Assessment of the management of neutropenic fever in adult patients with hematologic malignancies at Tikur Anbessa Specialized Hospital

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Abstract

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Cancer patients with hematologic malignancies are at a greater risk of complications either from the disease itself or from the drug treatment. Among the disease complications, neutropenic fever is the most common cause of morbidity and mortality. Although practically challenging, initiation of appropriate empirical antibiotic treatment within the first hour of the infection is lifesaving. The objective of this study was to assess the management practice of neutropenic fever in adult patients with hematological malignancies at Internal Medicine ward of Tikur Anbessa Specialized Hospital. The study was conducted using a retrospective cross-sectional study design and a five-year data was collected from patient medical charts. Simple descriptive statistics and logistics regression were employed to analyze and present the data. Out of the total 682 hematologic malignancy admitted patients, 294 (43%) patients were developed neutropenic fever. Acute Myelogenous Leukemia (AML) and Acute Lymphocytic Leukemia (ALL) were the two most common hematological malignancies that developed neutropenic fever (NF). Common pathogens identified as a cause of NF were *Coagulase negative staphylococcus* and *Escherichia coli*. AML, ALL, culture and sensitivity test being done and positive culture and sensitivity test are associated with appropriate management practice. Based on standard treatment guideline of Infectious Disease Society of America (IDSA), more than half of the patients with NF received unnecessary use of empiric combined antibiotic (52.4%), additional antifungal with antiviral therapy and modification of antibacterial. However, it is difficult to decide whether appropriate or not with limited institutional setup. Since the prevalence of NF in TASH is high and the management practice of it seems inadequate, improvement in institutional setup and developing specific protocol is recommended to optimize treatment of such patients.

Key words: Hematologic malignancy, Neutropenic fever, Management practice, Monotherapy, Combined therapy, Treatment modification

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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
ESBL	Extended spectrum B-lactamse
NF	Neutropenic fever
HL	Hodgkings lymphoma
HM	Hematologic malignancy
IDSA	Infectious disease society of America
MASCC	Multinational association for supportive care in cancer
MDR	Multi drug resistance
MICs	Minimum inhibitory concentrations
MRSA	Methicillin resistant staphylococcus aureus
NCCN	National cooperative for cancer network
NHL	Non-hodgkings lymphoma
PRSP	Penicillin resistant streptococcus pneumonia
TASH	Tikur Anbessa specialized hospital
VRE	Vancomycin resistant enterococcus

1. Introduction

1.1 Background

Patients with cancer are subject to infections because of several factors, notably breakdown of normal skin and mucosal barriers, alteration of host defenses secondary to infiltration of bone marrow, reduced or altered immunoglobulin or cytokine production, or neutropenia related to chemotherapy. Neutropenia is the most frequently encountered host cell defect in patients with cancer and predicts the development of bacteraemia caused by gram-positive and gram-negative bacteria. In the absence of preventive measures, between 48 to 60% of neutropenic patients who become febrile have an established or occult infection, and around 16% to 20% or more of patients with profound neutropenia have bacteremia (Gafter-Gvili *et al*., 2014).

Neutropenia is usually defined as an absolute neutrophil count (ANC) < 1500 cells/mm^3 and when severe it is < 500 cells/ mm^3. It is expected to decrease below 500 cells/ mm^3 during the next 48 hours but if ANC is < 100 cells/ mm^3 known as profound neutropenia (Flowers *et al*., 2013). Fever in neutropenic patients is classically defined as a single oral temperature of >38.3^{0}C (101^{0}F) or a temperature ≥ 38 °C for 1 hour continuously or at two times with a minimum interval of 12 hours (NCCN , 2014).

Neutrophils are a subset of leukocytes, and neutropenia may be only one aspect of a patient's myelosuppression. Neutrophils play a critical role in protecting the body from foreign antigens, including bacteria. In addition, neutrophils have a profoundly rapid life cycle and they are made in the bone marrow at a rate of approximately 80 million per minute, living only 2 to 3 days, compared to a macrophage, which typically lives months. This makes them particularly at risk during chemo- and radiotherapies, treatments that target rapidly dividing cells. The importance and extreme fragility of neutrophils makes them a critical prognostic indicator (Yarbro *et al*., 2010).

Febrile neutropenia may represent as the only sign of severe infection in cancer patients, because the symptoms and signs of inflammation are typically attenuated due to a reduced absolute neutrophil count. The frequent need for indwelling central venous catheters in association with damage to the gastrointestinal mucosa caused by anticancer agents provides a portal of entry for

pathogenic bacteria, which in turn predispose patients to bacteremia. This fact in association with an impaired host response to infection, due to neutropenia and decreased cellular immunity secondary to intensive chemotherapy, leads to increased risk for severe infections in cancer patients (Regis *et al*., 2014).

Febrile neutropenia is one of the most serious adverse events in patients with hematological malignancies receiving chemotherapy. Untreated infections in neutropenic patients can rapidly progress, leading to life-threatening complications (Natarjan *et al*., 2011). The risk of infection rises as the neutrophil count falls below 500 cells/ mm^3 and is higher in those with a prolonged duration of neutropenia (>7 days). A prompt initiation of empirical antibiotic therapy is advisable for patients with NF in order to avoid progression to sepsis (Villafuerte-Gutierrez *et al*., 2014).

Generally, in order to reduce mortality and re-hospitalization of neutropenic patients with hematologic malignancies evidence based guidelines have a great role by improving and maintaining the quality of care. Hence, setting quality care indicators or standards, which are derived from the standard treatment guidelines, are recommended in order to evaluate the service given by the health care facilities (Freifeld *et al*., 2011). This study is focused on evaluating pharmacological management practice of neutropenic fever based on the criteria set by a standard treatment guideline of infectious disease society of America (IDSA).

1.2 Statement of the problem

Managing cancer patients with neutropenia must be considered as a medical emergency since any delay in initiating appropriate empirical antibacterial therapy may result in high rates of mortality and morbidity. Emerging antibacterial resistance in bacterial pathogens infecting febrile neutropenic patients complicates its management (Mendes *et al*., 2007). The Infectious Diseases Society of America (IDSA) and the European Conference on Infections in Leukaemia (ECIL) suggested that, low-risk patients may be treated with oral antibiotics in the outpatient setting, and high-risk patients usually need to be admitted to hospital and receive parenteral broad-spectrum antibiotics until the neutrophil levels recover (Alp and Akova, 2013).

Patients with malignancies receiving intensive chemotherapy have an increased risk of development of neutropenia and febrile episodes. Although documented infectious etiology is encountered in about 25% of these febrile neutropenic patients, defervescence is achieved in up to 60% of patients with the use of empirical broad-spectrum antibacterial therapy (Freifeld *et al*., 2011; Klastersky, 2004). Patients who have febrile neutropenia that makes them sick enough to be admitted to hospital have a high risk of an unfavorable outcome. A study by Kuderer et al, (2006), which looked at more than 40,000 adult cancer patients treated in large US hospitals, found a mortality rate of 9.5% and increased to 21.4% in those with more than one comorbid condition.

In Ethiopia, there is no standard protocol established for the management of neutropenic fever hence the facilities to be fulfill in the institution set up limit the development of guideline. In addition, studies are not found in this area to evaluate the management of NF, as studies are important for the development of guidelines. According to the studies shown in US and other European countries, great emphasis was given to minimize mortality and to improve quality of life. Studies conducted in this area can strengthen and update the management strategies of neutropenic fever (Perkins *et al*., 2002).

Hence, assessment of the management practice of neutropenic fever will help us to improve the quality of service and to design strategies for development of standard treatment guideline as well as a base line for future studies in Ethiopia.

1.3 Literature review

1.3.1 Incidence of neutropenic fever infection

Despite major advances in prevention and treatment, NF remains one of the most serious complications of cancer chemotherapy. Infectious complications are a serious cause of morbidity and mortality in cancer patients, especially those with underlying hematological malignancies were approximately 60 % of deaths are infection related (Zembower and Stosor, 2014). A retrospective cohort study conducted in Uruguay on assessing the results of a standardized protocol for the treatment of febrile neutropenia from patients with high-risk neutropenia in a hematology–oncology showed that the incidence of febrile neutropenia was 61.4%. Pathogens were isolated from different sources in 59.3% of the episodes with bacteremia isolated from blood being the most prevalent (81.3%). Multiple drug-resistant gram-negative *bacilli* were isolated in 62.5% of all microbiologically documented infections. Treatment of 63% of the episodes in which the initial treatment was piperacillin/tazobactam needed to be escalated to meropenem. The mortality rate due to febrile neutropenia episodes was found 18.5% (Burutaran *et al*., 2015). Similarly about 16% overall mortality was documented in another study and 11% of which was in patients with hematologic malignancies (ESMO, 2010).

1.3.2 Risk factors and complications

As infection in patients with neutropenia is primarily the direct consequence of chemotherapy-induced neutropenia, attempts to prevent NF episodes during chemotherapy administration requires the evaluation of the risk factors associated with the development of significant neutropenia. In patients with hematological malignancies, aggressive chemotherapy regimen was the major predictor of NF (Moreau *et al*., 2009). The development of NF was higher in patients of younger age groups and male sex according to a study carried out in India (Biswal and Godnaik, 2013), while elderly patients clearly have a higher rate of complications during NF than younger patients treated with similar regimens (Bagnasco *et al*., 2012).

In the Multinational Association for Supportive Care in Cancer (MASCC) study, associated factors with good prognosis in cancer patients were severity of the illness (mild or moderate clinical symptoms at presentation) including hypotension, chronic obstructive pulmonary disease, solid tumor or, in patients with hematologic malignancies, previous fungal infection,

outpatient status, dehydration and age lower than 60 years. A patient with a MASCC score > 21 points is considered "low risk" that can be treated using oral antibiotics, whereas "high risk" with MASCC scores < 21 is treated with parenteral antibiotics (ESMO guideline working group, 2010). However, the IDSA guideline favors the expert clinical criteria and considers low-risk patients as those who are expected to be neutropenic (ANC < 500 cells/ mm^3) for ≤7 days and those who have no active co-morbidities or evidence of significant hepatic or renal dysfunction. Similarly, high-risk patients are those who are expected to be neutropenic (ANC < 500 cells/ mm^3) for >7 days. Patients with neutropenic fever who have on-going co-morbidities or evidence of significant hepatic or renal dysfunction are also considered high risk, regardless of the duration of neutropenia (Flowers *et al*., 2013).

In general, factors potentially associated with an increased risk for developing febrile neutropenia during chemotherapy can be older age, disease conditions such as metastases, prior febrile neutropenia, anemia and cardiovascular disease. Others are abnormal liver tests, history of multiple cytotoxic chemotherapy regimen or high-dose intensity chemotherapy, poor performance status, poor nutrition, more than one co-morbidity and lymphoma histology (Klastersky, 2014).

A prospective multicenter survey conducted in Belgium showed that infection with gram-negative organisms is associated with higher mortality and have been more prevalent among high-risk than low-risk patients (59% vs. 31%), whereas the opposite applies to infection with gram-positive organisms (38% vs. 62%). In addition, 76% of low-risk patients were free of complications, compared with 32% of high-risk patients. Mortality was also much higher in the high risk than in the low-risk group: 28% vs. 2% (Klastersky, 2004).

Neutropenia, resulting from cytotoxic chemotherapy is the most common risk factor for severe infections in hematological malignancies and duration of neutropenia contributes significantly to the risk of serious infections. This risk is significantly greater in lower neutrophil counts; patients with ANC < 100 cells/mm^3 develop documented infections (Sharma *et al*., 2005). The type of chemotherapy such as alkylating agents, purine analogs and monoclonal antibodies can also be an important risk factor for neutropenia. According to a study by Lustberg, (2012), longer durations of neutropenia have been associated with bone marrow transplantation and

chemotherapy for hematologic malignancies, whereas many of the chemotherapy agents for solid tumor malignancies are associated with a shorter duration of neutropenia.

1.3.3 Common malignancies and pathogens in NF

The study conducted in a Turkish hospital on patients admitted with hematological malignancies showed that 32% of patients had acute myeloid leukemia, 20% acute lymphoblastic leukemia, 15% non-Hodgkin's lymphoma, 8% multiple myeloma, and 8% chronic myeloid leukemia. Gram-positive *cocci* were isolated from 52%, while from Gram-negative *bacilli* 42% and yeasts from 6% of the sepsis patients, respectively. The most frequently isolated Gram-positive bacteria were methicillin-resistant *Coagulase-negative staphylococci*, while the most frequently isolated Gram-negative bacteria were *Escherichia coli* (Goruk *et al*., 2015).

A study performed at four centers in Iran found that 41.6% of patients had ALL and the remaining 58.4% had AML. The most common pathogen isolated was found to be *Escherichia coli* (25.8%), *Enterobacter* (18%) and *Coagolase-negative staphylococcus* (13.5%). Other pathogens such as *Candida* and *Pseudomonas aeruginosa* were found rarely. Among gram-positive colonies, 92.3% were due to C*oagolase-negative staphylococcus*, and from gram-negative colonies, 30.3% were caused by *Escherichia coli* and 21.1% by *Enterobacter* colonies (Ahmadzadeh *et al*., 2013).

Comparable results obtained within the two HMs, (ALL & AML) and 18.9% of other types of malignancies were found from a study conducted in Iran. The most observed microorganism in this study was *Escherichia coli* (27.7%), followed by *Pseudomonas aeruginosa* (16%), *Acinetobacter baumannii* (10.5%), *Klebsiella pneumoniae* (8%), *Coagulase positive staphylococci* (8%) and *Coagulase negative staphylococci* (8%). One fungal infection was also observed. Overall, 67% of the organisms were gram-negative, 29.8% gram-positive, and 3.2% polymicrobial (Yadegarynia *et al*., 2013).

The main microorganisms recovered from cancer patients found by Nurian et al, (2015), were *Proteus spp.* (23.5%), *Escherichia coli* (22.2%), *Pseudomonas aeruginosa* (21.0%) and *Staphylococcus aureus* (20.2%). The most frequent isolates from hospital environments were *Bacillus* spp. (50.0%), *Staphylococcus aureus* (14.2%) and 11.5% of *Pseudomonas aeruginosa*.

According to the study conducted by Duke Comprehensive Cancer Center, more than 50% of *Staphylococcus aureus* isolates are methicillin resistant. Vancomycin resistance among *enterococci* constitutes nearly 30% of enterococcal isolates nationwide. Additionally, reduced susceptibility or resistance to penicillin is being reported increasingly with *viridians* group (Lyman & Rolston, 2010). Multiple drug-resistant gram-negative *bacilli* were isolated in 62.5%, in other study conducted in Uruguay (Burutaran *et al*., 2015).

1.3.4 Management of neutropenic fever

Early studies documented mortality rates of up to 70 % if initiation of antibiotics was delayed (Schimpff *et al*., 1971). Therefore, the evaluation of such patients should occur promptly and broad-spectrum antibiotics should be given as soon as possible. In all cancer patients presenting with neutropenic fever, empiric antibacterial therapy should be initiated immediately after blood cultures have been obtained and before any other investigations have been completed. The aim of empiric therapy is to cover the most likely and most virulent pathogens that may rapidly cause serious or life-threatening infection in neutropenic patients (Freifeld *et al*., 2011).

Clinical trials carried out by Pizzo et al, (1986), with ceftazidime, imipenem-cilastatin, or meropenem has demonstrated equivalent outcomes compared to two-drug regimens. In addition, fewer adverse events have generally been seen with monotherapy regimens compared with combination regimens (Paul *et al.*, 2013) and also an increased mortality were shown from combined therapy (Yahav *et al*., 2007).

A randomized controlled clinical trial conducted on beta-lactam combinations to aminoglycoside regimens for empiric therapy found that similar overall efficacy for clinical cure and mortality (Bliziotis *et al.*, 2005). Similarly, none has been shown to be clearly superior to monotherapy in a study by Paecock et al (Paecock *et al*., 2002).

Routine addition of antibiotics indicated for gram-positive bacteria to the initial empiric antibiotic regimen has not been associated with significant clinical benefit (Vardakas *et al*., 2005). A meta-analysis of seven randomized trials found that addition of gram-positive antibiotic coverage to standard empiric therapy did not reduce all-cause mortality in patients with cancer and neutropenic fever (Aoun, 2006). Moreover, the addition of empiric vancomycin did not improve outcomes rather it was associated with increased toxicity (Dompeling *et al*., 1996). The

risk of promoting resistance among *enterococci* and *Staphylococcus aureus* is an important reason to avoid empiric vancomycin use while it should be added in the case of instability or other signs of sever sepsis, pneumonia, suspected central venous catheter, sever mucositis and skin or soft tissue infections (Jaffe *et al*., 2004).

An evaluation of NF episodes conducted in Germany confirmed the efficacy of ceftazidime as initial empiric monotherapy resulted clinical response in 58% of patients within 48 hours while 14% responded to the addition of vancomycin within the next 72 hours. In addition, 10% required antifungal agent to the ceftazidime/vancomycin combination regimen before the patient became afebrile (Koepler *et al*., 1989). Management of NF initiated by piperacillin/tazobactam in another study conducted in Uraguay found that 63% of patients needed the treatment to be escalated to meropenem (Burutaran *et al*., 2015).

A study conducted by Hathorn and Lyke, (1997), in patients with NF at Duke noted that 66% of patients who were randomized either to ceftazidime monotherapy or combined with gentamicin were treated throughout their neutropenic episode without a change in the antibiotic regimen. Thirty-three percent required the addition of another antibacterial agent or the addition of an antifungal or antiviral drug to the original empirical regimen.

In a study by Klastersky, (2004), resolution of fever occurs in approximately 40 to 50 % of patients given antifungal therapy. However, undiagnosed fungal infection was found in early studies in many patients who died during prolonged neutropenia and the incidence of fungal infection especially those caused by *Candida* or Aspergillus spp rises after patients have experienced more than seven days of persistent neutropenic fever (Wingard and Leather, 2001).

2. Objectives

2.1 General objective

- To assess the management practice of neutropenic fever in adult patients with hematologic malignancies at internal medicine ward of TASH.

2.2 Specific objectives

- To determine the prevalence of NF in adult patients with HM
- To determine factors related to development of NF
- To determine pathogens responsible for NF
- To determine common antimicrobials utilized for management of NF patients

3. Methodology

3.1 Study setting

The study was conducted on adult patients with hematologic malignancies in the wards of department of internal medicine at TASH, Addis Ababa, Ethiopia. TASH is the largest specialized hospital in Ethiopia that serves as a training center for undergraduate and postgraduate medical students, dentists, nurses, midwives, pharmacists, medical laboratory technologists, radiology technologists, and others who shoulder the health problems of the community and the country at large. It provides specialized medical, surgical and gynecology services for adults and pediatrics patients. It is the primary hospital for oncology and hematology cases in the country. Patients with solid tumors are managed separately in oncology unit, whereas those with hematologic malignancies are treated in internal medicine department of the hospital.

Internal medicine department where patients with hematologic malignancies are treated, is one of the departments in the hospital with 120 beds, 4 hematologists and 25 different specialists. It provides specialty training in internal medicine. Hematology sub-specialty training is one of the various programs in the department. The department provides services to approximately 15,800 hematologic patients (inpatient and outpatient) per year.

3.2 Study design and period

A cross-sectional retrospective study design was employed. A five year data was collected retrospectively (from 2011 to 2016) using data abstraction format from medical charts of patients with hematologic malignancies admitted to Internal medicine ward of TASH and self-administered questionnaire to Hematologists.

3.3 Source population

All adult patients admitted with hematologic malignancies.

3.4 Study population

All adult patients admitted with hematologic malignancies and neutropenic fever.

3.5 Inclusion and exclusion criteria

3.5.1 Inclusion criteria

- Patients with HM whose age was 14 years and above
- Patients diagnosed with HM and NF.

3.5.2 Exclusion criteria

- Patients with fever other than HM with NF
- Patients who have documented antimicrobial resistance
- Patients who have prior infections to NF episode
- Patients who are readmitted with recurrent NF

3.6 Sample size determination

All patients admitted within the study period were included

3.7 Study variables

3.7.1 Dependent variable

- Appropriate management practice of NF

3.7.2 Independent variable

- Age
- Type of hematologic malignancy
- Comorbid medical features and/or symptoms
- Culture and sensitivity test done
- Clinical features after 2 days of empiric therapy
- Positive culture and sensitivity test
- Persistent fever after 4 days of therapy

3.8 Data collection and management

3.8.1 Instruments

The data was collected from patient medical charts using a structured data abstraction format. The data abstraction format (Annex 10.1) is composed of detailed information on patient demographics including age and sex. Clinical data includes diagnosis/assessments, type of hematologic malignancy, co-morbid medical conditions, amount of absolute neutrophil counts, body temperature measurements, culture and sensitivity test results, selected empiric and definite therapy for NF including name of the drug(s), duration of therapy and treatment modifications made (if any). Self-administered questionnaire to hematologists' (Annex 10.2) composed of the guideline (s) they used, selection of empiric antibiotics, when and how culture and sensitivity test were used, modification and duration of treatment, and when additional antifungal and/or antiviral agents added was used. Detailed information about their management practice and the institutional set up were also included

3.8.2 Recruitment and training of data collectors

A 5 year data (between September 2011 and August2016) was collected retrospectively from medical charts of patients who were admitted in the Department of Internal medicine at TASH. The total patients admitted with HM in the 5-year period were 682 and the required data was collected from those HM patient charts (294) that also develop NF. Data was collected by trained data collectors (one nurse and two pharmacists working in TASH) using a structured data abstraction format from the medical records. Half-day training was given to data collectors on objectives of the study, methodology used, how to extract important data from medical charts and ethical issues to be considered. In addition, self-administered questionnaire was used for Hematologists opinion about their management practice.

3.8.3 Data quality assurance

In order to maintain quality of the data, initially training was given to data collectors. Then, during the process of data collection, the principal investigator conducted close follow-up and data checking. Random charts was also taken and re-abstracted and compared with the data already recorded to see data quality. The collected data was also evaluated for completeness and consistency.

3.9 Data entry and analysis

The data was entered into a computer database Epi-info 7 cleared and exported to statistical program for social sciences (SPSS) version 20. The data was then analyzed using SPSS software. Simple descriptive statistics such as mean ± SD, Odds, frequency and percentages were determined. Logistics regression was used to see association between and within the variables. Significance level was considered as $P < 0.05$ and adjusted odds ratio (AOR) with 95% confidence interval (95% CI).

3.10 Ethical considerations

Ethical clearance and approval was obtained from the ethical review committee of School of Pharmacy, Addis Ababa University. Then, the study was conducted at TASH after obtaining the permission from the clinical service directorate office of the hospital. During the data collection process, the patients' cards were maintained with extreme care. Confidentiality was also maintained by avoiding the use of names in the data abstraction format rather patient initials were used.

3.11 Operational definitions

Neutropenia: an absolute neutrophil count (ANC) <1500 cells/mm3, and severe neutropenia is usually defined as an ANC <500 cells/mm3, or an ANC that is expected to decrease to <500 cells/mm3 over the next 48 hours (Flowers *et al*., 2013).

Neutropenic fever: an absolute neutrophil count (ANC) <1500 cells/mm3 with a single oral temperature measurement ≥ 38.3 °C, or a temperature ≥ 38 °C for 1 hour continuously or at two times with a minimum interval of 12 hours (NCCN guidelines version 2, 2014).

Empiric therapy: a treatment given at initial assessment of neutropenic fever that have broad-spectrum coverage (ASCO guidelines, 2012).

Definite therapy: A treatment given to patients after two days of empiric therapy

Appropriate management: (IDSA guideline, 2011)

- Use of combined therapy if co-morbid medical features identified in addition to neutropenic fever or positive culture with gram-positive pathogen,
- Appropriate treatment modification applied according to culture result and symptoms observed on follow up

- Appropriate additional antifungal and antiviral agents according to the patient feature of persistent fever after four days of therapy and/or laboratory findings.

4. Results

From a five-year registry of adult patients admitted with hematologic malignancy comprising 682 patients, a total of 294 HM patients developed NF based on the criteria set by a standard treatment guideline of infectious disease society of America (IDSA) giving a prevalence of NF in admitted adult HM patients 43%.

4.1 Demographic characteristics

About half (51.4%) of the patients who developed NF were younger age groups (14 to 29 years) and males (64.6%) predominate as compared to females. Majority of patients who developed NF with mean and median age was found to be 32.85 & 29 years respectively (R=14-80) and older age groups above 45 years had only 20.4% to develop (Table 1).

Table1: Demographic characteristics of neutropenic fever patients in Tikur Anbessa Specialized Hospital

Demographic variables	**Number (%)**		
Age (years)	**Male**	**Female**	**Total**
14-29	111(73.5)	40(26.5)	151(51.4)
30-45	59(71.1)	24(28.9)	83(28.2)
46-59	12(28.6)	30(71.4)	42(14.3)
≥ 60	8(44.4)	10(55.6)	18(6.1)
Total	190(64.6)	104(35.4)	294(100)

4.2 Clinical characteristics and laboratory findings

Among 294 NF patients, 101(34.4%) were identified with co-morbid medical conditions and other medical features that the patient may lead to deteriorate, could be associated to the development of NF. Out of the total patients who developed NF, 156 (53.1%) and 97 (33.0%) had AML and ALL, respectively. However, the development of NF with other malignancies was found very low (14%). Deterioration after two days of empiric therapy and persistent fever after four days of therapy were seen in 37 and 28% of patients respectively that might lead to make

modification of antimicrobials or to add antifungal and/or antiviral agents (Table 2). With respect to ANC value, almost all patients with NF had severe neutropenia (98.9%), majority of which was found to be ANC less than 100 cells/mm^3 (63.9%). Of the 294 patients, culture and sensitivity tests were done only to 196 (66.7%) patients and out of this only 67 (34.2%) showed microbial growth. *Coagulase -ve staphylococcus* and *Escherichia coli* were the most common pathogens identified from the positive culture results obtained (Table 3).

Table 2: Clinical characteristics in neutropenic patients at Tikur Anbessa Specialized Hospital

Clinical variables	**Number**	**Percent**
Type of hematologic malignancy		
AML	156	53.1
ALL	97	33.0
NHL	12	4.1
CML	12	4.1
CLL	9	3.1
MM	3	1.0
AA	3	1.0
AML + ALL	2	0.7
Comorbid or other medical features at initial assessment	101	34.4
Deterioration after 2 days of empiric therapy		
Yes	108	36.7
No	186	63.3
Fever persisted after 4 days of therapy		
Yes	83	28.2
No	211	71.8

*AML=acute myelocytic leukemia; ALL= acute lymphocytic leukemia; NHL= non-hodking's lymphoma; CML=chronic myelocytic leukemia; CLL=chronic lymphocytic leukemia; MM=multiple myeloma; AA=aplastic anemia; ANC=absolute neutrophil count

* Comorbid features: pneumonia, diabetes mellitus, hypertension and advanced diseases

* Other medical features: unstable vital signs such as heart rate pulse rate and blood pressure

Table 3: Laboratory findings in neutropenic patients at Tikur Anbessa Specialized Hospital

Laboratory variables	Number	Percent
Neutropenia (ANC value)		
Profound neutropenia	188	63.9
Sever neutropenia	103	35.0
Neutropenia	2	0.7
Culture result		
Coagulase –ve staphylococcus	27	40.3
Escherichia coli	17	25.4
Accinobactor spp.	6	8.9
Enterococcus spp.	6	8.9
MRSA	5	7.5
Enterobacter Clocae	3	4.5
Yeast cell	3	4.5
No growth	129	65.8

4.3 Treatment and related characteristics

A combined antimicrobial regimen was prescribed to treat patients with NF in the majority of patients in both empiric 84.4% (Figure 1) and definite 84.7% (Figure 2) treatment practices. Ceftazidime with vancomycin combination was the most common regimen prescribed (51.7%) as empiric treatment (Table 4), while vancomycin with meropenem (30.6%) and vancomycin with ceftazidime (30.3%) were the two most common regimens prescribed in combination for definite treatment (Figure 2). Patients who received monotherapy with cefipime were 33(11.2%) followed by ceftazidime 9(3.1%) but others ceftriaxone and meropenem were selected rarely at the empiric period (Figure 1). Monotherapy in the definite treatment period were used meropenum (9.2%) followed by cefipime (5.1%) and the use of ceftazidime was found very low (1%). Unnecessary drug combination with cefipime and meropenem were received by 2.7% of patients that might lead the patient to an overlapping toxicity (Figure 2). Sixty seven percent, 12.6% and 2 % of patients received additional antiviral-antifungal, antifungal and antiviral

treatments respectively (Table 5). About three fourth of patients were received antimicrobial treatment for more than 7 days of duration.

Figure 1: Selected empiric therapy regimen in neutropenic patients at Tikur Anbessa Specialized Hospital

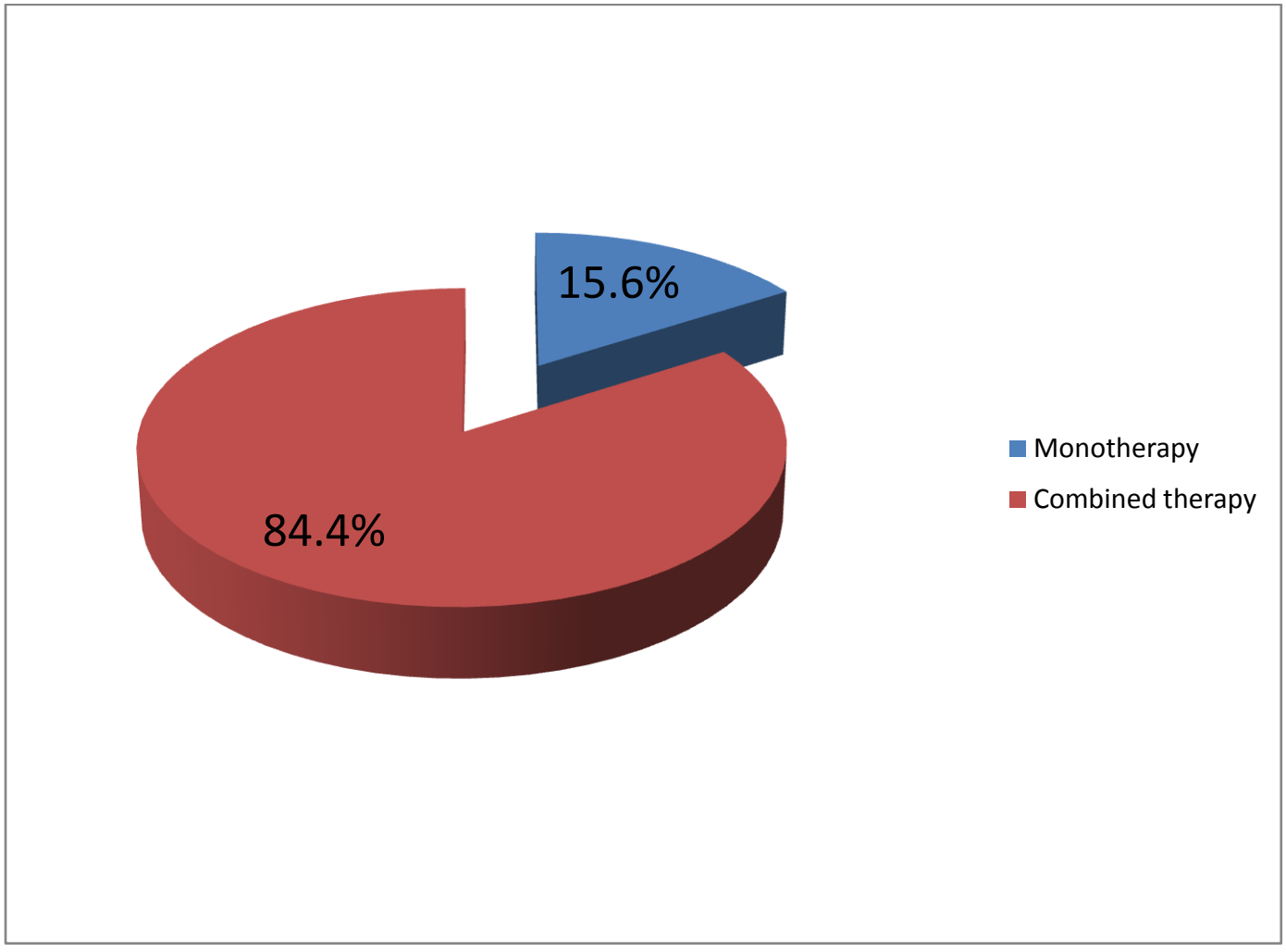


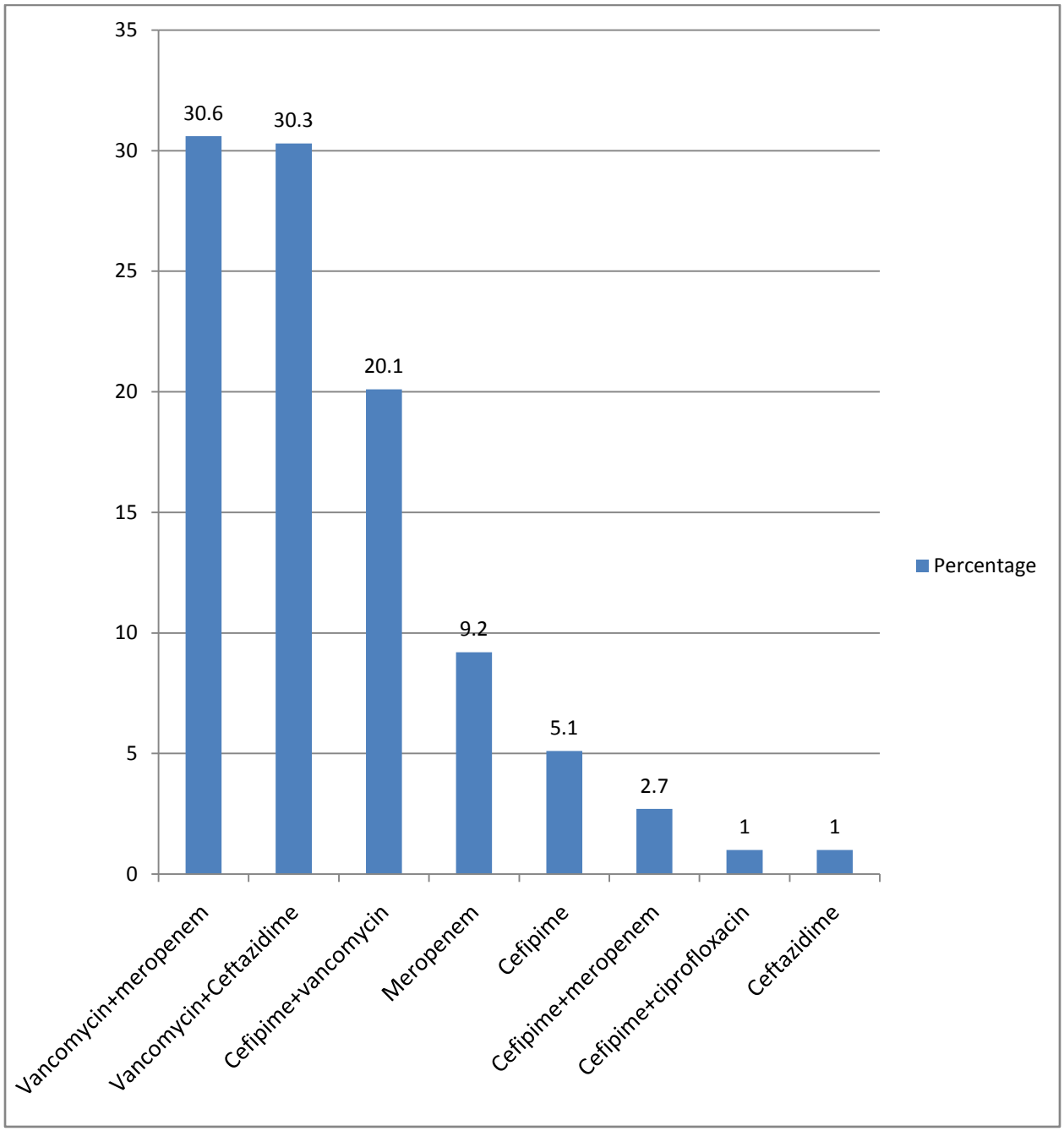
Table 4: Drugs prescribed for the treatment of neutropenic fever empirically at Tikur Anbessa Specialized Hospital

Treatment variables	Number	Percent
Ceftriaxone	1	0.3
Meropenem	3	1.0
Ceftazidime	9	3.1
Cefipime	33	11.2
Ceftazidime+ciprofloxacin	3	1.0
Ceftazidime+gentamycin	5	1.7
Vancomycin+meropenem	9	3.1
Cefipime+vancomycin	76	25.9
Ceftazidime+vancomycin	155	52.7

Table 5: Distribution of patients received additional treatment and modified drugs at Tikur Anbessa Specialized Hospital

Treatment variables	Number	Percent
Treatment modification		
Yes	173	58.8
No	121	41.2
Additional treatment		
Antifungal + Antiviral	198	67.3
Antifungal	37	12.6
Antiviral	6	2.0

Figure 2: Percentage distribution of definite antimicrobials given for neutropenic fever patients at Tikur Anbessa Specialized Hospital



4.3.1 Management practice of NF

Based on the clinical practice guideline for the use of antimicrobial agents in neutropenic patients for cancer (2011), Infectious Disease society of America (IDSA) each indicator below showed that 52.4% of patients received unnecessary empiric combined treatment regimen and those who received antifungal and antiviral agents were 36.4 and 67.3% respectively. In addition, treatment modification was not carried out for 41.7% of patients while it was required and modification was done for 37.6% of patients while it was not required (Table 6). This outcome might vary because of variation between institutional settings or standards.

Table 6: Indicators for inappropriateness of management practice of Neutropenic fever based on IDSA

Indicators	Number	Percentage
Patients received empiric combined treatment that was not needed	154	52.4
Patients needing combined treatment that received mono-therapy	7	6.9
Treatment modification for patients that was not needed	65	37.6
Patients needing treatment modification that was not done	45	41.7
Additional antifungal treatment that was not needed	107	36.4
Patients needing antifungal treatment that was not received	17	15.3
Patients received undesired combination of drugs(cefipime+meropenem)	8	2.7
Antiviral therapy without documented evidence	198	67.3

4.3.2 Factors associated with appropriate management practice of NF

Data were analyzed to determine whether there was any relationship between different variables and appropriate management practice of NF. Initial bivariate analysis showed that appropriate management practice of NF and patients' age, comorbid medical features either at initial assessment or after 2 days of empiric therapy did not show any significant association. Hence multivariable analysis showed AML given (P=0.04), ALL given (P=0.022), culture and sensitivity test done (P=0.026), and positive culture and sensitivity test (P=0.001), have statistically significant association with appropriate management practice of NF (Table 7).

Table 7: Association of appropriate management practice of neutropenic fever with independent variables

Variables	Appropriate management practice		COR	AOR
Age (yrs)	**Yes (%)**	**No (%)**		
14-29	131(86.8)	22(13.2)	4.168(1.447, 12.007)	2.546(0.353, 18.340)
30-45	75(90.4)	8(9.6)	5.966(1.805, 19.720)	2.599(0.366, 18.459)
46-59	33(78.6)	9(21.4)	2.333(0.702, 7.751)	1.280(0.191, 8.598)
≥ 60	11(61.1)	7(38.9)	1.00	1.00
Comorbid medical features at initial asst of NF				
Yes	73(73)	27(27)	1.418(0.736, 2.734)	2.716(0.797, 9.252)
No	85(43.8)	109(56.2)	1.00	1.00
Type of HM				
AML	130(83.3)	26(16.7)	1.613(.705, 3.691)	5.598(1.078, 29.069)*
ALL	89(91.8)	8(8.2)	3.589(1.300, 9.908)	8.265(1.348, 50.665)*
Others	31(75.6)	10(24.4)	1.00	1.00
Culture done				
Yes	167(85.2)	29(14.8)	1.041(0.529, 2.047)	5.705(1.236, 26.335)*
No	83(84.7)	15(15.3)	1.00	1.00
Deteriorated features /fever/ after 2 days of empiric therapy				
Yes	54(50.0)	54(50.0)	0.85(0.538, 1.391)	1.207(0.705, 2.065)
No	92(49.5)	94(50.5)	1.00	1.00
Fever persisted after 4 days of therapy				
Yes	47(56.6)	36(43.4)	0.578(0.333, 1.004)	0.593(0.273, 1.289)
No	110(52.0)	101(48.0)	1.00	1.00
Positive culture				
Yes	43(64.2)	24(35.8)	8.627(4.699, 15.839)	12.486(4.344, 35.886)*
No	207(91.2)	20(8.8)	1.00	1.00

4.4 Key informant interview

Based on the criteria set by IDSA, most of the results described above seem that the management practice was inappropriate. Hematologists' opinions were included in addition to the information obtained from the patients' charts admitted within the study period. According to the hematologists; working at TASH, the commonly used guideline for the management of NF in the institution is IDSA. They also use other standard guidelines alternatively. However, it is difficult to manage patients appropriately based on IDSA treatment guideline in the current situation due to the presence of unfavorable institutional setup that affect the management practice. Patients may receive antimicrobials at the time of emergency room before the specimen was collected for culture and sensitivity test or inadequate sampling technique/procedure or environmental factors that can result in a no growth of pathogens. In addition, the time taken to obtain culture result and availability of culture as well as drugs are contributing factors. Sometimes patients may not afford the cost of laboratory investigation or drugs and culture results and other registered data may lose from the chart due to the charts are seen by several students in the ward. On the other hand, the use of combined empiric therapy and additional antifungal-antiviral agents is common mainly based on prior history of patients receiving various types' antimicrobials from other institution. In addition, there might be loss of information from the charts or inappropriate registration and documentation. Moreover the time to make modification of antibacterial is not specific rather it depends the patient's condition with respect to cost and availability of drugs in addition to medical symptoms and laboratory results. Generally, the current set up of the institution is poorly established. In this situation, giving appropriate management based on the protocol set by IDSA standard treatment guideline is very difficult.

5. Discussion

This study aimed at assessing the management practice of NF in adult patients with HM admitted in internal medicine ward of TASH. In the current study, 294 patients were included to determine the prevalence of NF, factors related to develop NF, responsible pathogens to develop NF and to assess antimicrobial treatment practice in patients with HM. The current study revealed that the prevalence of NF in adult admitted patients with HM is 43 %. Higher prevalence in the present study might be because of absence of institutional protocol practiced on preventive aspects and limitation on personal or environmental hygiene in the study setting. However, the standard in infection control procedures including hand hygiene, hospital environment, standard barrier precautions and private rooms make infection prevention and control of transmission better. A study conducted by Cameron; (2009); found evidence on serious shortcomings in patients or health-care professional education/ awareness, prevention and the availability and implementation of clear protocols for patient assessment as well as treatment and hospital admission.

In the current study, higher proportion (79.6%) of younger patients (14 to 45 years) with HM developed NF. Out of this, 51.4% of them were in the age of 14-29 years. In addition, a higher proportion of male sex (64.6%) was found to develop NF. This result is in line with a study done at tertiary care teaching hospital of India reported higher incidence of NF in younger patients and a male-to-female ratio of approximately 3:1 (Biswal and Godnaik, 2013). Another study in Turkey also found that the incidence to develop NF is higher in males (Goruk *et al*., 2015). Nevertheless, the risk of developing NF and its complications is high in older patients. The reason why young patients developed NF in the current study remains to be seen.

In this study, higher proportion of patients having AML (53.1%) developed NF followed by ALL (33.0%).This result is similar with a study done in southern Brazil tertiary referral hospital, which documented NF in 48.5% AML patients (Rosa and Goldani, 2014). Comparable results also reported in Iran, where 58.4% of patients had AML and the remaining 41.6% had ALL (Ahmadzadeh *et al*, 2.013). Majority (63.9%) of the patients who developed NF were found to have lower ANC value (ANC ≤ 100 cells/mm^3). This is in line with the fact that risk of serious infection with fever including NF is extremely high when the neutrophil count is very low as the

most numerous leukocytes and the body's primary phagocytic agents (neutrophils) that play a critical role in protecting the body from foreign antigens, including bacteria (Yarbro *et al*., 2010).

Out of the total patients studied, culture and sensitivity tests was done for 196(66.7%) patients and out of this, 67 (34.2%) showed at least one organism growth, which gives a 'no growth' result of 65.8%. From the bacteria's grown in the culture, coagulase negative staphylococcus was the most common (40.3%) bacteria identified followed by Escherichia coli (25.4%). Similar results were reported in a study conducted in Turkey which showed methicillin resistant coagulase negative staphylococci were the most frequently isolated Gram-positive bacteria while *Escherichia coli* was the most frequently isolated Gram-negative bacteria (Goruk *et al*., 2015). Other comparable results were also reported in a study conducted at Uraguay, where coagulase negative staphylococcus accounted for 26.6% and Escherichia coli for 9.7% (Burutaran *et al*., 2015). However Escherichia coli was found 27.6% which was dominant over coagulase negative staphylococci, 8.2% in a study found by Yadegarynia *et al*, (2013). Escherichia coli were also dominated according to a study result in Tehran, Ahwaz (Ahmadzadeh *et al*., 2013). This might be because of institutional variation in the prevalence of bacterial species or pathogens, also the changing pattern of infectious agents over time postulates the necessity of other studies to give the most up-to-date insight of the organisms to clinicians; as a result, the treatment guidelines might vary accordingly (Coullioud *et al*., 1993). With respect to the 'no growth' result, our study reported a higher proportion (65.8%) as compared to other similar study done in India which reported 'a none growth' result of 21.3% (Biswal and Godnaik, 2013). This high percentage of negative culture might be due to antibiotics given prior to take specimen for culture and sensitivity test in our setting and other shortcomings related with microbiological sampling and specimen transport or environmental and personal factors in the hospital (Goruk *et al.*, 2015). Regular practice of culture and sensitivity test for all NF patients could be mandatory in relation to the protocol provided by IDSA (Freifeld *et al*., 2011). However, in our study culture and sensitivity was not done for 33.3% of patients, which might make selection of appropriate treatment regimen and modification difficult. This might be due to cost, availability of reagents, poor registration or lost from the patient's charts.

Administration of empiric antimicrobial therapy is standard practice in the management of neutropenic fever, but there remains considerable debate about the selection of an optimal

regimen (Tam *et al*., 2011). In this study, 84% of NF patients received combined treatment regimen (81.6% with vancomycin) empirically, however, vancomycin could be needed for 34.4% of patients based on the criteria recommended by IDSA. This might be due to the common pathogen identified by the institution could be coagulase negative staphylococci. In most institutions, vancomycin is used to treat infections caused by MRSA and resistant viridans streptococci. Nevertheless, treatment with vancomycin can be stopped for those patients whose blood cultures show no growth at 48 h (Sepkowitz, 2005) until the fever and neutropenia resolved or for a minimum of seven days (Freifeld *et al*., 2011). A clinical trial carried out by Pizzo et al, (1986), found that a single drug has demonstrated equivalent outcomes compared to combined drug regimen which is the same as a study finding in Belgium (Klastersky, 2004) and Sweetherland (Jandula *et al*., 2001). Bliziotis et al, (2005), and Paecock et al, (2002), also showed similar finding in their study. Clinical benefit has not been associated with routine addition of vancomycin to the initial empiric antibiotic regimen according to a study by Vardakas et al, (2005). A meta-analysis of seven randomized trials also demonstrated that there is no reduction in all-cause mortality too (Aoun, 2006). This is true also in a study conducted in Korea showed that, there was no significant reduction of mortality rate rather routine use of vancomycin can lead to the emergence of resistant bacteria and nephrotoxicity (Lee *et al*., 2011). Moreover, beta-lactam monotherapy is advantageous compared with combination therapy with regard to survival and adverse events (Poul *et al*., 2013). Similar study result carried out by Yahav *et al*, (2007), also found that the use of empiric combined treatment regimen had subject to patients with an increase in adverse events. Clinicians would benefit from local guidelines that aid the selection of an appropriate empiric regimen while giving due consideration to the risks inherent across different patient groups (Tam *et al*., 2011). In general, no guidelines recommend combined regimen including vancomycin routinely in the initial drug treatment and not adding it empirically for persistent fever (Freifeld et al, 2011).

In the definite therapy period, 84.7% of patients received combined regimen with vancomycin however, based on the finding from culture results and other documented deteriorated features, the use of combined treatment with vancomycin was high in the current study. According to a study conducted at Duke the addition of another antibacterial agent or an antifungal or antiviral drug to the original empirical regimen were required only 33% (Hathorn and Lyke, 1997). Clinical evidence found by Gea-Banacloche has demonstrated monotherapy is considered

effective and safer than combination therapy. If clinical deterioration or isolation of a resistant pathogen occurs, then therapy is escalated using an antibiotic with a broader spectrum or a combination of antimicrobials (Gea-Banacloche, 2013). In addition to this Pizzo, (2009), offered a need for modifications of the initial monotherapy are more likely for patients who present with haemodynamic instability or who have evidence of multiresistant infection require that the initial monotherapy be complemented by the addition of an aminoglycoside and vancomycin. The IDSA guideline strongly recommends adding vancomycin in cases of hemodynamic instability, pneumonia, clinically evident catheter-related infection, skin and soft tissue infections, severe mucositis and known colonization with MRSA (Freifeld *et al.*, 2011). This is also true in an evidence-based study found by Zafrani and Azoulay, (2014). That is why vancomycin should generally be reserved (Villafuerte-Gutierrez *et al.*, 2014).

Selected drug regimens in this study showed that combination of ceftazidime and vancomycin had higher proportion (52.7%), following cefipime with vancomycin (25.9%) and cefipime alone (11.2%) empirically, whereas meropenem with vancomycin (30.6%), ceftazidime with vancomycin (30.3%) and 20.1% was cefipime and vancomycin combination for definite therapy. The use of meropenem monotherapy is about 9%. Combined therapy with ciprofloxacin and gentamicin was very low. This might be due to low gram-positive coverage and prophylaxis use of ciprofloxacin and burden of adverse event from gentamycin. Regarding monotherapy, use of single drug regimen with cefipime as empiric and meropenum in the definite period were common in this study. However, piperacillin/tazobactam is the first line used for empiric therapy in a study shown by Burutaran et al, (2014), which is similar with a study shown in India (Biswal and Godnaik, 2013). This might be due to availability of drugs and the prevalence of specific pathogen within the institution. Overall vancomycin was highly prescribed in combination with cephalosporins and carbapenems while practice of selecting monotherapy regimen for both empiric and definite therapy protocol were very low. Unfortunately, 2.7% of patients received meropenum and cefipime combination. Since meropenem can cover both gram positive and gram-negative pathogens, the addition of cefipime is unnecessary that may predispose patients for drug resistance.

In addition to bacterial pathogens, fungal and viral pathogens were common and highly suspected by the clinicians. Majorities (67%) of patients were received antifungal-antiviral

drugs, which was higher compared to a study conducted in UK approximately 22%–34% of NF patients will receive an antifungal drug (Cameron, 2009). A study by Klastersky, (2004), in Belgium also found approximately 40 to 50 % of patients. This might be due to a difference in the present risk factors and duration of neutropenia. Zafrani and Azoulay, (2014), strengthens the IDSA recommendation on addition of an empiric antifungal agent after four to seven days in high-risk neutropenic patients who are expected to have a total duration of neutropenia >7 days who have persistent or recurrent fever. This is the same as a study by Elting and his colleagues, (2000). In addition, a review update by Gutierrez provided the use of antifungal therapy in patients who remain febrile for more than 5-7 days (Villafuerte-Gutierrez *et al*., 2014). Moreover, when fever persists later, a deep-seated focus of infection, atypical organisms such as viruses should be considered and antiviral agent might be added (Elting *et al.*, 2000). In the current study, 67% of patients received antiviral agent, which may indicate that viral infection could be common in the institution due to prolonged fever with neutropenia and duration of admission. According to a study by Lee et al, (2011), antiviral prophylaxis against HSV is advisable in HSV-seropositive patients and considers using prophylactic antiviral agents in consecutive chemotherapy if HSV was reactivated in the previous chemotherapy.

Patients who had been treated for greater than seven days of duration were high as compared to patients treated for less than seven days of duration. This might be due to most of the patients who received treatment greater than seven days of duration might have complications or comorbid features and other deteriorated symptoms. For this group of patients the duration of antibiotic therapy should be adequate for the effective eradication of the infection based on the severity and type of pathogen identified. The presence of co-infections with NF such as most of bacterial bloodstream infections, soft tissue infections and pneumonias require 10 to 14 days of antibiotic therapy; treatment may therefore extend beyond the resolution of fever and neutropenia (Natarjan *et al.*, 2011).

According to multivariable analysis, patients who had AML were 5.6 times more likely (AOR=5.598; 95% CI: 1.078, 29.069) and ALL were 8 times more likely (AOR=8.265; 95% CI: 1.348, 50.665) respectively to receive appropriate management compared to those patients with other types of malignancies.

For patients who had culture result during admission were 5.7 times more likely (AOR=5.705; 95% CI: 1.236, 26.335) to receive appropriate management as compared to patients who have no culture result. This might be because the specific pathogen identified by laboratory investigation can lead to select an appropriate drug regimen easily. This result gives clue that regular practice of culture and sensitivity test for all NF patients could be mandatory in relation to the protocol provided by IDSA (Freifeld *et al*., 2011). However, in our study culture and sensitivity test was not done for 33.3% of patients, which might make selection of appropriate treatment regimen and modification difficult.

Patients who had a positive culture result were 12 times more likely (AOR=12.486; 95% CI: 4.344, 35.886) to receive appropriate management as compared to those who had a negative culture result. This might be because when culture result showed positive for a specific pathogen it is simple to give the right drug to the patient. However, culture and sensitivity test result was showed none growth on 65.8% of patients which is difficult to select appropriate treatment regimen and drugs for modification

6. Limitations of the study

Since the research design was retrospective, it was not possible to capture all the necessary data on the patient chart. Moreover, the study did not consider the availability and price of medications as a factor for inappropriate management practice in TASH. Finally, though the current study tried to assess the practice of NF management in TASH, it did not include children/pediatric population, and treatment outcome as one parameter.

7. Conclusion

AML and ALL were the two most common malignancies among HM on patients developing NF. In addition, the presence of profound neutropenia (<100cell/mm3) were also highly responsible in the occurrence of NF. The common pathogens identified as a cause of NF in this study were *Coagulase negative staphylococcus* and *Escherichia coli*. Combined antibacterial therapy with vancomycin was commonly prescribed and ceftazidime was highly utilized for these combinations while, the use of single drug regimen was low in both empiric and definite treatment periods. Majority of the patients received antifungal-antiviral agents and modification of antibacterial were carried out in above half of the patients.

8. Recommendation

Based on the findings of the current study, the following recommendations were forwarded:

- The institution setup should improve in order to give more appropriate management practice and increase the quality of service delivered.
- Health professionals should find a means to update themselves and monitor their patients strictly based on appropriate guidelines even if in the absence of local guideline.
- The choice of which antibiotic(s) to use needs to be established as a local policy and preparation of hospital guideline will solve the problem.
- Febrile neutropenia is a common and serious complication of chemotherapy, and hence it is important to have locally agreed protocols (guideline) that are well publicized.
- Culture and sensitivity test should be done for all patients as soon as possible to improve appropriateness of treatment.
- A prospective designed study should be carried out mainly on management and treatment outcome of NF and the cost or economic impact of treatment.

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10. Annex

10.1 Data abstraction format

<table>
<tr><td colspan="2">Patient card No……</td><td colspan="2">Demographic charactorstics
Age……Sex……..</td></tr>
<tr><td colspan="4">Patient characteristics at admission</td></tr>
<tr><td colspan="2">Type of patient</td><td>Type of hemaologic Malignancy</td><td>Co-morbid medical features at the time of NF episode</td></tr>
<tr><td colspan="2">Neutropenic with ANC of 1000-1500 □
Neutropenic with ANC of 500-999 □
Neutropenic with ANC of 100-499 □
Neutropenic with ANC of <100 □
Other----------</td><td>ALL □
AML □
CLL □
CML □
NHL □
Other----------</td><td>3.1. Infection □
3.2. Other deteriorated sign & symptoms:
a. BP----------
b. Fever----------
c. Respiratory rate--------
d. Pulse rate----------
e. Other----------</td></tr>
<tr><td colspan="4">Treatment and Culture</td></tr>
<tr><td rowspan="2">Empiric therapy</td><td>Monotherapy</td><td colspan="2">Combined therapy</td></tr>
<tr><td>Cefipime □
Meropenum □
Ceftazidime □
Ceftriaxone □
Other----------</td><td colspan="2">Ceftazidime + vancomycin □
Cefipime + vancomycin □
Ceftazidime + meropenum □
Meropenum + vancomycin □
Ceftazidime + gentamycin □
Other----------</td></tr>
</table>

Culture & sensitivity results

	Drug susceptibility reading		
Type of bacteria	**Growth of bacteria**	**No growth of bacteria**	**Culture not done**
Coagulase-negative staphylococci.			
(MDR) Pseudomonas aeruginosa			
Acinobacter baumanni			
Extended-spectrum betalactamase (ESBL) -producing gram-negative bacteria			
Carbapenemase- producing gramnegative Bacteria			
Methicillin-resistant Staphylococcus aureus (MRSA)			
Vancomycin-resistant enterococci (VRE)			
Other			

Investigation provided after two days of empiric therapy

Symptoms & other results

Sign of deterioration: BP---------- Fever---------- Respiratory rate-------- Pulse rate---------- Others----------	WBC/ differential------- BUN---------- Glucose---------- LDH----------	b. Positive culture □ c. Fever after 4 days □ d. Other----------

Drugs prescribed (definite therapy)		
Monotherapy	**Combined therapy**	**Treatment modification**
Cefepime □ Meropenem □ Ceftazidime □ Vancomycin □ Other……..	Cefta + Genta □ Cefta + Vanco □ Cefta + Merop □ Merop + Vanco Other……	Yes □ No □ If yes; When……. Other drug related Problems----------
Additional treatment	**Duration of therapy**	
Antifungal drug……. Antiviral drug…… Both……... Other…….	≤ 7 days □ > 7 days □	

10.2 Questionnaires

1. Demographic information

   Specialty:

   Specialist ☐

   Resident ☐

   General practitioner ☐

2. Is there adequate set up in the institution

   Yes ☐ No ☐

3. If no why?
4. Have you ever used IDSA treatment guideline?

   Yes ☐ No ☐

5. If no which guideline do you use and why?
6. Do you use combined antibacterial regimen for all patients **empirically**?

   Yes ☐ No ☐

7. If yes when?
8. Are all drugs and other investigations available?

   Yes ☐ No ☐

9. Are they (No-6) affordable for all patients
10. How long do you use empiric therapy?
    a. 48 hours ☐
    b. 72 hours ☐
    c. If other, specify
11. When do you modify empiric antibacterial?
    a. After 2 days of empiric therapy
    b. After 3 days of empiric therapy
    c. Other specify

12. Which drug (s) do you commonly used?

Combined regimen	Single drug

13. Do you order culture & sensitivity test for all patients?

Yes ☐ No ☐

14. If no why?

15. Are patients received antimicrobials before the specimen taken for culture test?

Yes ☐ No ☐

16. If yes why?

17. When do you use antifungal agents?

a. At initial assessment of NF(empirically) ☐
b. After 4 days of therapy ☐
c. Other, specify when?

18. When do you use antiviral agents?

a. At initial assessment of NF(empirically) ☐
b. the same time with antifungal agents ☐
c. After antifungal agents when fever persists ☐
d. Other, specify when?

10.3 Consent Form

Addis Ababa University

College of Health Science

Post Graduate Studies

School of Pharmacy

Department of Pharmacology and clinical pharmacy

Informed consent form prepared to assess management practice of neutropenic fever among patients with hematologic malignancy who admit Internal Medicine Hematology ward of TASH.

Part I: Information about the Study

My name is Tadesse Girma Bezabih; currently I am a graduate student at the department of Pharmacology and Clinical Pharmacy, College of health science, Addis Ababa University. I am conducting a study entitled "Assessment of the management of neutropenic fever in adult patients with hematologic malignancies at Tikur Anbessa Specialized Hospital. If you participate in the study, it is important to know the management practice of neutropenic fever. Furthermore, the result of this research is important to show the management practice of neutropenic fever (NF) according to the criteria set by a standard treatment guideline of infectious disease society of America (IDSA). The information which obtained from the study will also contribute for determining the guide line used and problems with respect to institutional set up to give appropriate treatment for NF patients with hematologic malignancy. I kindly request you to participate in this study by providing response for all the following questions. This information will be used only for research purpose. Your participation in this study is completely on voluntary bases and you have a right to refuse or interrupt the participation at any time. You will not write your name on the questionnaires. Your genuine participation is very important for the outcome of the research and all of your information is kept confidentially. If you need clarification, you can ask questions .I would like to appreciate your participation.

Part II: consent

Are you volunteer to participate in the study 1. Yes _____ 2.No_____

In signing this document, I am giving my informed consent to participate in the study entitled "Assessment of the management practice of neutropenic fever in adult patients with hematologic malignancy at Tikur Anbessa Specialized Hospital". I have been informed that the purpose of

this research. I have been informed that my participation in this study is willing full and voluntary even. I have right to refuse or interrupt from participating in the study any time and my name will not be mentioned on the questionnaire. I undersigned, have understood the purpose of the study and fully agreed to participate in the study.

Participant's

Name _____ Signature _____ Date _____

Data Collector's

Name _____ Signature _____ Date _____

Supervisor's

Name _____ Signature _____ Date __

10.4 IDSA treatment guideline protocol