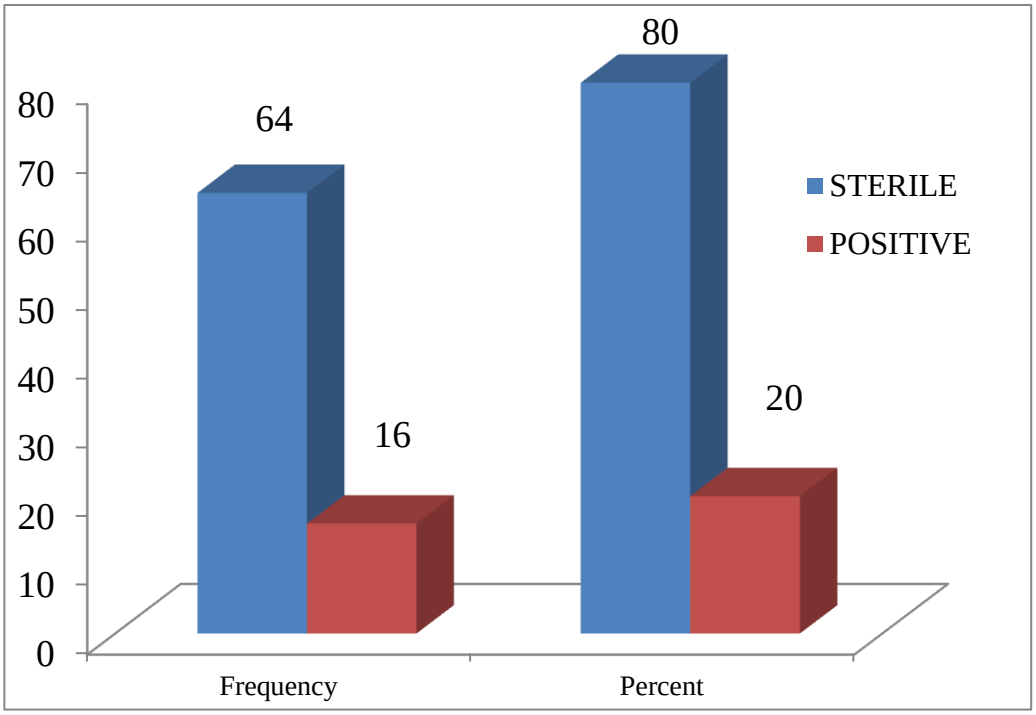


Figure 3: Presence of central line in blood culture-positive patients

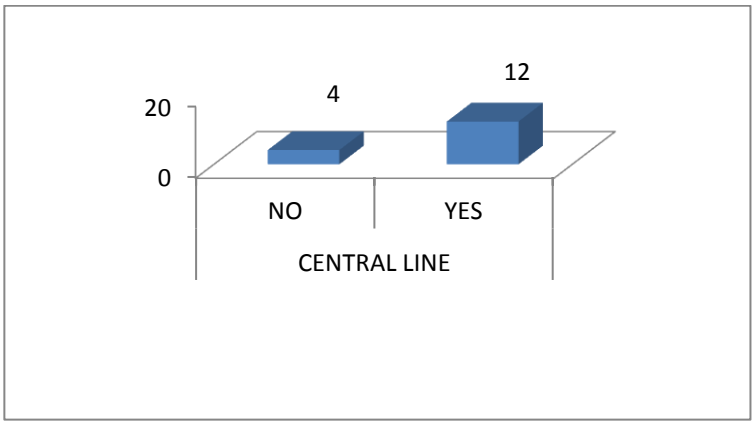


Figure 4: Spectrum of pathogens isolated during the study

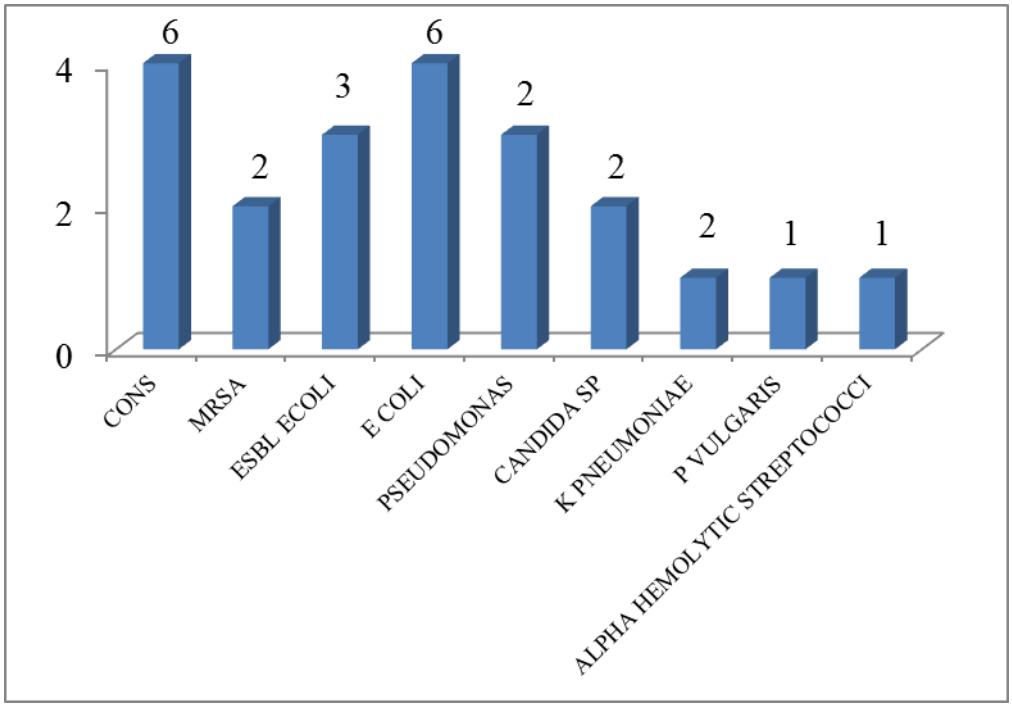
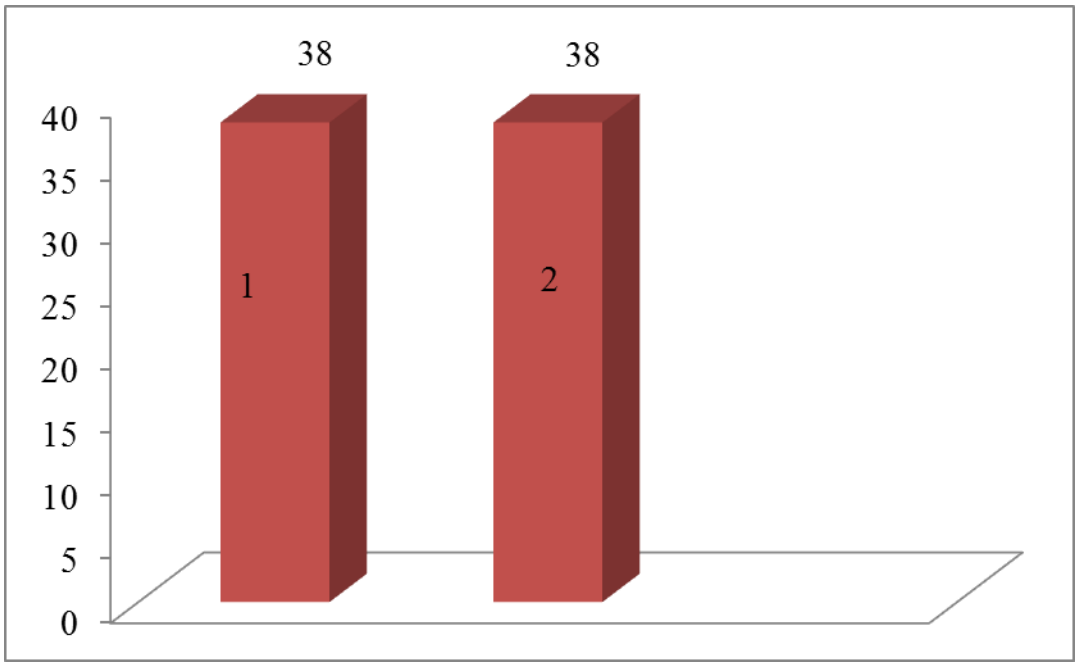


Figure 5: Initiation of azoles in high-risk neutropenia with oral candidiasis



1. *Number of patients with oral candidiasis; 2. Number of patients in whom azoles were initiated*

Figure 6: Initiation of empirical gram-positive coverage in patients with febrile neutropenia

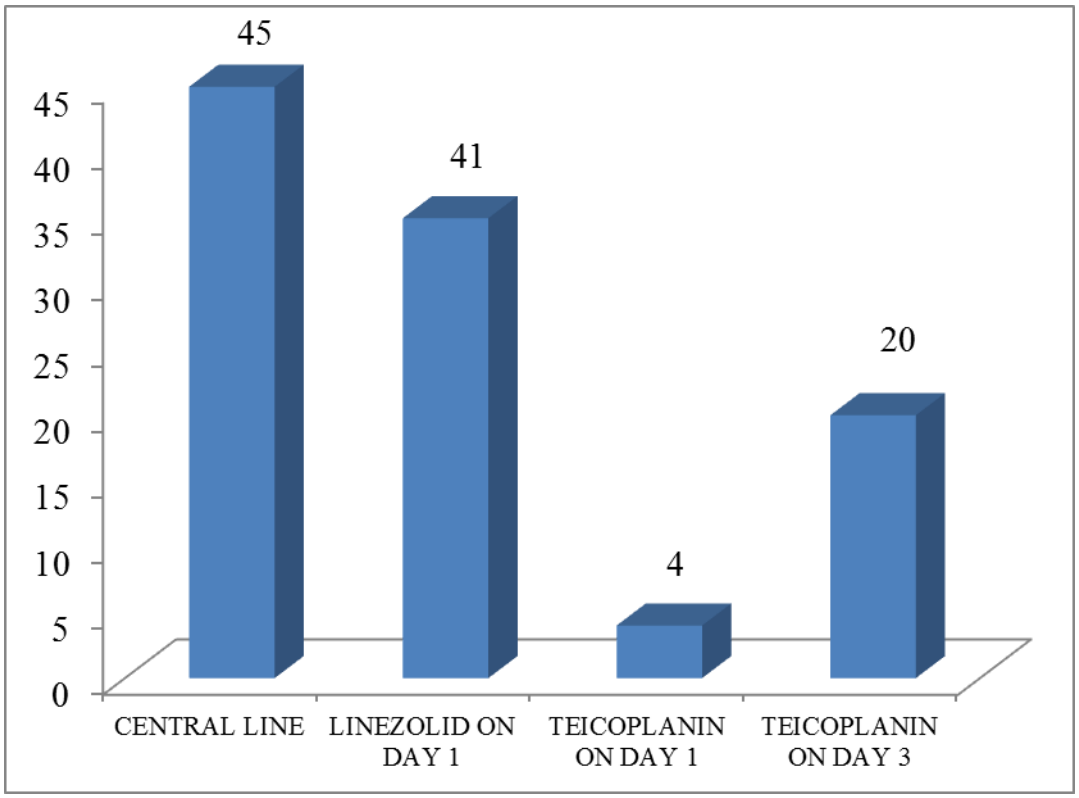


Figure 7: Outcome