ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

DEPARTMENT OF INTERNAL MEDICINE

Research Title

Clinical, laboratory, treatment profiles and outcome of neutropenic fever among high-risk hematologic patients in Tikur Anbessa Specialized Hospital 2019, Ethiopia.

A manuscript submitted to the Department of Internal Medicine, College of Health Sciences, Addis Ababa University, in partial fulfillment of residency/post graduate study in Internal Medicine.

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Contents

Acronyms

ALL Acute lymphocytic leukemia

AML Acute myelocytic leukemia

ANC Absolute neutrophil count

ASCO American society of clinical oncology

CLL Chronic lymphocytic leukemia

CML Chronic myelocytic leukemia

CONs Coagulase negative streptococcus

ESBL Extended spectrum B-lactamase

NF Neutropenic fever

HL Hodgkin's lymphoma

HM Hematologic malignancy

ICU Intensive care unit

IDSA Infectious disease society of America

MDR Multi drug resistance

MICs Minimum inhibitory concentrations

MRSA Methicillin resistant staphylococcus aureus

NCCN National cooperative for cancer network

NHL Non-Hodgkin's lymphoma

PRSP Penicillin resistant streptococcus pneumonia

TASH Tikur Anbessa specialized hospital

VRE Vancomycin resistant enterococcus

Abstract

Background

Patients with hematologic malignancy are at a higher risk to develop neutropenic fever. The febrile neutropenia episodes are associated with increase in morbidity and mortality of these patients. Outcome of each of the episodes of febrile neutropenia is associated with the clinical, laboratory, microbiological, imaging for source of infection and antimicrobial and chemotherapy regimen the patients is taking.

Objectives

The purpose of this study was to assess the correlation of the clinical, laboratory and treatment profiles of the patients with neutropenic fever and hematologic malignancy with all-cause mortality in 30 days of diagnosis of the neutropenic fever episode at Tikur Anbessa Specialized Hospital.

Methods

A single center, cross sectional retrospective study was conducted in hematology and medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia for the year 2019. The clinical profiles with history and presumed site of infection, treatment plans and outcome in 30 days of diagnosis of the NF episode were retrieved from medical charts. Chest imaging results during the diagnosis of the febrile neutropenia episode were taken from the Med Web intranet database of the institution. The microbiology data for the specimens collected for culture was retrieved form the log book at the microbiology department of the Hospital. The data was subjected to bivariate and multivariate analysis using SPSS Ver 26.

Results

A sample of 132 patients with hematologic malignancy and neutropenic fever episode in the year 2019 were assessed. The study revealed that among patients with febrile neutropenia male to female ratio was 13:10. The patients had ALL (43.2%) and AML (40.9%) as the common underlying diseases. Frequent site of primary infection was chest focus (33%). More than half of the patients were on combination therapy with Cefepime and Vancomycin (40.9%). The odds of dying in 30 days of diagnosis was 5.4 times higher in patients with Medical ICU admission [AOR= 5.4; 95% CI: 1.22 - 23.92] and 3.8 higher in those with past history of febrile neutropenia [AOR= 3.8; 1.44 - 10.16].

Conclusion

The history of prior treatment for febrile neutropenia and medical ICU admission during the course of treatment of febrile neutropenia of patients with hematologic malignancy predicted all-cause in hospital mortality in 30 days.

Key words

Febrile neutropenia, hematology malignancy, all-cause mortality

Introduction

Background

Neutropenic fever is one of the commonest complications in hematology malignancy patients. The patients with cytotoxic antineoplastic treatments have disrupted myelopoiesis. The integrity of the GI mucosa is at risk of invasive infection due to colonizing microorganisms. This puts them at risk to develop a neutropenic fever.

It is estimated that 10% of patients taking chemotherapy will develop febrile neutropenia and 1% will die from it. [1] Most of the hematologic malignancies cause high-risk neutropenia. Risk stratification correlates to the management approach and etiology of the neutropenic fever.

The diagnosis of febrile neutropenia is based on a reliable measure of the temperature of the patient. Temperature rise with the neutropenia needs further investigation to locate the source and cause of infection.

The management of neutropenic fever is difficult because the number of neutrophils does not always predict the capacity to respond to infections. In setups with available resources, neutropenic fever is an emergency prompting antibiotic initiation immediately.

In developing countries the data on epidemiology and management outcomes of patients with febrile neutropenia are limited. The rise of cases with resistant organisms in febrile neutropenia with limited studies made in the continent call for more studies to be conducted in the area.

Statement of the problem

Cancer is now a growing cause of death and disability in the developing world. In sub-Saharan Africa, a marked increase in burden with more than a million incidents of cancer and nearly 800,000 cancer-related deaths were projected for 2030. Of all cancers occurring in sub-Saharan Africa, Hematopoietic malignancies have emerged as a major cause of morbidity and mortality. Non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma, and multiple myeloma accounted for 9.9% of cancer-related deaths.[2]

A retrospective study in Gondar Specialized Hospital, Ethiopia, showed that NHL accounted for 32.8% of all hematologic malignancies[3]. This was followed by CML (25.4%) and CLL (19.4%).

The majority of NHL patients had advanced disease at presentation (77%) and high grade in type with B symptoms (73%). Acute leukemia patients, especially ALL patients presented with cytopenias and their complications.[3]

After risk stratification of patients, prophylaxis antibiotics should be initiated. In the meantime the patients must be frequently assessed for fever. Prompt initiation of antibiotics will prevent sepsis syndrome and death. Once the diagnosis of febrile neutropenia is made, initiation of antibiotics according to the IDSA 2010 updated guideline is necessary. If the center has an antibiogram and suggested empiric management, it should be initiated once appropriate investigations are sent.[4]

In a study conducted in search for prevalent infections in hematologic malignancy patients in Europe, 29 papers from 13 countries were reviewed. The different papers had a median observation time of five years. The median reported pathogen ratio of gram-positives for gram-negatives was 60:40. The main pathogens were coagulase-negative streptococcus (CONs) at 25%, Enterobacteriaceae (24%), *Pseudomonas aeruginosa* (10%), and *Staphylococcus aureus* (6%). The antimicrobial resistance rates in isolates from adult patients were evaluated and the most frequent resistance was for methicillin among CONs (80%) and *S. aureus* (56%). The resistance for fluoroquinolones in Enterobacteriaceae was 56% and *P. aeruginosa* 33%. The most alarming of all resistances was a median of 44% for carbapenems by *P. aeruginosa* in seven studies.[5]

Significance of the study

This study is a contribution to the management of neutropenic fever patients with hematologic malignancies. It has shown the profile of neutropenic patients, their risk categories, etiology of neutropenic fever, management and outcome. The results will help to improve the practice of treating neutropenic fever patients. It will pave the way to have better institutional guidelines and improve the outcome of hematologic malignancy patients.

Literature review

Definitions of neutropenia and fever

Neutropenia defined for neutropenic fever has different cut off points. The number used by the United States Department of Health and Human resources for severe neutropenia is < 500/mm3 and or if it is expected to drop below 500/mm3 in the next 48 hours. [4]

The IDSA has the temperature as oral temperature as 38.3^0c or if the oral temperature is 380c for >1 hour. There are different guidelines that agree with such a cut off for temperature records. [6]

The effects of the chemotherapy use or use of glucocorticoids that may give false readings were noted as confounding factors. The suggestion of different experts is even in an afebrile patient suspected of febrile neutropenia the clinician should look for SIRS, tachycardia, tachypnea, and or hypotension. [7]

In the 1990s there was a tendency to classify febrile neutropenia as a syndrome. It was initially divided into 3 categories;

a. Microbiologically documented infection in neutropenic patients with clinical features of infection and associated pathogen
b. Clinical infection with focus but not isolated in a neutropenic patient
c. Unexplained fever with no site or focus no pathogen recovered. [8]

Most patients with neutropenic fever foster an underlying malignancy and the neutropenia can be related to the chemotherapy initiation.

a. Chemotherapy related neutropenic fever
b. Non-chemotherapy related neutropenic fever

Timing and episodes of the neutropenic fever can be used as a classification scheme.[4]

a. First neutropenic fever is the first febrile episode during chemotherapy-induced neutropenia.
b. Persistent neutropenic fever is when the patient stays without defervescence for at least 5 days.

c. Recrudescence neutropenic fever is when the fever recurs in a neutropenic patient following the initial defervescence during a course of broad-spectrum antibacterial therapy.

Incidence of febrile neutropenia

Neutropenic fever is the most common complication in cancer patients. In such cases the common underlying diseases are hematology malignancies. More episodes of febrile neutropenia are also seen in these patients.

In a retrospective study done in Saudi Arabia, hematologic malignancies constituted 56.6% of all neutropenic fever episodes. High-risk hematologic malignancies like leukemia are prone to serious infections. In a study done in Louisville, patients that had diagnoses of AML, ALL, CML, CLL, and MDS were prospectively followed. The highest case of febrile neutropenia was noted in those with AML (69%) followed by ALL (24%).[9] In terms of age of the patients that frequently developed febrile neutropenia, an Indian study showed that the majority of patients were under the age of 35.[10] In contrast to this, a prospective study in England showed that older patients with hematologic malignancies developed febrile neutropenia more frequently.[11] Most patients with neutropenic fever were also found to be males in the Indian study.[10]Similar results of male predominance were observed in a Turkish study.[12]

Pathogenesis and risk factors

Patients with neutropenic fever have several contributing factors that make them infection-prone. In those on cytotoxic chemotherapy, the integrity of the GI mucosa is affected. They are at risk of invasive infections due to colonizing bacteria or fungus that translocate from the intestinal mucosa. Obstruction of the lymphatic channels, biliary tract, bronchial or GI tract, or urinary system directly by the tumor or any invasive procedure done for the disease can contribute to the development of neutropenic fever.

The effect of the malignancy on the immune system is considered a risk factor for patients with neutropenia. Especially those with hematologic malignancies have suppressed neutrophil function as the neutrophils have less phagocytic activity. The neutrophils might be pre-activated and have reduced function prior to chemotherapy initiation.[13],[14]

Specific malignancies can be a risk factor to or result in specific infections. This is related to either cellular or humeral defects that the particular malignancy might have. In cases where antibody production becomes abnormal or when clearance of immune complexes becomes abnormal, patients are prone to infection with encapsulated gram negative bacteria.

Much is known about the nature and risk factors of febrile neutropenia. The risk of febrile neutropenia is in direct relationship with the duration and severity of neutropenia. This can be seen in studies going back as far back as 1966. Bodey and colleagues showed that the percentage of days with infection decreased with increasing granulocyte levels. They also demonstrated that patients had rapid and fatal outcome while awaiting results of cultures which grew gram-negative bacteria. This has laid the path to current practice of immediate hospitalization of patients with febrile neutropenia.[15]

In a retrospective study evaluating patients with intermediate-grade NHL, risk factors for first febrile neutropenia episodes were assessed. The risk was significantly associated with those Age> 65 years, cardiovascular diseases, renal diseases, baseline hemoglobin<12g/dl, >80% planned average relative dose of chemotherapy and no prophylactic colony stimulating factor(CSF) use. The first febrile neutropenic events occurred on day 14 of cycle 1 in about half of the patients. [16]

Prior use of chemotherapy in patients with hematologic malignancy is associated with an increased risk of febrile neutropenia. The relationship between the type of chemotherapy and febrile neutropenia is not clearly associated. Some models have tried to classify the types of chemotherapy as being low-risk (<10%), intermediate risk (10-20%), or high-risk(>20%) for febrile neutropenia.[17]In a prospective study to predict chemotherapy effect for febrile neutropenia, it showed that aggressive chemotherapy was the major predictor (odds' ratio 5.2{3.2-8.4}).[18]

Timing is not uniform among all treatment cycles in many cancer types. There is a cumulative risk of neutropenic fever with each cycle. The risk in each cycle is dependent on dose intensity, previous treatments, comorbidities, antibiotics, and other treatments such as growth factors. [16]

Epidemiology of pathogens and primary site of infection

An infectious source is found in 20-30% of neutropenic fever patients. Out of this 80% of the identified organisms are endogenous flora. Bacteria are the most common cause of neutropenic fever. The commonest bacterial pathogens in the 1980s were the gram negatives. [19]

The trend now has shifted towards gram-positive bacteria, especially gram-positive cocci. The contributing factors towards this shift are the frequent use of indwelling catheters, the empiric coverage for *Pseudomonas aeruginosa* and the usage of prophylaxis for gram-negatives.[20],[21] There are some scholarly articles indicating a re-shift towards gram-negative infections.[22],[23] But the ratio gram-positives: gram-negatives is 60:40. [5]

Gram-negative bacteria are associated with the most serious infections. *Staphylococcus epidermis* is the commonest gram-positive in neutropenic constituting about 50% of all cases.[5]*Staphylococcus aureus* (methicillin-resistant) some *Streptococcus viridians* and Enterococcus cause serious infections. Anaerobic bacteria are not common but they may cause necrotizing mucositis, sinusitis, periodontal cellulitis, typhylitis or pelvic infections.

Fungal infections are common in high-risk neutropenic patients. Invasive fungal infection risk is high for patients with linger duration of neutropenia with greater severity, those with prolonged antibiotic use and those that have taken more cycles of chemotherapy. The commonest fungal infections in neutropenic fever are candida from the GI flora and Aspergillus species from airborne spores. In candidemia the sole symptom maybe fever. Sometimes erythematous macro nodular skin nodules may occur. The time to candidemia in AML patients is about 16 days post remission induction when the cytotoxicity effect of the chemotherapy is at its peak causing maximum epithelial damage. [24],[1] In those with disseminated candidiasis post chemotherapy, hepatosplenic involvement is common. The hepatosplenic involvement is mostly 26 days from the 1st day of chemotherapy initiation. This is the time where the neutropenia resolves. [24]

The majority of fungal infections are caused by *Candida albicans*. If fluconazole was used as a prophylaxis in neutropenic patients, then non-albicans will be more common. Candida is also common fungal infection that causes in catheter associated infections and can cause disseminated candidiasis. Aspergillus manifests as pneumonia and can also cause sinusitis. The diagnosis of invasive aspergillosis should be supported with clinical, laboratory, and imaging findings of patients. High-risk patients should be evaluated by chest CT scan imaging and patients should be

grouped as having proven, probable and possible invasive aspergillosis infection.[25],[26]Infections from new or endogenous fungi like *Histoplama capsulatum*, *Blastomyces dermatides,* and Coccidiodes species can occur. Risk factors such as prolonged period of immunosuppression, glucocorticoids use and travel to endemic areas are known to cause such infections. [1]

Viral infections, especially Herpes are common in high-risk neutropenic patients. It is caused by reactivation in seropositive patients. The risk for reactivations is directly related to the intensity of the chemotherapy regimen the patients are taking. [27]The common manifestation of herpes in neutropenic patients are ulcerations of the esophageal mucosa, vesicles on the lips, skin, genitalia, and perineal area. Herpes Zoster can have atypical presentation affecting multiple dermatomes with wide-spread skin infection. Such presentations are common in those that receive allogenic HSCT.[28]Infections caused by tuberculosis should be considered in endemic areas. The prolonged use of glucocorticoids or TNFα inhibitors is a risk factor for such infections.

In a cross-sectional study done in Tikur Anbessa Specialized Hospital in 2011, blood cultures from febrile cancer patients were performed. The majority of the isolates were gram-positive bacteria (60.5%), S. *aureus* was predominant (72%) and out of the *S. aureus* isolates 68% were resistant to ceftriaxone and oxacillin. Gram-negative isolates were 39.5% and *Stenotrophomonas maltophilia* was the most frequent isolate (17.9%). In gram-negative bacteria, the most resistance was for Amoxicillin-clavulanic acid (80%) followed by ceftriaxone (73.3%).[29]

The commonest sites of infection for febrile neutropenic episodes were assessed in an Indian study in patients with acute leukemia following chemotherapy. They found that the most frequent site of infection was the respiratory tract (32.6%), followed by oral mucosal infections (20.4%), GIT (18%), genitourinary tract (6.4%) and skin and soft tissue (3.5%).[10]A study in Turkey reported a similar result where the commonest site of infection was in the respiratory tract.[12]

Diagnosis of febrile neutropenia

Temperature is the trigger for initiation of the treatment protocol for neutropenic fever. The temperature record should be reliable as neutropenic fever is an emergency. A neutropenic patient has additional burdens of toxicity of antimicrobials, risk of developing drug-resistant

infection, and hospitalization costs once diagnosed with febrile neutropenia. The plan is to pick early and treat early.[30]

There is no universal way of measuring temperature. Most centers use peripheral methods. But central methods are more sensitive. Central methods may not be practical or safe in neutropenic patients. Oral temperature measurement may be painful and may overestimate body temperature as compared to tympanic membrane thermometry. Infrared tympanic membrane readings are easy but may give false readings from the dependent ear and give falsely low readings if cerumen is in the ear canal. Rectal readings are not recommended because of bleeding and can cause bacteremia. [31],[32],[33]

Treatment of febrile neutropenia

Hematologic malignancy patients receive cytotoxic antineoplastic therapy that affects myelopoiesis. Such patients cannot mount a strong inflammatory response, serious infections can occur with minimal symptoms and signs. Fever is often the sole sign. The infection can lead to hypotension and other complications rapidly. So it is important to recognize such signs and symptoms early and start on empiric therapy.[34]

Initially, patients suspected of neutropenia should have their ANC calculated. The nadir of the ANC is at a median of 12-14 days from day 1 of chemotherapy. For patients who take chemotherapy treatment, 70% of them develop systemic therapy-related complications within 4 to 6 weeks of taking the treatment.[35]

Then once neutropenia is ascertained, patients should be monitored for temperature rise. Patients should be informed of the neutropenia and the possibility of developing an infection. Identification of sepsis in neutropenic fever is difficult. Therefore, clinical assessment at the Emergency should include looking for SIRS. Patients with signs of organ damage should be managed promptly because it is a sign of severe infection.[36],[37]

Empiric use of broad spectrum antibiotic therapy is advocated by many guidelines. The IDSA and the NCCN recommend antibiotic initiation soon after blood samples are drawn for cultures.[4],[34] Other guidelines advocate initiation of treatment within 60 minutes of clinical diagnosis.[38],[37],[36]

The empiric therapy in high-risk patients should be intravenous antibiotics. Bactericidal antibiotics are the preferred choices with patients' history of allergic reaction and prior infections and culture yields inconsideration. Afebrile neutropenic patients with signs and symptoms consistent with infection should also be managed as febrile neutropenia.[39],[40]

The initial regimen choice for high-risk patients for febrile neutropenia is dependent on many factors. There growing risk of ESBL producing gram-negative bacteria in such patients and a delay in their management will increase the risk of mortality. The risk factors for MDR pathogens in neutropenic fever are prior exposure to broad-spectrum antibiotics, the severity of the underlying malignancy, presence of comorbidities, and presence of indwelling catheters. These patients should have cultures for current and prospective infections to control the selection of β lactam empiric therapy. The choice of antibiotics for patients not at risk of ESBL gram-negative will be piperacillin-tazobactam or Cefepime or Ceftazidime while those with risk will need to receive Carbapenems. Antibiotic trials conducted on patients with sepsis and neutropenic fever showed that addition of Vancomycin to monotherapy had a non-significant effect on outcome.[41],[42],[43],[23],[44]

Persistent febrile neutropenia is a febrile neutropenia that does not resolve despite broad-spectrum antibiotics for at least 5 days. [45]One of the most common causes of persistent febrile neutropenia is a fungal infection. Persistent febrile neutropenia that has neutropenia lasting for more than 7 days should be investigated for invasive fungal infection. The IDSA guidelines recommend lipid formulations of Amphotericin B, Caspofungin , Voriconazole, or Itraconazole as empiric antifungals.[4],[1]

A retrospective study at Tikur anbessa specialized hospital that assessed the rate of antibiotic consumption showed that most of the antibiotics were ordered in the internal medicine wards (57.5%) and neutropenic fever diagnosis was the third most common reason for these subscriptions (9.5%). On average 2.1 antibiotics were prescribed per patient in the internal medicine wards. Third-generation cephalosporin were the most commonly prescribed antibiotics. Half of all the patients in the medical wards were exposed to ceftriaxone after admission to the hospital.[46]

The outcome of febrile neutropenia

The morbidity and mortality risk febrile neutropenia has on hematologic malignancy patients is precedent. In a retrospective study from a database of patients admitted to a cancer center, in-hospital mortality was 9.5% concerning febrile neutropenia. Patients without any major comorbidities had a 2.6% risk of mortality, whereas 1 major comorbidity was associated with a 10.3% and more than 1 major comorbidity with a 21.4% risk of mortality, respectively.[47] In the study done in Turkey diagnosis of pneumonia was associated with a higher mortality rate in patients with febrile neutropenia and hematology malignancy.[12]

The effect of prior history of febrile neutropenia on mortality among patients with hematologic malignancy had been evaluated in a study done in Delaware, USA. They found out that patients with prior neutropenic fever had at least a 15% higher risk of mortality when compared to those who had none.[48]

Medical ICU admission in patients with febrile neutropenia affects in hospital mortality and outcome. This was seen in studies done in Germany, France, and the USA where an initial presentation requiring ICU admission or transfer to ICU during hospitalization increased mortality by 50%.[49],[50],[51]

Objectives

General Objective:

- To assess the management and outcome of neutropenic fever patients in hematology wards of Tikur Anbessa Specialized Hospital

Specific objectives:

- To determine clinical profile of patients with febrile neutropenia and high risk hematologic condition
- To determine diagnostic methods used in neutropenic fever patients
- To determine pathogens involved in febrile neutropenia
- To assess primary site of infection in febrile neutropenia patients with high risk hematologic condition
- To assess antibiotic usage in patients with febrile neutropenia

  To determine the outcome of neutropenic fever episodes within 30 days of diagnosis in patients with high risk hematologic disease

Method

Study area

Tikur Anbessa Specialized Hospital is a referral and teaching Hospital located in Addis Ababa, Ethiopia. The hospital was established in 1974. It has teaching programs for undergraduate and postgraduate medical programs. Different specialty and subspecialty personnel are operating the internal medicine ward is comprised of the intermediate or waiting ward, hematology wards, pulmonology and critical care, and gastroenterology ward, and Endocrine and infectious disease wards. It is the pioneer and one of three centers where hematologic malignancies are treated in a governmental hospital.

Study Setting

The study was conducted in the medical and hematology wards of TASH

Study design:

The study was a retrospective, observational and single center

Study Period

The study period was from January 1, 2019 up to December 31, 2019

Source population

All patients with Acute Leukemia, High-grade NHL and Aplastic anemia admitted to Tikur Anbessa specialized hospital in 2019

Study population

All patients with acute leukemia, High grade NHL or Aplastic anemia that had developed neutropenic fever admitted to Tikur Anbessa Specialized Hospital in 2019

Sampling procedures

All patients in the study population that fulfill the inclusion criteria were included.

Inclusion Criteria

Patients with all the characteristics below were included:

- Patients age >13 years old*
- Patients admitted to Tikur Anbessa Specialized Hospital Medical and Hematology wards in the time period of January 1 up to December 31, 2019.

- Known or suspected with hematologic disease at the time of diagnosis and treatment of febrile neutropenia- acute leukemia, high-grade lymphoma, aplastic anemia
- The diagnosis of the underlying disease documented on the charts and included Peripheral morphology, BMB, BMA, and/or lymph node biopsy
- ANC< 500 cells/ mm3 or ANC <1000 cells/mm3 with prediction to fall in 48 hours and documented as a diagnosis of febrile neutropenia
- Neutropenic fever assessment diagnosed and documented in the time period
- Only the first neutropenic fever episode with in the year of the study to be documented for every patient (may not be the first episode of febrile neutropenic fever: the first episode documented after admission in the year 2019)

Exclusion Criteria

- Patients not fulfilling all the above criteria
- Patients whose chart had a missing clinical profile, treatment plan and documentation of outcome within 30 days of diagnosis of the febrile neutropenia
- Subsequent episodes of febrile neutropenia of patients in the study

Study variables

Dependent variable

- Death / All-cause mortality within 30 days of diagnosis of febrile neutropenia episode

Independent variables

- Age of the patient
- Comorbidities of the patient before the diagnosis of febrile neutropenia
- Type of underlying hematology condition diagnosed before febrile neutropenia
- Prior history for treatment of febrile neutropenia
- Use of prophylactic antimicrobials before febrile neutropenia
- Use of chemotherapy prior to diagnosis of febrile neutropenia
- WBC count at the diagnosis of febrile neutropenia
- ANC at the diagnosis of febrile neutropenia
- Platelet count at the diagnosis of febrile neutropenia
- Serum creatinine at the diagnosis of febrile neutropenia
- The primary site of infection
- Chest imaging suggestive of invasive aspergillosis

- Medical ICU admission within 30 days of diagnosis of febrile neutropenia

Data collection procedures

After a structured questionnaire was prepared (Annex), the eligible patient's card numbers and identifications were retrieved from HMIS logbook for admissions of the year 2019 to hematology and medical wards. The clinical profile, the onset of febrile neutropenia, treatment given, and outcome within 30 days of diagnosis of febrile neutropenia were taken from the patient's medical chart. The first episode of neutropenic fever of the eligible patients was taken as the febrile neutropenic episode to be filled in the questionnaire. Subsequent neutropenic fevers in the same patient were excluded.

Laboratory results documented on the medical charts were included. Culture and sensitivity results of specimens collected from patients with febrile neutropenia and hematologic disease were registered from the Microbiology unit in the Laboratory department of the hospital. Chest imaging results documented on the charts were crosschecked with the Med Web intranet registry of the institution.

Data quality assurance

The questionnaire was filled and completeness of the data was checked by the primary investigator. Missing data of laboratory values were taken from the automated logbook found at the laboratory of the hospital.

Data collection instruments

Structured Questionnaire to evaluate the objectives was implemented.

Data Analysis and interpretation

The collected data was filtered and entered to the Statistical Package for Social Sciences (SPSS) version 26. Variables were defined, categorized and recoded. Demographic and clinical data were described with descriptive statistics including means, standard deviation, and percentages, and frequency distribution tables. Comparisons between groups were made by Chi-square or Fisher's exact test. The associations between clinical and biochemical tests were assessed using multivariate regression analysis. A 95% confidence interval was used for the determination of the significance of probabilities i.e. the difference was significant when p value is < 0.05.

Operational definitions:

(By IDSA 2010 guidelines)

- **Severe Neutropenia –** ANC< 500 cells/mm3
- **Profound Neutropenia-** ANC< 100 cells/mm3
- **Site of infection-** a confirmed site as a source of infection as documented on the medical chart
- **Evidence of source of infection**-Imaging of the patient- x rays, Ultrasounds, CT scans, MRIs and/or any specific specimen culture yielding a pathogen
- **Empiric antimicrobial treatment** - a treatment that was given during the initial assessment of neutropenic fever. (ASCO 2012)
- **Definitive antimicrobial/Second antimicrobial regimen**- a treatment regimen that was given after change of the first antimicrobial therapy
- **Monotherapy**- use of a single antimicrobial
- **Combination therapy**- use of more than one antimicrobial as a combination in the treatment of febrile neutropenia
- **Persistent neutropenic fever**- neutropenic fever without defervescence for at least 5 days and on broad-spectrum antibiotics.
- **Relapse**- recurs after initial defervescence during a course of broad-spectrum antibacterial therapy.
- **Death in 30 days/all-cause mortality on 30 days** –death in 30 days pf diagnosis of febrile neutropenia

Ethical consideration

Ethical clearance was obtained from the Department of Internal Medicine and Research and Publications Committee of the School of Medicine, College of Health Sciences, Addis Ababa University.

Results

Identification of the study participants

A total of 132 patients with hematologic disease and febrile neutropenia participated in the study. Among the participants of the study, 75 (56.8%) of them were male and the remaining 57 (43.2%) of them were female. The median age of the study participants was 25 years with a

mean age of 29±14.31years, the most frequent age stratum being 13-29 years (Quartile1 and quartile3 of 18 and 37 years respectively). Most of the patients are from Addis Ababa (56%) as documented on their medical charts.

Table 1. Age and sex distribution and address of high-risk hematology patients with febrile neutropenia admitted at TASH, Addis Ababa, Ethiopia, 2019

		Sex of the patient		Percent
		Male	Female	
Age Group (years)	**<30**	56	27	69.1
	>30	19	25	30.9
Address of the patient		**No.**		**Percent**
Addis Ababa		74		56.0
Oromia		32		26.6
SNNPR		9		7.5
Others		17		9.3

Clinical profiles of the study participants

In the study, 39 (29.5%) of them had a history of prior admission; of which, 18 (46.2%) had one prior admission and the remaining 21 (53.8%) had more than one prior admission. While less than one fifths (18.9%) of the participants had prior episodes of febrile neutropenia, only about one tenths (9.8%) of them had past medical history. There were three patients on follow-up for chronic hepatitis B infection and two patients had hypertension. The number of patients on prophylactic antibiotics before the current febrile neutropenia episode was 96 (72%), and 19(14.4%) were on prophylactic G-CSF. Among the study participants, 57 (43.2%) of them had acute lymphoid leukemia (ALL) and 10 (7.6%) had an admission in medical ICU. (Table 2)

Table 2. Clinical profiles of hematologic disease patients with febrile neutropenia admitted at TASH, Addis Ababa, Ethiopia, 2019

	No.	Percent (%)
Hematologic disease (n=132)		
ALL	57	43.2
AML	54	40.9
Aplastic anemia	11	8.3
Others*	10	7.6
Medical ICU admission (n=132)		
Yes	10	7.6
No	122	92.4
Prior episode of febrile neutropenia (n=132)		
Yes	25	18.9
No	107	81.1
Frequency of prior episodes of febrile neutropenia (n=25)		
One	11	44.0
Two and more	14	56.0
Site of prior episode of febrile neutropenia (n=25)		
Chest focus	17	68.0
Others	8	32.0
Comorbidity prior to the neutropenic fever (n=132)		
Yes	13	9.8
No	119	90.2
Use of Prophylactic Antibiotics (n=132)		
Yes	96	72.7
No	36	27.3
Types of Prophylactic Antibiotics Used (n=96)		
Ciprofloxacin, Acyclovir, Fluconazole	40	41.2
Co-trimoxazole, Acyclovir, Fluconazole	57	58.8
Use of G-CSF as a prophylaxis (n=132)		
Yes	19	14.4
No	113	85.6

**NHL,AML-ALL Biphentotypic*

Clinical presentation of the febrile neutropenia

The presumptive sites of infection at diagnosis were assessed. The most common site presumed was chest focus in 44 patients (36.6%), GIT focus in 29 patients (24.9%), and 31 (23.4%) patients had an undetermined focus of infection at the diagnosis of febrile neutropenia.

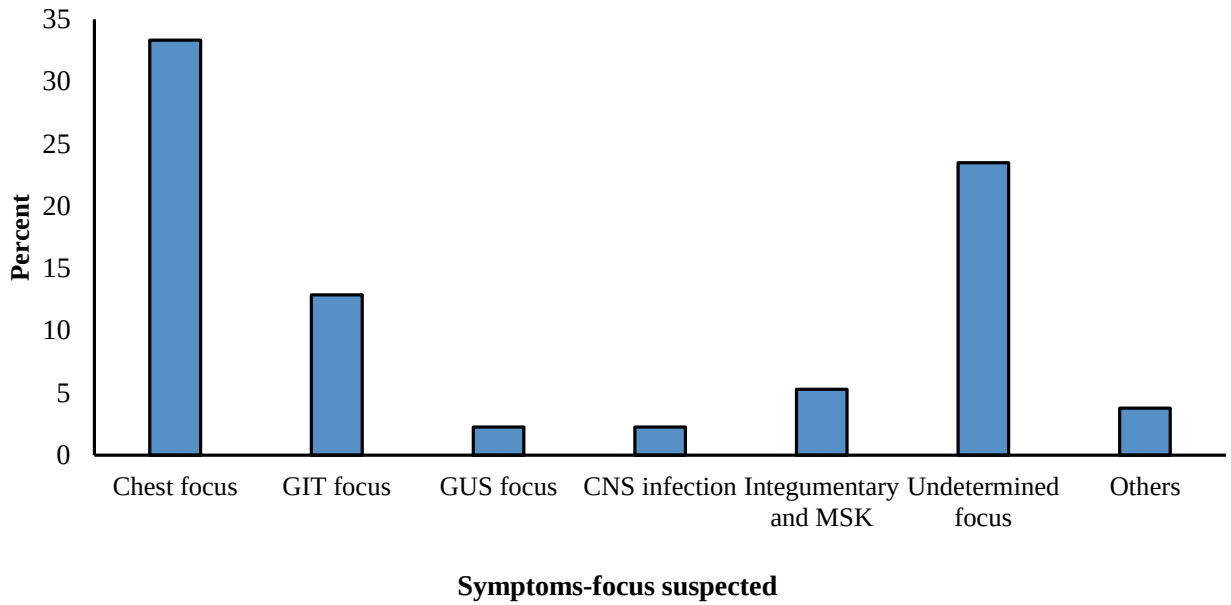

Figure 1.Primary site of infection at time of diagnosis of high-risk hematology patients with febrile neutropenia admitted at TASH, Addis Ababa, Ethiopia, 2019

Laboratory profiles of the study participants

The total WBC count on the diagnosis of febrile neutropenia ranged from 100 cells/mm^3 to 80,000 cells/mm^3 with a median (Q1, Q3) count was 1115 (677.5, 2777.5) cells/mm^3. With respect to the ANC count, 55 (41.7%) of the patients had profound neutropenia at the diagnosis and a median of 200 (48.5, 400) cells/mm^3.(Table 3). The platelet count, and serum creatinine level of the study participants at neutropenic fever diagnosis was 1115 (677.5, 2777.5) cells/mm^3, 18000 (8000, 32000) cells/mm^3 and 0.7 (0.5, 0.8) mg/dl, respectively.

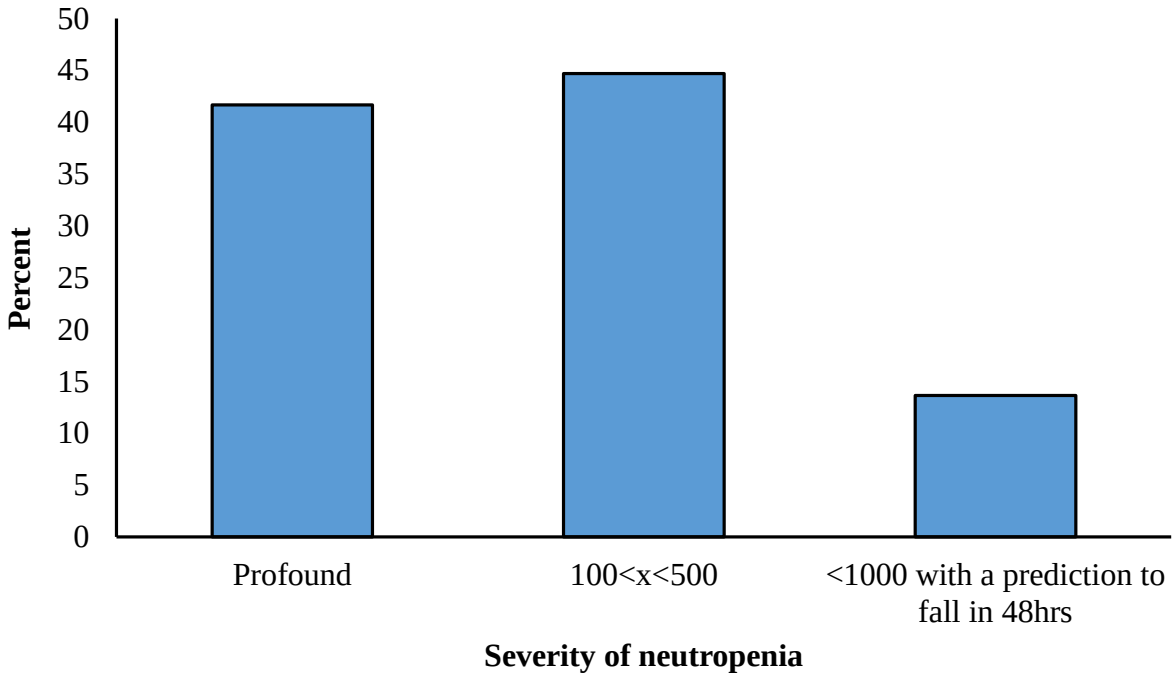

Figure 2. Severity of neutropenia at time of diagnosis of high risk hematology patients with febrile neutropenia admitted at TASH, Addis Ababa, Ethiopia, 2019

Microbiological profile of febrile neutropenia

Among the participants of the study, specimen was sent for culture for 112 (84.8%) of the study participants. Of the specimen sent for culture, 42 (37.5%) accounted for blood and there was growth in 18 (15.7%) of the cultures (Table 4).

From the total of 112 specimens sent for culture and sensitivity, only 19 (16.5%) had a microbial growth and blood specimens had the most yields (68.4%). The common pathogens were *Coagulase-negative Staphylococcu*s (31.6%), *Klebsiella, Pneumoniae* and *Escherichia coli* (Fig. 3).

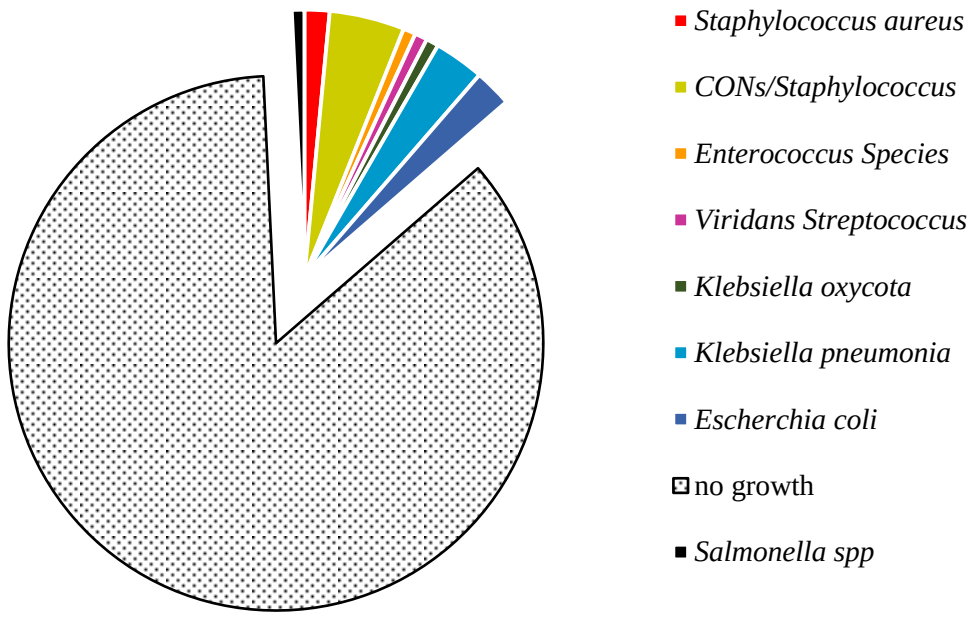

Figure 3. Culture growth pattern of specimens of high-risk hematology patients with febrile neutropenia admitted at TASH, Addis Ababa, Ethiopia, 2019

Table 3. Microbiological profile of febrile neutropenia among high risk hematologic disease patients with febrile neutropenia admitted at TASH, Addis Ababa, Ethiopia, 2019.

	No.	Percent (%)
Any specimen sent for culture (n=132)		
Yes	112	84.8
No	20	15.2
Types of specimen sent for culture (n=112)		
Blood	42	37.5
Blood and Urine	41	36.6
Blood , Stool and Urine	13	11.6
Others	16	14.3
Presence of any yield (n=115)		
Yes	19	16.5
No	96	83.4
Type of specimen with yield (n=19)		
Blood	13	68.0
Others	6	32.0

Imaging profile of febrile neutropenia episode

In the study, chest imaging was taken during the diagnosis of the episode of febrile neutropenia. A total of 120 patients (90.9%) had chest imaging with 100(83.3%) of the images chest x-rays. Findings suggestive of pneumonia were in 34 patients (28.3%) and those diagnosed with Invasive Aspergillosis were in 11 patients (9.1%) (Fig. 4).

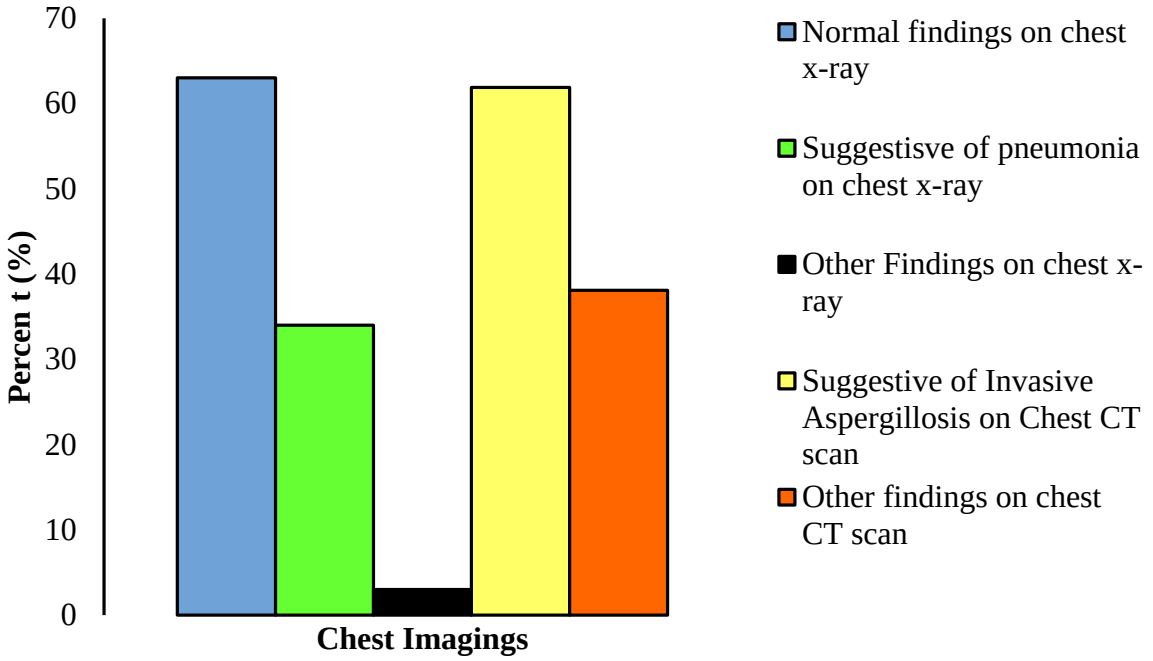

Figure 4. Chest Imaging Findings on febrile neutropenia episode of hematologic disease patients with febrile neutropenia admitted at TASH, Addis Ababa, Ethiopia, 2019

Treatment of episode of febrile neutropenia

As an initial antimicrobial regimen, a total of 82 patients (62%) were given combined antibiotics as an empiric regimen to treat their febrile neutropenia episode. Cefepime with Vancomycin combination was the most common combination regimen prescribed (40.9%). There were 47(35.6%) patients that were on the first antibiotic Cefepime monotherapy.

The empiric regimen of 74 patients (56%) was changed to a definitive therapy after clinical, microbiologic, and imaging results. Persistent fever record was the commonest guide to change the first regimen alone (65.5%) or with confirmed change of site of infection (28.3%) (Fig. 5).

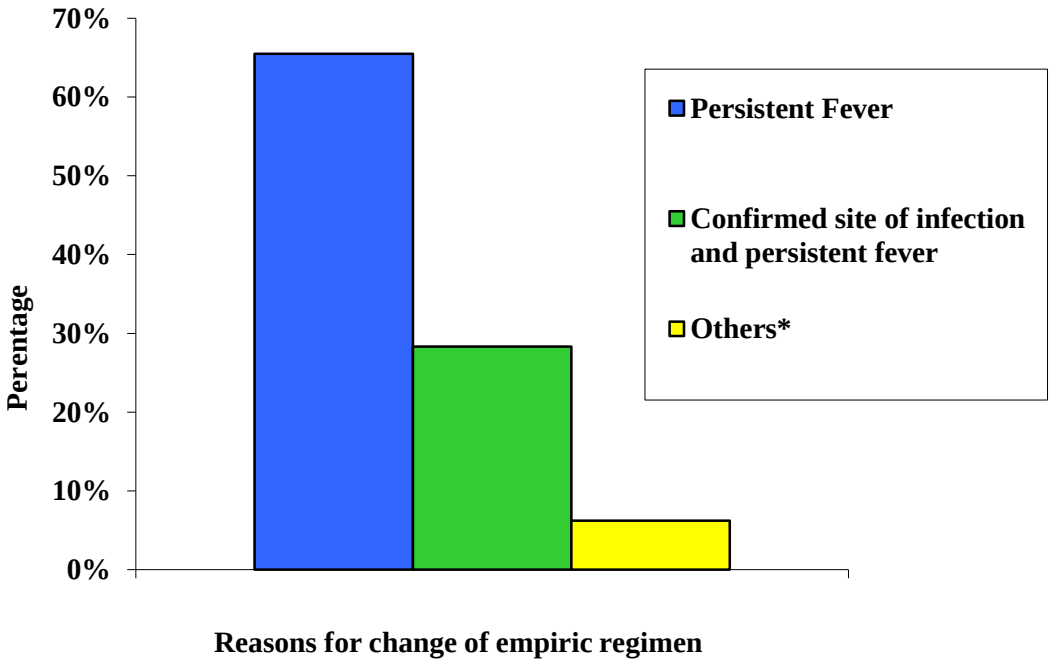

Figure 5. Guide for change of empiric antibiotic regimen of febrile neutropenia episodes in hematologic disease patients with febrile neutropenia admitted at TASH, Addis Ababa, Ethiopia, 2019

Among the second line antimicrobials patients received, combination therapy with Meropenem and Vancomycin was the most common regimen (55.4%). Antifungals that were given as therapeutic doses in 22 patients (29.7%), out of which Amphotericin B was given in nine patients (40.9%), Itraconazole in three (13.6%) and Fluconazole in ten (45.5%) (Table 4).

Table 4. Second antimicrobial regimen of febrile neutropenia among hematologic disease patients with febrile neutropenia admitted at TASH, Addis Ababa, Ethiopia, 2019

Second antimicrobial regimen(n=74)	No.	Percent
Meropenem and Vancomycin	41	55.4
Meropenem , Vancomycin and Amphotericin B	9	12.1
Others*	24	32.5

Chemotherapy factors of the study participants

Out of the patients that had a diagnosis that warranted chemotherapy (121), 75 (58.1%) of the participants had a record of using chemotherapy before the current episode. Around half of the patients (50.6%) were on AML chemotherapy regimens. Of those that had previous chemotherapy for acute leukemia, 52 (78.8%) of the participants had completed induction remission phase of chemotherapy (Table 5).

Table 5. Chemotherapy factors of hematologic disease patients with febrile neutropenia admitted at TASH, Addis Ababa, Ethiopia, 2019

Variables		No.	Percent (%)
Use of chemotherapy before current episode (n=121)			
	Yes	75	61.9
	No	46	38.1
AML chemotherapy Regimen (n=38)			
	7+3 regimen	25	65.8
	Others	13	34.2
ALL chemotherapy Regimen (n=31)			
	CALGB 8811/9111	17	55.0
	Others	14	45.0

Outcome of the study participants 30 days after neutropenic fever episode

Of the participants of the study, the majority (60.6%) recovered within 30 days of the neutropenic fever episode. A total of 45 patients died in 30 days of onset of the febrile neutropenia episode, more than one fourths (26.5%) died due to conditions attributable to febrile neutropenia (Fig. 6).

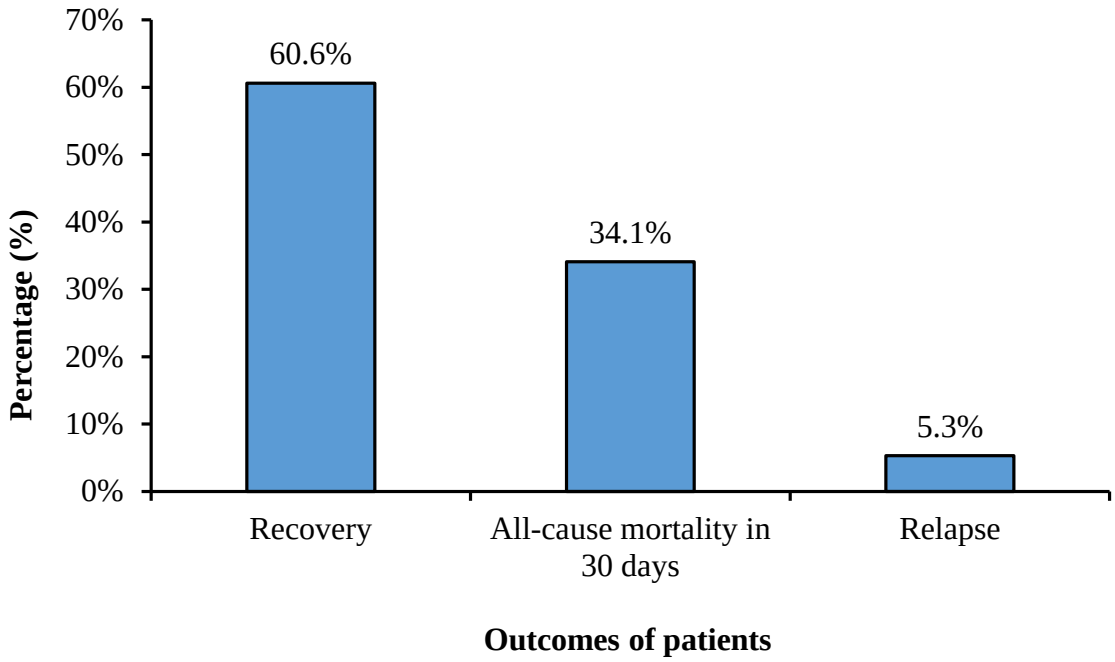

Figure 6. Outcomes of patients 30 days after neutropenic fever episode among hematologic disease patients with febrile neutropenia admitted at TASH, Addis Ababa, Ethiopia, 2019

Factors associated with death within 30 days of febrile neutropenia among the study participants

In the bivariate analysis of this study, from clinical profiles of prior episode of febrile neutropenia (p=0.002), and prior use of chemotherapy (p=0.018) were statistically significant. Among the laboratory and chest imaging studies done WBC, count at the time of diagnosis (p=0.033) chest CT scan suggestive of Invasive Aspergillosis (p=0.00012) had significance. Medical ICU admission during the febrile neutropenic episode also showed a significant correlation (p=0.04).

However, after conducting a multivariable analysis, admission at medical ICU, and prior episode of febrile neutropenia were identified as independently associated factors with death in 30 days of diagnosis of febrile neutropenia episode.

Medical ICU admission was found as one of the significantly associated factor with the death in 30 days after diagnosis of febrile neutropenia (Table 6).

Table 6. Bi-variable and Multivariable Logistic Regression analysis results of factors associated with death in 30 days of diagnosis of neutropenic fever among hematologic disease patients with febrile neutropenia admitted at TASH, Addis Ababa, Ethiopia, 2019

Explanatory Variables		Death in 30 days of NF diagnosis		COR 95% CI	AOR 95% CI
		Yes	No		
Medical ICU admission					
	Yes	7 (70%)	3 (30%)	7.8(1.9,32.3)	5.4 (1.2, 23.9)*
	No	28 (23%)	94 (77%)		1
Prior Episode of febrile neutropenia					
	Yes	13 (52%)	12 (48%)	4.1(1.6,10.4)	3.8(1.44 - 10.16)
	No	22 (20.6%)	85 (79.4%)		1

Discussion

This study aimed at assessing clinical, laboratory, and imaging profiles and treatment factors of febrile neutropenic episodes in high-risk patients. Additionally, these factors are correlated to outcomes within 30 days of diagnosis of the febrile episode. A total of 132 febrile neutropenic episodes in high-risk patients in hematology wards of Tikur Anbessa specialized Hospital in 2019 were included.

The age distribution showed that a higher proportion (62.8%) were younger patients (14-29 years old). More male patients had episodes of febrile neutropenia (56.8%). This result was in line with the Indian study where most of the patients were under the age of 35(56.6%) .[10] The male predominance is also seen in a study from Turkey where 56% of the febrile neutropenia episodes were in men. [12]But in a prospective study done in the United Kingdom those with median age to develop neutropenic fever 60 years old.[11]

In terms of underlying hematologic malignancies, higher proportions of patients in this study had ALL (43.2%), followed by AML (40.9%). This is unlike studies from Saudi Arabia and Turkey where AML patients had the most incidence of febrile neutropenia episodes.[9],[12] From the past clinical profiles of neutropenic fever of patients in this study, a prior febrile neutropenic episode was found in 18.9%. The most common infection focus of the past episode febrile neutropenia was of chest focus (68%).

The use of prophylactic antibiotics prior to the episode of febrile episode was reported in 72% of the patients with a slightly higher prescribed combined regimen that consists of Co-trimoxazole, acyclovir, and fluconazole (58.8%). A few numbers of the patients in this study had prior known comorbidity for which they were on follow up (9.8%).This may be due to poor documentation of their prior history on the medical charts and few people seek treatment for chronic illnesses like hypertension.

From the presumed primary sites of infections at the time of diagnosis, the most common focus was on the chest (36.6%). This goes in line with the Turkey study where pneumonia was the most common source of infection. [12]Regarding the microbiology profile in this study, the common isolates were Gram-positive cocci (52%) from which Coagulase-negative Staphylococcus was isolated in 65%. This correlates with the paradigm shift with higher Gram-positive cocci isolates since the 1980s.[20],[21] It is also comparable with the study from Turkey and a cross-sectional study in Tikur Anbessa Hospital in 2011.[12],[29]

The incidence of invasive aspergillosis in patients with febrile neutropenia and high-risk hematology disease is higher. Different parameters including clinical, radiologic, histologic, culture, and serology are used to make the diagnosis of invasive fungal infection.[25],[26],[26] In this study, chest imaging of patients with febrile neutropenia in hematology wards were reviewed. The most common diagnosis was pneumonia (28.3%) and evidence of invasive aspergillosis in chest CT scans was seen in 11 patients (9.1%). This result is lower when compared to the Turkish study in which 155 of the patients had radiologic evidences for invasive aspergillosis.[12]

The empiric antimicrobial therapy in higher-risk neutropenic fever patients should cover ESBL producing Gram-negative bacteria. Regimens of choice for monotherapy are cefepime and piperacillin-tazobactam.[41],[42],[43] In this study most of the patients had combination therapy (62%).

The frequently used combination was of Cefepime with Vancomycin (40.9%). Monotherapy with Cefepime was given to 35.6% of the patients. Treatments trials of febrile neutropenia have proven that the monotherapy to be the regimen of choice and the addition of Vancomycin was not found to be beneficial.[44] According to this study, 56% of the patients had a change of the empiric therapy based on clinical, laboratory, and imaging results. Most of the patients had a persistent fever with or without a new focus of infection as a reason for the change of regimen (65.5%). The IDSA updated guideline on management of neutropenic fever recommends the addition of antifungals in such patients. This study had a total of 22 patients (30%) patients with a therapeutic antifungal added to the combination therapy out of the patients that had a change of the first antimicrobial regimen.[1,4]

The history of prior treatment with a myelosuppressive agent is the main risk factor for developing febrile neutropenia.[18]In this study, among the patients with a hematologic condition in need of chemotherapy, 61.9% had a history of prior chemotherapy use.

Overall, 60.6% of the patients recovered from the febrile neutropenia episode within 30 days of diagnosis while 41 (34.1%) patients died. In the bivariate analysis of this study, prior episode of febrile neutropenia (p=0.002), prior use of chemotherapy (p=0.018), WBC count (p=0.033), Chest CT scan suggestive of Invasive Aspergillosis (p=0.0012), and Medical ICU admission (p=0.04) showed significant correlation. Meanwhile, prior episode of febrile neutropenia and admission to the Medical ICU was found to be associated with death in 30 days of diagnosis by multivariable analysis. The odds of dying for hematologic disease patients with febrile neutropenia was 5.4 times higher for those who had admission at medical ICU than those who had no admission at medical ICU [AOR= 5.4; 95% CI: 1.22 - 23.92]. Besides, the odds of dying for hematologic disease patients with a prior episode of febrile neutropenia was 3.8 times higher than the counterparts [AOR= 3.8; 1.44 - 10.16]. The significant association of medical ICU admission with death within 30 days was also seen in a study in Texas were 18 admissions to the ICU resulted in death (p=0.001).[51]This was also seen in the German and French studies that showed that mortality rates increased by 50 % for those with admission to the medical ICU.[49,50]

Limitations of the study

This study had a design that was retrospective; exploring all the variables that determine the outcome of the patient was difficult. Culture results from specimens collected were not automated and readily available. In this study, the steep price and lack of proper antifungal medications were not considered as affecting the outcome of the patients.

Conclusion

According to this study, in patients admitted to the hematology wards with the diagnosis of febrile neutropenia the commonest underlying disease were ALL and AML. From the laboratory profiles, the commonest microbiologic isolates were *Coagulase-negative Staphylococcus*, *Klebsiella*, *Pneumonia* and *Escherichia coli.*

In relation to the choice of empiric antimicrobial therapy, a combination of Cefepime and Vancomycin was commonly prescribed. The patients past history of treatment for febrile neutropenia and current admission to the Medical ICU had a significant association with the primary outcome of death in 30 days of diagnosis.

Recommendations

Hematology patients with high-risk for febrile neutropenia are one of the vulnerable groups of patients treated in Tikur Anbessa Specialized Hospital. The hospital needs to improve implementation of treatment protocols according to the IDSA. Hematology wards and medical ICUs should have a checklist for such patients in the event of diagnosis, follow up, and treatment.

The microbiology of the institution should digitalize culture and sensitivity results of specimens. A manual recording system is cumbersome and difficult to retrieve individual specimen results for ongoing or past treatment history of patients. In order to capture all the confounding factors towards the outcome of febrile neutropenic patients, a prospective multicenter study should be conducted.

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Annex:

Questionnaire to be filled by primary physician

Identification

No	Question	Response	Skip
1.	Patient's card /icare number	…….	
3.	Age	___ years old	
4.	Sex	Male ……..1 Female……2	
5.	Number of prior admissions	__ times(1,2,3…)s	
6.	Address		

Past Clinical information

No	Question	Response	Skip
1.	Underlying Hematology malignancy	AML……1 ALL……..2 Non-Hodgkin's Lymphoma….3 Hodgkin's lymphoma……4 Other- specify_____	
4.	Past medical history	Diabetes mellitus…….1 Hypertension……...2 CKD……....3 Heart failure……4 Other- specify _____	
3.	Prior Neutropenic Fever Episode	Yes ……..1 No…… 2	
5.	Number of prior episodes of febrile neutropenia	__ times(1,2,3…)s	

6.	Site of infection on prior episodes	Chest focus……1 GI focus……2 GUS focus……3 Mucositis ……4 CNS infection……5 Bacteremia……6 Others: specify_____	
7.	Positive culture growth on prior neutropenic fever episodes(blood, stool, urine etc.)	Yes……1 No……2	
8.	If the Answer is 'Yes' for #7, what was the specimen type?	_____	
9.	If the Answer is 'Yes' for #7, what was the growth?	_____	
10.	If the Answer is 'Yes' for #7, what was the sensitivity pattern?(In terms of drug susceptibility)	Sensitive to_____ _____ _____	
11.	If the Answer is 'Yes' for #7, what was the resistance pattern?(In terms of drug susceptibility)	Resistance to_____ _____ _____	
12.	Documented MIC	_____	
13.	Type of antibiotics used for prophylaxis of neutropenic fever(can choose more than one antimicrobial)	Cotrimoxazole……1 Ciprofloxacin……2 Acyclovir……3 Fluconazole……4 Others- specify_____	
14.	Use of prophylaxis G-CSF	Yes……1 No……2	

Laboratory values on diagnosis of the neutropenic episode

No	Question	Response	Skip
1.	WBC count in cells/mm3	_____	
2.	Absolute neutrophil		

	count in cells/mm3	_____	
3.	Platelet count	_____	
4.	Renal function Test – creatinine in mg/dl	_____	

Diagnosis of current episode of febrile neutropenia

No	Question	Response	Skip
1.	Symptoms on diagnosis	Chest……1 GI…….2 Mouth/Mucosal……3 GUS…….4 Skin……..5 Nervous system……6	
2.	Severity of Neutropenia	Profound ANC< 100 cells/mm3……..1 100cells/mm3<ANC<500 cells/mm3…..2	
3.	Was any specimen sent for culture and sensitivity	Yes…….1 No…….2	
4.	If the answer is 'yes' for #3, what kind of specimen was sent?	_____ _____ _____	
5.	If the answer is 'yes' for #3, what was the growth?	_____ _____	
6.	If the Answer is 'Yes' for #3, what was the sensitivity pattern?(In terms of drug susceptibility)	_____ _____ _____ _____	
7.	If the Answer is 'Yes'	_____	

	for #3, what was the resistance pattern?(In terms of drug susceptibility)	_____ _____ _____	

Treatment of current episode of febrile neutropenia

No	Question	Response	Skip
1.	Time to initiation to antibiotics(from diagnosis of current episode of febrile neutropenia) in days	Same day……1 Others specify(in days)_____	
2.	Time of initiation of antibiotics in relation of collected specimen culture results	After arrival of culture results-------1 Before arrival of culture results…….2	
2.	Place of initiation of antibiotics	Intermediate ward ……..1 hematology wards.....2	
3.	First Antibiotic regimen, single antibiotic	Cefepime……1 Ceftazidime……2 Ceftriaxone…….3 Ciprofloxacin…….4 Meropenem……5 Others, specify_____	
4.	First Antibiotic regimen, antibiotic combination	Ceftriaxone+ Vancomycin……1 Cefepime+ Vancomycin……2 Ceftazidime + Vancomycin……...3 Ceftazidime+ metronidazole …….4 Cefepime+ Metronidazole……5 Cefepime+ Vancomycin+ metronidazole…6 Others , specify_____	

5.	Change of first antibiotic regimen	Yes……1 No……..2	
6.	Second antibiotic regimen	Specify _____	
7.	If the response for # 5 is 'yes', reason for change of antibiotic was	Confirmed change on site of infection…1 Persistent Fever……2 Culture and sensitivity pattern…….3	
9.	If the Answer is '1' for #7, what was the confirmed site of infection?	Chest……1 GI…….2 Mouth/Mucosal……3 GUS…….4 Skin……..5 Nervous system……6 Others specify	
10.	If the Answer is '3' for #7, what was the specimen that yielded growth?	_____	
11.	If the Answer is '3' for #7, what was the sensitivity pattern?(drug susceptibility	_____	
12.	G-CSF used for the treatment of the current NF	Yes……1 No……..2	

Chemotherapy factors

No	Question	Response	Skip
1.	Did the patient receive chemotherapy before febrile neutropenia	Yes……1 No…….2	

	episode		
2	If the answer is " yes'' on question number 1 Specify the type chemotherapy regimen		
3	Number of Cycles of prior chemotherapy	_____specify in numbers (1,2,3…)	
3.	Administration of current chemotherapy	Not delayed……1 Delayed……..2 Stopped…….....3 Dose reduction……..4	

Outcome of patient

No	Question	Response	Skip
1.	**Outcome of patient** *After induction phase –If AML After phase I consolidation- if ALL After the last cycle within 30 days of admission – Lymphomas Within 30 days of NF episode in aplastic Anemia patients*	Recovery……1 Death due to the febrile neutropenia…….2 Death due to other causes…….3 Relapse…….4	