BACTERIAL ISOLATES, ANTIMICROBIAL SENSITIVITY AND CHARACTERISTICS OF CHILDREN WITH FEBRILE NEUTROPENIA ON TREATMENT FOR CANCER AT MOI TEACHING AND REFERRAL HOSPITAL, KENYA.

BY

SAMUEL KIPKEMOI KIPCHUMBA

SM/PG/CHP/05/18

THESIS SUBMITTED IN PARTIAL FULFILMENT IN THE AWARD OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF MEDICINE CHILD HEALTH AND PAEDIATRICS SCHOOL OF MEDICINE, MOI UNIVERSITY.

© 2023

DECLARATION

Student's declaration

This thesis is my original work done during the pursuit of a Master of Medicine in Child Health and Paediatrics degree course at Moi University School of Medicine. It has not been presented for the award of any degree in any university. I attest to the best of my knowledge, it contains no material previously published by another person, except where due acknowledgement has been made in the text.

Dr. Samuel Kipkemoi Kipchumba

SM/PGCHP/05/18

Sign: .... Date: ....28/03/23................................

Supervisor's declaration

This research thesis has been submitted for examination with our approval as university supervisors.

Prof. W. Nyandiko (MBChB, MMed, MPH)

Professor, Department of Child Health and Paediatrics, Moi University

Sign: .... Date: ......30/03/2023..................

Dr. F. Njuguna (MBChB, MMed)

Paediatrician

Senior Lecturer, Department of Child Health and Paediatrics, Moi University

Sign: .... Date: ......28/3/2023.................

DEDICATION

I dedicate this work to my family; my wife, parents and siblings.

ACKNOWLEDGEMENT

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS, ACRONYMS, DEFINITION OF TERMS

AML	ACUTE MYELOID LEUKEMIA
ALL	ACUTE LYMPHOBLASTIC LEUKEMIA
ANC	AN ABSOLUTE NEUTROPHIL COUNT
AST	ANTIBIOTIC SENSITIVITY TEST
BSI	BLOOD STREAM INFECTION
CBC	COMPLETE BLOOD COUNT
CIN	CHEMOTHERAPY INDUCED NEUTROPENIA
CONS	COAGULASE NEGATIVE STAPHYLOCOCCUS
EDTA	ETHYLENEDIAMINE TETRAACETIC ACID
ESBL	EXTENDED SPECTRUM BETA-LACTAMASES
FN	FEBRILE NEUTROPENIA
Hb	HAEMOGLOBIN
HIV	HUMAN IMMUNODEFICIENCY VIRUS
ID	IDENTIFICATION
IDSA	INTERNATIONAL DISEASE SOCIETY OF AMERICA
IREC	INSTITUTIONAL RESEARCH ETHICS COMMITTEE
KENAS	KENYA ACCREDITATION SERVICE

LYM   LYMPHOCYTES

MDR   MULTIPLE DRUG RESISTANT

MTRH   MOI TEACHING AND REFERRAL HOSPITAL

MRSA   METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS

NEU   NEUTROPHILS

P. I   PRINCIPAL INVESTIGATOR

PLT   PLATELETS

POC   PAEDIATRIC ONCOLOGY CENTRE

R. A   RESEARCH ASSISSTANT

RBC   RED BLOOD CELLS

S4A   SHOE 4 AFRICA

S. I. O. P   INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

SPP.   SPECIES

VGS   VIRIDANS GROUP STREPTOCOCCUS

WHO   WORLD HEALTH ORGANIZATION

WBC   WHITE BLOOD CELLS

XDR   EXTENSIVELY DRUG RESISTANT

OPERATIONAL DEFINITIONS

- **Fever**: according to the International Society of Paediatric Oncology (SIOP), fever is defined as a temperature of 38°C sustained over an hour.

- **Neutropenia**: refers to an absolute neutrophil count of < 1000 cells/μL.

- **Febrile Neutropenia**: is defined as two separate readings of a temperature of 38°C or more taken one hour apart, in a patient with an absolute neutrophil count (ANC) of <1,000 cells/μL (SIOP).

ABSTRACT

Background: Febrile neutropenia is a common complication of chemotherapy induced myelosuppression. It is one of the most common causes of morbidity and mortality among children with cancer undergoing treatment with chemotherapy. At MTRH the bacterial organisms that cause febrile neutropenia are not known. This study aimed to find out the bacterial organisms associated with febrile neutropenia in children with cancer and the patient characteristics.

Objective: The main objective of this study was to identify the bacterial organisms associated with febrile neutropenia in children with cancer admitted at MTRH, their sensitivity patterns and the patient characteristics.

Methodology: A descriptive cross sectional study was carried out at the Moi Teaching and Referral Hospital, paediatric oncology ward, for a period of 10 months from June 2021 to April 2022. Children in the ward who developed a fever and neutropenia while receiving treatment with chemotherapy were recruited and blood samples were drawn aseptically for blood culture. The blood culture samples were received in the lab and were incubated in the BACT/ALERT automated blood culture machine. The patients' characteristics in terms of clinical diagnosis and demographic data were presented in frequency tables. Blood culture isolates results were presented in table form and grouped according to gram positive and gram negative bacteria. Antimicrobial sensitivity patterns were plotted in tables against the bacterial isolates cultured. Chi square/Fischer's exact test were used to analyse and test for association between patient characteristics and bacterial growth.

Results: Out of the 110 children included in the study, 66 (60%) were males. The median age of the children was 6.3 (SD 3.7) years. Majority of the patients 71 (64.5%) had a diagnosis of heamatological malignancies with the most common diagnosis being Acute Myeloid Leukaemia (AML). There was a significant association between severity of neutropenia and haematological malignancies p=0.028. From a total of 110 blood culture specimens collected, 31 (28.2%) were positive for bacterial growth. Gram positive bacteria were more frequent at 20 (58.1%). The most common organism from this study was *Escherichia coli* 6 (18.2%), followed by *Staphylococcus aureus* at 5 (15.2%). All the bacterial organisms were sensitive to linezolid and vancomycin and also showed good sensitivity towards meropenem at 10/11 (90.9%). High resistance to cephalosporins was noted with ceftriaxone at 5/6 (83.3%), cefepime at 4/7(57.1%) and ceftazidime 3/4 (75%).

Conclusion: The most common malignancy associated with febrile neutropenia was AML. Gram-positive bacteria were the most common source of BSI in patients with febrile neutropenia in our set up. The most common gram negative organism was *Escherichia coli* while *Staphylococcus aureus* was the most common gram-positive isolate. The organisms isolated had resistance to cephalosporins and benzylpenicillin but all were sensitive to linezolid and vancomycin.

Recommendations: Empirical antimicrobial management of febrile neutropenia in the paediatric oncology unit at MTRH should target gram-positive bacteria. First line antibiotics should be meropenem as monotherapy or in combination with an aminoglycoside such as amikacin.

CHAPTER ONE: INTRODUCTION

1.1 Introduction

Each year, an estimated 400 000 children and adolescents of 0-19 years old develop cancer. In high-income countries, more than 80% of children with cancer are cured, but in many Low- and Middle-Income Counties (LMICs) only 30% are cured (Lam et al., 2019).

Some of the reasons for lower survival rates in LMICs include delay in diagnosis, an inability to obtain an accurate diagnosis, inaccessible therapy, abandonment of treatment, death from toxicity (side effects), and avoidable relapse (Gupta et al., 2015).

The most common categories of childhood cancers include leukaemia, brain cancers, lymphomas and solid tumours, such as Wilms tumour and neuroblastoma. Most childhood cancers are treated with chemotherapy and other forms of treatments including surgery and radiotherapy (Steliarova-Foucher et al., 2017). Childhood cancer treatment requires specialized diagnostic and therapeutic capabilities, as well as the ability to manage potential complications (Gupta et al., 2015).

Infectious complications are a serious cause of morbidity and mortality in cancer patients. Among those with underlying haematological malignancies, autopsy studies have shown that approximately 60 % of deaths are infection related, whereas, in patients with solid organ tumours, approximately 50 % of these patients are estimated to have an infection as either the primary or an associated cause of death (Zembower, 2014).

Children on treatment for cancer are at an increased risk for infections due to frequent hospitalization, chemotherapy induced myelosuppression and a prolonged hospital

stay which predisposes them to nosocomial infections often from multiple drug resistant pathogens.

Myelosuppression due to chemotherapy puts children on treatment for cancer at risk for a wide array of infectious diseases, especially bacterial infections. Underlying immune deficiencies, associated comorbidities and treatment-related adverse effects are among other risk factors for infection (Zembower, 2014).

Chemotherapy-induced myelosuppression continues to represent the major dose-limiting toxicity of cytotoxic chemotherapy, which can be manifested as neutropenia, lymphopenia, anaemia, and thrombocytopenia. As such, myelosuppression is the source of many of the adverse side effects of cancer treatment including infection and sepsis (Bisi et al., 2016). The induction phase for certain malignancies such as Acute Lymphoblastic Leukaemia (ALL) and acute myeloid leukaemia (AML), are usually associated with the most potent myelosuppressive effects, and with severe and prolonged episodes of neutropenia (Mohammed et al., 2015).

Children on treatment for cancer who develop chemotherapy induced neutropenia are often at risk of developing febrile neutropenia as a complication of treatment. In patients who develop febrile neutropenia, the prevalence of blood stream infections is about 20% (Siddiqui et al., 2018). A study in South Africa found a prevalence rate of 11%-38% with an overall mortality reaching about 40% (Montassier et al., 2013).

Febrile neutropenia (FN) is defined by a temperature of >38°C, in patients with an absolute neutrophil count (ANC) <1,000 cells/µL with a predicted decrease to < 500cells/µL in the next 48 hours (S.I.O.P.).

Neutropenic fever is a medical emergency and patients who develop it are at risk of life threatening bacterial infections due to lack of inflammatory response (Bos et al., 2013). The severity of infection is directly related to the degree and duration of

neutropenia. According to Rondinelli et al, neutrophil counts of less than 500 cells/microlitre, represented a risk factor for severe complications in patients with febrile neutropenia (Rondinelli et al., 2006).

FN leads to chemotherapy dose reductions and dose delays and the resulting reduction in chemotherapy dose intensity can have a significant negative impact on clinical outcomes, notably survival (Chirivella et al, 2006).

Advances in the treatment of cancer have led to the introduction of more intensive regimens leading to increased cure rates but also increased risk of infections due to chemotherapy induced febrile neutropenia. (Mvalo et al., 2018)

Despite advances in the therapy, including more effective empirical broad-spectrum antibiotics, antifungals, and the use of granulocyte colony-stimulating factors, febrile neutropenia remains a therapeutic challenge. It prolongs hospital stays, increases health-care costs, and compromises chemotherapy efficacy, due to delays and dose reductions (Babu et al., 2016). Patients with febrile neutropenia therefore should be investigated early for bacteraemia and started on treatment early in order to avoid and prevent complications.

The development of antimicrobial resistance is a growing concern since drug resistant pathogens are the most common cause of nosocomial infections and prove difficult to manage. These bacteria also circulate among human beings, animals, in food and water and transmission is influenced through trade, human and animal migration (WHO, GLASS 2014). Despite antimicrobial prophylaxis being well tolerated, considerations have to be put into the understanding of the general interactions between the microorganisms and their human host in the development of antimicrobial resistance and the spread of multidrug resistant organisms (Classen et al., n.d.).

The challenge in the management of febrile neutropenia is made even more difficult with the increase in antimicrobial resistant bacterial species. Resistance to antibiotics develops when bacteria continue to thrive and adapt in the presence of antibiotic treatment. The development of antimicrobial resistance is driven by a lack of proper antimicrobial surveillance and stewardship measures. A study by Marin et al, stated that the extensive emergence of multi-drug (MDR) resistant bacteria has increased the burden of morbidity and mortality among cancer patients with blood stream infections (Marin et al., 2014).

There are different categories of antibiotics and many antibiotics may belong to a particular category. When bacteria develop resistance to a particular antibiotic, this may lead to the development of resistance to other antibiotics in the same category. This is an issue of concern since the development of multi-drug resistant organisms threatens the achievements made through the use of broad spectrum antibiotics in reducing mortality from blood stream infections in neutropenic patients (Blennow & Ljungman, 2016b).

The indirect impact of antimicrobial resistance, however, extends beyond increased health risks and has many public health consequences with wide implications, for instance on development. Antimicrobial resistance is a drain on the global economy with economic losses due to reduced productivity caused by sickness (of both human beings and animals) and higher costs of treatment (WHO, GLASS 2014).

The emergence of multi-drug resistance (MDR) bacteria is an important healthcare problem worldwide and patients with MDR bacteraemia are at increased risk of mortality (Islas-Muñoz et al., 2018). The development of resistance to the common antimicrobial agents used in the chemoprophylaxis and treatment of infections in patients with febrile neutropenia is a growing concern (Nesher & Rolston, 2014).

There's a need for more frequent antimicrobial surveillance to identify the prevalence of common bacterial organisms and their pattern of change over time in different health centres and institutions.

Having frequent data on the local organisms and their pattern of change over a duration of time will better help in understanding the shift in prevalence of bacterial isolates and will also provide information on the resistance and sensitivity towards locally available antibiotics.

This will aid in better antibiotic stewardship by providing clinicians with information on the choice of antibiotics for prophylaxis and treatment against the local organisms in their institutions or healthcare centres.

1.2 Problem Statement

Childhood cancers are increasingly representing a substantive contributor to the global disease burden and childhood morbidity even as the burden of communicable diseases is being controlled. According to (WHO-CureAll Framework, 2021) of the estimated 400,000 children between 0-19 years developing cancer each year, the majority, about 90% occur in low and middle income countries (LMIC).

The burden of cancer in LMICs is further increased by the low survival rates of cancer patients as compared to high-income countries. Survival probabilities range from over 80% in HIC to 50% in upper-middle-income countries and less than 30% in LMIC and low-income countries (LIC) (WHO-CureAll Framework, 2021).

Chemotherapy is the main mode of treatment for childhood malignancies. It, however, leads to myelosuppression that predisposes patients to complications of neutropenia, which includes febrile neutropenia. According to Klastersky in their study, the

incidence of febrile neutropenia varies between 10-50% in solid tumours and more than 80% in haematological tumours (Klastersky et al., 2016).

FN is the most frequent complication and the leading cause of morbidity and mortality in oncology patients undergoing intensive chemotherapy; it is also associated with a significant economic and social burden on the health system (Dulisse B, Li X, Gayle JA et al., 2013). Despite advances in treatment and prevention, mortality rates in patients with cancer and FN can range from 5% to 20%. Higher mortality rates are associated with patients who have higher occurrences of infectious complications and more comorbidities (Lyman GH et al 2016).

FN continues to be a burden to patients and their caregivers because of the negative impact it has on them. It is associated with dose reductions of chemotherapy and delayed treatment of children with cancer. This leads to an increase in the length of hospital stay, increased costs of care and an increase in morbidity and mortality due to increased risk of hospital acquired infections (Badr et al., 2016).

Chemotherapy induced neutropenia is a risk factor for blood stream infections in paediatric patients with cancer and most febrile neutropenia episodes are often associated with bacterial infections. As stated by Nesher in his study, infections occur in patients with neutropenia frequently and are the most common cause of morbidity and mortality (Nesher & Rolston, 2014).

Factors such as the environment, local chemotherapy regimens and antibiotic selection, influence the variation in the risk factors for infections, patient morbidity and mortality, pathogens and antibiotic sensitivity patterns in different regions (El-Mahallawy et al., 2005). There is no study that has highlighted or looked at bacterial organisms associated with febrile neutropenia in our setting, thus its management

continues to be a challenge since the local bacterial organisms and their sensitivity patterns are not well known.

Management of febrile neutropenia in children with cancer involves the use of antibiotics, hence there is a need for the local bacterial organisms and their sensitivity patterns to be known. Kenya being a LIC, many centres lack local antibiogram profiles and laboratories that are able to do blood cultures may not be available in some healthcare facilities, hence most patients are started on empirical antibiotics without knowing the local pathogens and their antibiotic sensitivity/resistance patterns, further contributing to the burden of antimicrobial resistance. This will help guide the clinicians on the suitable antibiotics to start the patients on as empirical therapy as they await blood culture results which usually take about 3 to 5 days.

Therefore, this study sets out to know the local bacterial organisms associated with febrile neutropenia and their antibiotic susceptibility patterns among children on treatment for cancer in our set-up. This is crucial to achieving optimal and appropriate therapy and guiding in developing treatment algorithms, by providing evidence-based data to guide the use of antibiotics in children with febrile neutropenia.

The risk factors associated with febrile neutropenia in the paediatric set-up are also not well understood. This is because there are no studies looking into febrile neutropenia in children with cancer. The type of malignancy, chemotherapy regimen, age, malnutrition and comorbid conditions have been shown to be associated with febrile neutropenia in children with cancer. According to a study by Gupta, chemotherapy regimens have different intensities for maximum cure rates; for example, the chemotherapy for Wilms tumour is far less intense than for acute myeloid leukaemia (AML) (Gupta et al., 2015).

At MTRH, there is no literature that highlighted factors associated with febrile neutropenia. Thus, those at risk of developing severe neutropenia and febrile neutropenia are not known. Therefore, the high morbidity and mortality associated with febrile neutropenia continues to persist.

1.3 Justification

Pathogens usually vary in different geographical areas and may also even vary in different institutions (H. A. El-Mahallawy et al., 2016). The prevalence of multidrug resistant pathogens is also a growing concern. Different institutions have different antimicrobial policies based on local pathogens.

At MTRH, there is no literature available on local organisms associated with FN and their sensitivity patterns among children being treated for cancer. Hence little is known about the common bacterial pathogens associated with febrile neutropenia and their antimicrobial sensitivity patterns. Patients who are at a high risk of febrile neutropenia are also not known.

The negative impact of febrile neutropenia on patients' healthcare adds to the already existing heavy burden of cancer management. These include increased cost of patient care due to prolonged hospital stay, chemotherapy dose reductions or delay of chemotherapy treatment and increased risk for mortality from hospital acquired infections.

In Egypt, a study found that neutropenia was responsible for the treatment discontinuation (13.3%), dose delay (13.3%) and dose reduction (5.3%) in their patients. The mean cost for each episode in their institution was 9,386.5±6,688.9 Egyptian pounds, which represented a significant burden on health care providers (Badr et al., 2016).

Due to this fact, it is essential that healthcare facilities have guidelines on how to approach the management of febrile neutropenia by having data on local pathogens and their antimicrobial sensitivity patterns. Better management of febrile neutropenia will help prevent chemotherapy delays and dose reductions, hence improving chemotherapy efficacy. This in the long run will help decrease costs to the patients, and length of hospital stays and eventually decrease the morbidity and mortality of children on treatment for cancer at MTRH.

The aim of the study was to identify the bacterial aetiology of febrile neutropenia among paediatric cancer patients and their characteristics while being treated for both solid tumours and haematological cancers at the Moi Teaching and Referral Hospital.

By identifying the local bacterial organisms within our setting, the approach to the treatment of febrile neutropenia can be tailored to suit our local set up since the organisms and antibiotic susceptibilities differ. Without data from this study to provide information on bacterial isolates in FN, there won't be any evidence to provide a basis on policies on antimicrobial use in this population. Consequently, there will be a lack of proper antibiotic stewardship and inappropriate empirical antibiotic coverage which can further add to the already existing rise in antibiotic resistance.

1.4 Research Questions

What are the clinical and demographic characteristics of children with febrile neutropenia on treatment for cancer at MTRH?

What are the bacterial organisms and their antimicrobial sensitivity patterns, associated with febrile neutropenia in children on treatment for cancer at MTRH?

1.5 Objectives

1.5.1 Broad Objective

To describe the clinical and demographic characteristics of children with febrile neutropenia undergoing treatment for cancer at MTRH and to determine the bacterial aetiologies and their antimicrobial sensitivity patterns associated with it.

1.5.2 Study Objectives

1. To describe the clinical and demographic characteristics of children who develop febrile neutropenia while on treatment for cancer, at MTRH.

2. To determine the factors associated with febrile neutropenia in children on treatment for cancer at MTRH.

3. To identify the bacterial organisms associated with febrile neutropenia and their antimicrobial sensitivity patterns in children on treatment for cancer while admitted at MTRH.

CHAPTER TWO

2.0 LITERATURE REVIEW

Toxicities from the chemotherapeutic agents and the catabolic nature of the underlying malignancy, remain a significant cause of morbidity and mortality among children with cancer undergoing treatment with chemotherapy. However, febrile neutropenia is the most common complication of chemotherapy and continues to be a significant cause of death among children with cancer (Davis & Wilson, 2020).

Febrile neutropenia is a medical emergency that requires rapid administration of empirical antibiotics (Libuit et al., 2014). Furthermore, the risk of infection in neutropenic patients is increased and can lead to fatalities if administration of antibiotic therapy is not introduced immediately (Chan et al., 2013).

Prompt recognition and diagnosis are required to prevent severe complications including death (Davis & Wilson, 2020a). Chemotherapy-induced neutropenia (CIN) is the major dose-limiting toxicity of systemic chemotherapy, and it is associated with significant morbidity, mortality and treatment cost (Badr et al., 2016).

According to Boccia et al in the US, febrile neutropenia causes a significant burden on patients due to hospitalization and mortality (Boccia et al., 2022). Moreover, almost all patients who present to the hospital will end up requiring admission to the hospital with an average length of stay ranging from six to ten days. The patient diagnosis and severity of neutropenia are also often related to other patient related factors such as age, gender, nutritional status and comorbid disease, which influence the incidence of febrile neutropenia.

Febrile neutropenia was responsible for about 22.7% of admissions among paediatric patients with cancer in a study by (Mueller et al., 2016). A younger age of less than 10

years and a primary diagnosis of Acute Lymphoblastic Leukaemia were among the factors that were noted to be associated with an increased risk for hospitalization.

In LIC and LMIC, survival rates in paediatric patients with cancer are much lower compared to high-income countries. Febrile neutropenia in addition to late presentation, malnutrition, failure to complete treatment and less intense supportive care, are some of the challenges to the successful treatment of paediatric cancers in these countries. This leads to increased treatment-related mortality and the need to reduce the intensity of treatment (Israëls et al., 2013).

Management of febrile neutropenia is an integral component of the care of patients with cancer and is also vital for the success of cancer treatments (Israels et al., 2013). Additionally, the management of patients with febrile neutropenia should involve an initial evaluation comprising a good history, physical examination and a septic screen (Kebudi & amp; Kizilocak, 2018).

A study in Sweden observed that bacteraemia was the major contributor to morbidity and prolonged hospitalisation, causing the majority of life-threatening infections, fever, and intravenous antibiotic therapy (Johannsen et al., 2013). In Italy Cecinati et al stated that bacterial infections which can be caused by either gram-positive or gram-negative bacteria are common in children with malignancies and occur mainly during neutropenic periods (Cecinati et al., 2014).

In a study by Tohamy and colleagues, febrile neutropenia was quite prevalent, with 58% of patients having positive bacterial cultures. The majority (52.3%) of the cultures were positive for gram-negative bacteria, and up to 68.6% were multidrug resistant (Tohamy et al., 2018).

In the US, a 5-year retrospective study of 380 paediatric cancer patients noted a proportion of bacteraemia of 20.26% from blood cultures obtained on day one of identification of febrile neutropenia. Half of these patients (50.2%) had solid tumours, closely seconded by haematological malignancies (Petty et al., 2015).

In a multicentre study in sub-Saharan Africa, with Kenya included, the prevalence of febrile neutropenia was reported to be 41.2%, with a third of the patients observed to have profound neutropenia of less than $0.1 \times 10\ 9$ /L (Israels et al., 2021). In a study in Nigeria by Akinsete and collaborators, 12% of their study participants had febrile neutropenia. However, only one of their study participants was noted to have positive blood cultures (Akinsete et al., 2020).

Chauhan and collaborates in their study noted the proportion of culture-positive febrile neutropenia cases to be 28.2%. Of these, slightly over two-thirds of the infections were caused by gram-negative organisms that were resistant to carbapenem (Chauhan et al., 2021). In MTRH, according to a study by Van Weelderen and colleagues, chemotherapy-related sepsis was a key contributor to early death in patients receiving chemotherapy for acute myeloid leukaemia (van Weelderen et al., 2021).

In another study in MTRH in 2017, 10.5% of patients had neutropenia, but only 2.1% developed febrile neutropenia. However, this study was limited to patients with solid tumours (Kawinzi et al., 2017). Febrile neutropenia has been shown to have a direct relationship with treatment time, with a rising incidence noted as treatment time progresses (Shyirambere et al., 2016). In a study by Nesher and Rolston et al, the standard of care in patients with febrile neutropenia involved the prompt initiation of

broad-spectrum appropriate antibiotics prior to getting blood culture results (Nesher & Rolston, 2014).

Several risk factors for febrile neutropenia have been identified. Some include; duration of neutropenia, presence of profound neutropenia, nature of cancer and stage, involvement of bone marrow, use of central lines, the intensity of treatment, nutritional status and comorbid conditions (Kebudi & Kizilocak, 2018; Lyman et al., 2014; Petty et al., 2015).

According to Cennamo et al, the severity of neutropenia and its duration, relate directly to the development of sepsis in febrile neutropenic episodes (Cennamo et al., 2021). In another study in Turkey, it was reported that bacteraemia was associated with low neutrophil counts < 100 cells/μL, as well as low total white blood cell counts (Kara et al., 2019). A similar observation was made by Hughes et al in a study where he observed that a high incidence of bacteraemia was seen in patients with severe neutropenia < 100 cells/μL (Hughes et al., 2002).

Neutrophil count < 500 cells μL, represents a risk factor for severe complications in patients with febrile neutropenia (Rondinelli et al., 2006).

Treatment intensity differs in different courses and diagnoses. A study by Bansal et al stated that chemotherapy courses for remission induction and consolidation are typically accompanied by an extended period of myelosuppression during which there is significant morbidity and mortality (Bansal et al., n.d.). Another study in India by Bothra et al, stated that infection rates were six times higher in those receiving intense chemotherapy compared to those receiving less intense chemotherapy (Bothra et al., 2013).

Lyman and colleagues did not only report clinical risk factors but put forth from their study that some genetic polymorphisms are linearly correlated with the development of febrile neutropenia (Lyman et al., 2014). Contrastingly, in a study by Israels and collaborators, prolonged neutropenia and the presence of profound neutropenia were not significantly associated with febrile neutropenia (Israels et al.,2021).

Clinical trials involving cancer regimens with an estimated febrile neutropenia risk of 20% in chemotherapy-naïve patients have been described as high-risk therapies (Lyman et al., 2014). Additionally, nutritional imbalances – undernutrition, overweight and obesity have been shown to influence the pharmacokinetics of 19 chemotherapeutic agents leading to improper dosing and adverse effects (Ceppi et al., 2015).

A study done in Malawi stated that malnourished children are likely to develop profound neutropenia while on chemotherapy resulting in infections (Molyneux et al., 2017). The patient's nutritional state has been shown to have clinical significance on the response to treatment and tolerance to chemotherapy. According to Murphy-Alford et al, underweight children on treatment for cancer have been shown to have reduced tolerance to therapy, with more toxicities, longer duration of therapy, treatment delays, and prolonged periods of hospital stays in both HICs and LMICs (Murphy-Alford et al., n.d.).

Poor nutritional status in children undergoing treatment for cancer may result in poor clinical outcomes (Murphy-Alford et al., n.d.). In another study in India, it was noted that the deficiency of folate in children on treatment for cancer was associated with delayed marrow recovery (Tandon et al., 2015). They also reported that hypoalbuminemia, vitamin B12 and folate deficiencies were significantly associated with death from chemotherapy toxicities.

Freifeld and collaborators in their study, highlighted the need for patients with febrile neutropenia to be risk stratified as low and high risk and recommended that this be the starting point of management of these patients (Freifeld et al., 2011). A national multicentre study in the Netherlands stratified patients as low, medium, and high risk, and reported significantly shorter lengths of stay and duration of antibiotic therapy in the groups classified as low or medium risk patients (Miedema et al., 2016). Furthermore, febrile neutropenia may also impose delays in or complete cessation of chemotherapy, which hampers patient outcomes (Lyman et al., 2014). These poor outcomes have been noted even in patients classified as low risk patients. Miedema and colleagues reported a 12.8% failure rate in low risk patients who presented with recurrent fevers, and the organism isolated in these failures was CONS (Miedema et al., 2016).

On the other hand, a meta-analysis of 14 articles reported a mortality of 1.9% in paediatric cancer patients with febrile neutropenia, and there was no significant difference in the group of children who received inpatient treatment compared to those who received treatment on an outpatient basis (Teuffel et al., 2011). Israels and collaborators demonstrated that blood culture samples were collected before the start of antibiotic therapy in only 15% of cases. Therefore, to improve patient outcomes, they recommended the collection of blood cultures prior to starting antibiotics (Israels et al., 2021).

2.1 Patient Characteristics

The male gender has been associated with a higher prevalence of malignancies when compared to the female gender. The higher incidence of childhood cancers among male children is well established; however, the underlying biologic mechanisms remain unknown. Data obtained from Surveillance, Epidemiology and End Result

Program (SEER) 18 (2000-2015), which is a cancer registry in the US, male children made up 53% of the identified childhood cancers and were significantly associated with a majority of the cancer types. A study done on 'Sex ratio among childhood cancers' noted that the male sex was significantly associated with childhood cancer overall and was especially noted to be at risk of or frequently diagnosed with acute lymphoblastic leukaemia, lymphomas, intracranial embryonal tumours and rhabdomyosarcoma (Lindsay A et al., 2018). Additionally, in a study by Williams et al, they noted the male-to-female incidence rate ratio for all childhood cancers was 1.19:1 (Williams et al., 2019).

The predominance of childhood cancers among the male gender can be attributed to biological mechanisms such as germline variation and gene expression on the X and autosomal chromosomes, immune response and pubertal hormone profiles that increase the risk of childhood cancer among males. According to a study by Dunford, male-biased mutations in genes that escape X-inactivation were observed in combined analysis across many cancers and in several individual tumour types (Dunford et al., 2017) . Another study noted that birth defects were associated with an increased risk for childhood malignancies and concurrently another study by Michalski noted that birth defects occurred more among the male gender, hence the reason for a higher prevalence of childhood malignancies among males (Johnson et al., 2017; Michalski et al., 1997)

Age specific variations in the incidence of malignancies have been noted in a number of studies. A majority of studies have shown the bulk of childhood malignancies occurring below the age of 10 years with some noting the incidence to be higher in the age group of 0-4 years while in some studies the age bracket of 5-9 years has more occurrence of malignancies. A prospective study done in Yemen over a 12 year period

showed that the predominant age group was 5-9 years (Jawass et al., 2016). Similarly, a study done in Ghana also showed that the highest prevalence of cancer occurred in the age group of 5-9 years (Nguah, 2015). However, a retrospective descriptive study done in Kenyatta hospital over a period of 10 years found that a greater percentage of cancers are diagnosed between the ages of 0-4 years (Irene & Peter, n.d.). This coincides with the fact the peak age for the most common childhood malignancies is below the age of 10 years. The peak age for leukaemias (ALL) has been shown to be between the ages of 2 to 5 years; nephroblastoma peak incidence is between 1 to 4 years; non-Hodgkins lymphoma between 3 to 6 years (Juárez-Ocaña et al., 2004).

The pattern of distribution of malignancies varies across different regions. This could be due to biological and clinical diversities and also the effect of climatic and geographical change. In the US and Europe, the most common childhood malignancies are leukaemias followed by brain and other CNS tumours and lymphomas according to the National Cancer Institute and WHO 2021 respectively. However, a study done in Yemen showed that the most common malignancies were lymphomas followed by leukaemias (Jawass et al., 2016). Another study done analysing data from cancer registries across 21 centres from 18 sub-Saharan countries, showed that lymphomas, nephroblastoma, Kaposi sarcoma and retinoblastoma were the most common paediatric tumours (Cristina Stefan, 2015). The similarity in the common types of malignancies noted across these different centres is in keeping with the geographical pattern of distribution of paediatric malignancies across the equatorial region.

2.2 Bacterial isolates

Bacteraemia is present in about a quarter to a third of patients with febrile neutropenia. According to Babu et al in their study, they stated that bacteraemia is the

cause of fever in 25% of neutropenic patients (K. G. Babu et al., 2016). The most common cause of fever in neutropenic patients is blood stream infection however, bacteraemia is found in only about 10-25% of patients with febrile neutropenia (Ahmad et al., 2019). While according to a study by Zimmer and Freifeld et al, bacteraemia occurs in about 10-30% of neutropenic fevers (Zimmer & Freifeld et al., 2019).

A study done in Turkey found a growth rate of 23.3% (Kara et al., 2019). This was similar to studies done in Switzerland by von Allmen et al, which had a bacterial growth rate of 22% (154 episodes) detected (von Allmen et al., 2018), and a study done in Ghana by Obeng-Nkrumah et al, which found a rate of 22% (Obeng-Nkrumah et al., 2015). However, a study done in Qatar reported a higher (38%) growth rate from 185 blood cultures taken (Al-Mulla et al., 2014), while other studies done in Sweden and another in Switzerland reported lower rates of 16% and 19.06% respectively (af Sandeberg et al., 2017; Stergiotis et al., 2021).

Over the past thirty years, there has been a considerable change in the epidemiology of pathogens causing bacteraemia in patients with febrile neutropenia. In the 1970s gram negative bacilli caused 60-70% of bacteraemia in neutropenic patients, in the 1990s gram positive bacilli, were responsible for the majority of the blood stream infections in these patients (Viscoli et al., 2005).

This was also true according to Ola Blennow and Per Ljungman, who in their study stated that in the 1980s, bacteraemia caused by Gram-positive cocci increased with the use of central line catheters, the introduction of fluoroquinolone prophylaxis and the use of intensive chemotherapy, causing severe mucositis (Blennow & Ljungman, 2016b). Gram-positive bacteria have a predilection for colonizing central line

catheters, this could also be a reason for the increase in gram positive infections in these patients (Nesher & Rolston, 2014).

This was also supported by another study done in the United States (U.S.) which reported that gram-positive organisms are increasingly being isolated from blood cultures of patients with febrile neutropenia (Ramphal, 2004). Likewise, a study conducted in Sweden showed a predominance of Gram-positive bacteria in their cultures (af Sandeberg et al., 2017). In the Middle East in Qatar, another study also had similar results whereby gram positive bacteria were the most common isolates (55%) (Al-Mulla et al., 2014). This was the same case in a study done in Iran which also reported that gram positive bacteria were the most isolated organisms (Karimi et al., 2018). This was similar to a study in Cairo, Egypt that also showed a prevalence of gram-positive bacterial organisms (75% n=180) as the most common isolates of blood stream infections among patients who develop febrile neutropenia while on treatment with chemotherapy (Hadir A. El-Mahallawy et al., n.d.) and in Tunisia where another study also found a predominance of gram-positive bacteria (70%) (Fedhila et al., 2022).

Furthermore, a study done in Turkey, reported that the incidence of gram-positive bacteraemia was raised with the use of central venous catheters, quinolone prophylaxis and broad-spectrum empirical antibacterial therapy, although Gram-negative pathogens remained predominant (Alp & Akova, 2013a). This was also similar in a study done by Katrine Johannsen in Denmark, which reported that a more resistant gram-positive oral flora caused by the prophylactic use of sulfamethoxazole/trimethoprim and fluoroquinolones, and the increased use of central venous catheters also contribute to the higher prevalence of gram-positive bacteraemia (Johannsen et al., 2013).

In their study Freifeld et al, stated that febrile neutropenia is typically caused by gram-positive cocci such as Coagulase Negative Staphylococci (CONS), *Staphylococcus aureus* and gram-negative bacilli such as *Pseudomonas aeruginosa* (Freifeld et al., 2011).

This was the same case in a study done in India which found that the most commonly isolated organism was *Staphylococcus* aureus (31.034% 9/29) followed by CONS and Klebsiella (24.138% 7/29) (Chaudhuri et al., 2016).

Country and regional variations have been reported as regards the identified organisms in cancer patients with febrile neutropenia (Israels et al., 2013). Over time, the increased use of effective antimicrobial prophylaxis in patients with febrile neutropenia has led to the development of multidrug resistant, gram negative bacteria, especially as a cause of nosocomial infections in patients with febrile neutropenia. According to Ola Blennow and Per Ljungman, gram negative bacteraemia increased again in the recent years and is thought to be probably associated with an increase in fluoroquinolone resistant gram negative bacteria (GNB) (Blennow & Ljungman, 2016b). These have arisen from a wide application of fluoroquinolone prophylaxis and the prevalence of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, multidrug-resistant (MDR) *P. aeruginosa* and *Acinetobacter baumannii*. They further stated that increasing antimicrobial resistance in GNB is not unique to haemato-oncology patients but has increasingly been reported in health care facilities.

In their study, Gopal and collaborates, stated that gram-negative organisms, for which there are increasing antimicrobial resistance are likely to be the main cause of bacterial sepsis in febrile neutropenia due to the high endemic infection burden, lack

of antibiotic control use and other co-morbidities such as HIV and malnutrition (Gopal et al., 2012).

In other Paediatric Oncology Centres (POCs), gram negative bacteria have also been shown to be more frequent than gram positive bacteria. In Japan, it was found that gram negative bacteria were the leading pathogen in the blood stream infections of paediatric patients with acute leukaemia (Shen C. et al., 2017). This was also a similar finding to a study done in Kabul where gram-negative bacteria were more than gram-positive bacteria (51.71%) (Gentile et al., 2014) and it was also the observation in a study done in Jordan by Ahmed Hussein et al, who had a predominance of gram-negative bacteria at 57.1% (Ahmed Hussein et al., 2016). Whereas in India, a study showed that 76 (85%) out of 89 positive cultures were colonized by gram-negative bacteria (Siddaiahgari et al., 2014), while similarly a study done in Uganda in 2019 and another in Ghana, also found a prevalence of gram-negative bacteria (66.7% and 52.6%respectively) (Lubwama et al., 2019; Obeng-Nkrumah et al., 2015).

In India Babu et al found that gram‑negative bacilli were cultured more (58%) than gram‑positive cocci (40%) (Babu et al., 2016). Among the gram‑negative organisms, *Escherichia coli* followed by *Acinetobacter baumannii* and *Klebsiella pneumoniae* accounted for 78% of the isolates. For the gram‑positive cocci, *Staphylococcus* species accounted for 84% of the isolates. Similar findings were noted in studies by, who found that the most common gram-positive and gram-negative bacteria isolates in their studies were *E. coli* and *Staphylococcus aureus* (Bothra et al., 2013; Oberoi et al., 2017).

Comparably, a study in Tunisia found the most common gram positive isolates were coagulase negative *Staphylococcus* (50%-70%) followed by *Streptococci* while the

most common gram negative isolates were *E. coli* followed by *Pseudomonas aeruginosa* (Fedhila et al., 2022) while, in Jordan another study noted that the most common gram negative organisms were *E. coli*, *Pseudomonas* and *Klebsiella* spp., while CONS and *Streptococci spp.* were the most common gram positives isolated (Ahmed Hussein et al., 2016) and similarly, a study in Iran also found that the most common gram positive organisms isolated were *Staphylococcus epidermidis* (30%) followed by *Staphylococcus aureus* (15%). For the gram negative organisms, the most common were *E. coli*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* (Karimi et al., 2018).

In a study done in Uganda, out of 33 bacteria isolated from cultures, they found the majority to be gram negative at 66.7%, with *Enterobacteriaceae* being the most common gram-negative isolates. (Lubwama et al., 2019).

A study in Egypt found that bacteraemia caused by a group of pathogens known as 'ESKAPE pathogens 'which are *Enterobacter spp.,* methicillin-resistant *Staphylococcus aureus* (MRSA), *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterococci* was associated with more severe sepsis and most of the pathogens were Multiple Drug Resistant (MDR) (El-Wakil M et al., 2016).

Staphylococcus aureus and more so MRSA, *Enterococcus spp.*, *Enterobacteriae*, *Pseudomonas aeruginosa*, are often responsible for healthcare associated infections and are prone to being multidrug resistant (Magiorakos et al., 2012). Patients on treatment for malignancies are at risk for colonization with hospital-associated pathogens due to chemotherapy induced neutropenia and prolonged hospital stay (Al-Mulla et al., 2014).

In South Africa, a study showed the majority of BSI (40%) were caused by gram-positive cultures, while gram-negative were responsible for 36%. Of the gram-positive cultures *Enterococcus*, *Viridans* Group *Streptococci* and CONs, were the most frequently cultured, while *Enterobacteriaceae* were the most isolated gram-negative bacteria. (Mvalo et al., 2018). Similarly, Alp and Akova et al, noted a significant increase in the prevalence of methicillin resistant *Staphylococcus aureus* and vancomycin resistant enterococci (VRE) have become the most isolated pathogens from a number of centres (Alp & Akova, 2013).

Interestingly, in one study, in a little over half of the participants with febrile neutropenia, no cause was identified (Özdemir et al., 2016). Another study brought to light the fact that fungal organisms, especially *Aspergillus spp.* play a key role in febrile neutropenia and need to be investigated (Barton et al., 2015). However, febrile neutropenia in paediatric patients should be presumed to be of bacterial origin and treated accordingly till proven otherwise (Israels et al., 2013).

2.3 Antimicrobial sensitivity patterns

Chemoprophylaxis with broad spectrum antibiotics remains an essential aspect in the management of patients with febrile neutropenia. In their study Classen et al stated that the administration of antibacterial prophylaxis has been shown to reduce the incidence of febrile events and infections (Classen et al., 2013).

In addition to other measures such as infection prevention such as hand hygiene to curb pathogen transmission, pharmacological measures to prevent infections in neutropenic patients include the use of granulocyte colony stimulating factor (G-CSF) and the use of prophylactic antibiotics (Neumann et al., 2013; Vehreschild et al., 2014).

The Infectious Diseases Society of America (IDSA) and the American Society of Clinical Oncology (ASCO), both recommend the use of fluoroquinolones (levofloxacin and ciprofloxacin) as antimicrobial prophylaxis in patients who are at high risk for febrile neutropenia or profound, protracted neutropenia. Several studies have been shown to be in support of the use of fluoroquinolones as prophylaxis in patients with febrile neutropenia.

A multicentre study done in five hospitals across five countries in sub-Saharan Africa reported that antibiotic prophylaxis varied in the different centres and included either co-trimoxazole given three times a week or ciprofloxacin was given twice daily (Israels et al., 2021). A study done at MTRH, recommended the addition of ciprofloxacin prophylaxis in the supportive care regimen for neutropenic patients (van Weelderen et al., 2021a). Additionally, a study done in Australia noted that levofloxacin prophylaxis reduced the odds of febrile neutropenia, likely bacterial infection, and bloodstream infection by ≥70 % in newly diagnosed paediatric ALL patients (Wolf et al., 2017).

A study done in Turkey reported that the addition of oral ciprofloxacin to intravenous cefepime or vancomycin significantly reduced bacterial sepsis and days of hospitalization when compared to prophylaxis with oral cephalosporins alone (Zengin et al., 2017). Moreover, a study by Egan and collaborates, reported that the addition of rifampin to fluoroquinolone significantly reduced the risk of bacteraemia compared to fluoroquinolone alone (RR 0.36, 95% CI 0.17-0.77). However, more studies need to be done on this (Egan et al., 2019).

However, the use of fluoroquinolones as antimicrobial prophylaxis has been linked to increased infection rates due to fluoroquinolone-resistant organisms, particularly

fluoroquinolone-resistant *E coli*. (DeBraud et al., 1998). Fluoroquinolones have also been associated with increased rates of multi-drug resistant organisms (Zimmer & Freifeld, 2019).

Both IDSA and ASCO further recommend a combination of ciprofloxacin plus amoxicillin - clavulanate for oral prophylaxis. Contrastingly, in Ghana, Vanderpuye et al, found that their results did not support the use of prophylactic amoxicillin/clavulanic acid over cephalosporin due to low fever recovery rate in the event of febrile neutropenia. They, however, reported that aminoglycosides are an important component of empiric antibiotic combination treatment in their setting (Vanderpuye et al., 2011).

The choice of antibiotics to use in patients with febrile neutropenia should be tailored to the local pathogens and their sensitivity patterns. Furthermore, according to another study, fever during neutropenia warrants prompt empirical antibiotic therapy which should be active against the most frequent gram-negatives (Gustinetti & Mikulska, 2016). Moreover, Karimi et al   reported that the most prescribed antibiotics in patients with febrile neutropenia were meropenem followed by vancomycin (Karimi et al., 2018).

 In a multi-centre study conducted in Germany, Austria and Switzerland, across 51 POCs, 52% of the centres used antibacterial monotherapy while 48% used an empirical combination therapy. The preferred first-line antibiotic in most POCs (61%) is piperacillin-tazobactam, followed by ceftazidime (24%), cefepime and ceftriaxone (4%) each, the latter in combination with amikacin). Only three POCs (6%) use imipenem/cilastatin or meropenem as first-line treatment. (Scheler et al., 2020). While in another multicentre study done in Denmark across two POCs, the first line

antibiotic therapy in Centre A consisted of piperacillin-tazobactam and gentamicin, while in the second centre B, first line therapy consisted of meropenem and gentamicin (Johannsen et al., 2013). In the United Kingdom (UK), the National Institute for Health and Care Excellence (NICE) recommended the use of piperacillin-tazobactam as first line monotherapy. However, in the United States (US) a study done by Tamma et al reported that piperacillin-tazobactam was inferior to carbapenems for the treatment of ESBL bacteraemia and recommended the early use of carbapenems (Tamma et al., 2015).

A study done in Lebanon found an emerging resistance to third and fourth generation cephalosporins and to a lesser extent carbapenems in gram negative isolates (Moghnieh et al., 2015). A study done in South Africa found that gram negative bacteria (*Enterobacteriaceae*) had low resistance to carbapenems 0-2.3% but high resistance rates to cephalosporins 48.9-53.7% and also reported that 82.4% of the bacterial isolates of gram-positive bacteria were resistant to ampicillin; vancomycin resistance rates were low for CONS and VGS (*Viridans* Group *Streptococci)* but higher for *Enterococcus* species while two isolates were MRSA and 14 were ESBL producing bacteria (Mvalo et al., 2018).

In Uganda, a study showed that although most gram-negative ESBL bacteria showed susceptibility to imipenem, carbapenem resistance was seen in (4) 36% of *E. coli*; (4) 57% *K. pneumoniae*; 1 (50%) *Enterobacter* species. All *Staphylococcus*

species identified were methicillin resistant. (Lubwama et al., 2019)

In another study by Kebudi and collaborators, it was recommended that empiric antibiotic therapy in patients with cancer should consist of antibiotics with coverage against *Pseudomonas aeruginosa*, and modification of therapy instituted after culture results are made available (Kebudi & Kizilocak, 2018). Likewise, in their study,

Barton and colleagues alluded to the use of broad-spectrum antibiotics as a start-off treatment for febrile neutropenia (Barton et al., 2015).

In Austria, a study that was done found that *Viridans* sepsis occurred more in the group without systemic antibacterial prophylaxis administration in comparison to the group of teicoplanin/vancomycin prophylaxis (Boztug et al., 2017).

A combination of piperacillin-tazobactam and amikacin was found to be an effective empirical antibiotic regimen against most gram-negative and gram-positive bacteria in patients with febrile neutropenia. (Mvalo et al., 2018).

The development of bacteria that are multi-drug resistant creates a challenge for antimicrobial prophylaxis in patients with febrile neutropenia. The prevention of the emergence of multi-drug resistant strains (especially Gram-negative organisms) can be achieved through good prevention strategies and good antimicrobial stewardship (Davis & Wilson, 2020a). A study by Barton and colleagues reported 10-20% associated bloodstream infections in patients with febrile neutropenia and showed the occurrence of pathogens with high potential for multidrug resistance such as *Klebsiella spp.* and Streptococcus *viridans* (Barton et al., 2015). The increasing number of multi-drug resistant pathogens, noted in patients with febrile neutropenia, notably the ESKAPE pathogens and MRSA is of concern and calls for more antimicrobial vigilance and proper antimicrobial stewardship.

As per the IDSA guidelines, due to the increasing frequency MRSA, the early use of anti-MRSA agents like vancomycin, linezolid or daptomycin, is now more commonly considered. However, vancomycin should be used judiciously in order to prevent the development of vancomycin resistant *Enterococcus* (VRE) and preferably reserved for patients meeting the IDSA guidelines (Freifeld et al., 2011; Libuit et al., 2014).

According to IDSA, indications for vancomycin use include hemodynamic instability or evidence of severe sepsis, colonization with MRSA, penicillin resistant *Streptococcus penumoniae*, severe mucositis with prior fluoroquinolone prophylaxis and febrile neutropenia after empiric ceftazidime use. For VRE, the addition of linezolid should be considered.

2.4 Factors associated with febrile neutropenia.

In Italy, a study found that the risk of infection in children with febrile neutropenia is higher in those with haematological malignancies than those with solid tumours (Cennamo et al., 2021). This may be due to the fact that haematological malignancies affect the bone marrow and require more intensive myeloablative therapy, resulting in the disruption of normal immune function (Calitri et al., 2018; Viscoli et al., 2005).

A study by Girmenia et al reported that neutropenia was associated with BSIs in patients affected by ALL in 84% of cases, in comparison with 47% of patients with solid tumours (Girmenia et al., n.d.). This was also the case with a study done by Andersen and collaborates who found a strong association between neutropenia and malignant haematologic disease ($p < 0.001$) (Andersen et al., 2016). Similarly, a study El-Mahallawy et al noted that haematological malignancies were a risk factor for serious blood stream infections in patients with febrile neutropenia (El-Mahallawy et al., 2005).

Several studies have also shown that BSI occurred more in patients with haematological malignancies. In their study, Zengin et al, stated that the risk of severe infection complications may be attributed to prolonged neutropenia in patients with AML (Zengin et al., 2017). In a study in Sweden, it was noted that most of the cultures positive for bacterial growth (30%) were from children with AML (af

Sandeberg et al., 2017). These findings were similar to a study done by Kara et al who found a higher prevalence of bacteraemia 61.3% vs. 38.7% in patients with leukaemia compared to solid tumours (Kara et al., 2019) and also in a study done in India where haematological malignancies yielded the majority of bacterial growth from cultures (75.18%) (Bothra et al., 2013).

In Uganda, 73% of the positive blood cultures for BSI were from patients with haematological malignancies while 26% were from solid tumours and gram-negative bacteria were more likely to be isolated from patients with haematological malignancies (Lubwama et al., 2019). Those on treatment for haematological malignances are at an increased risk due to severe neutropenia as a result of intensive chemotherapy. In addition to this, a study in South Africa, reported that most blood stream infections occurred during the induction and consolidation phases of chemotherapy for haematological malignancies (Mvalo et al., 2018). Moreover, in that study, it was noted that patients with haematological malignancies had a higher frequency of blood stream infections from all the blood cultures taken. Among haematological malignancies, the highest rates of bacterial growth were seen in AML 27/33 (81.8%); ALL 23/62 (37.1%) compared to solid tumours 23/126 (18.3%).

The use of different chemotherapy regimens or agents plays a role in the development and severity of neutropenia). A study done in Egypt reported that early onset neutropenia was associated with the induction chemotherapy blocks of ALL and AML (Badr et al., 2016). While Classen et al in their study, reported that the incidence of febrile neutropenia ranged from as low as 0% in some treatment regimens for solid tumours to as high as 100% in the induction treatment for ALL (Classen et al., n.d.).

In another study, it was noted that febrile neutropenia occurred more in patients with relapsed disease when compared with their counterparts. This study further showed that the incidence of febrile neutropenia had a linear relationship with the intensity of the chemotherapy regimen that was administered (Özdemir et al., 2016). In Pakistan, a study done identified that age less than 5 years and AML were some of the risk

factors associated with prolonged febrile neutropenia (Alam, Muhammad et al., 2014).

In Kenya, a study done by Mwangi et al noted that the administration of cyclophosphamide a chemotherapeutic agent used in the treatment of lymphomas, sarcomas and leukaemia, was a risk factor for the development of neutropenia. In the same study, they reported that 45.7% of patients treated using cyclophosphamide developed neutropenia (Mwangi et al., 2019).

In another study done at MTRH in Kenya, it was noted that the main causes of early deaths among paediatric patients on treatment for acute myeloid leukaemia were attributed to a lack of supportive care which included unavailability of adequate antibiotics for febrile neutropenic patients (van Weelderen et al., 2021b).

In a guideline published by the American Society of Clinical Oncology (ASCO) an expert panel, classified chemotherapy induced neutropenia as mild (ANC of <1500 cells/μL), moderate (ANC <1000 cells/ μL) and severe, (ANC < 500 cells/ μL). The severity of neutropenia is directly related to the intensity of chemotherapy given and it also influences the incidence of febrile neutropenia (Klastersky et al., 2016).

Majority of the BSI (70%) occurred in the presence of severe neutropenia in a study done in Uganda (Lubwama et al., 2019). This was also similar to the study done in South Africa where 76.4% of BSI occurred in patients with severe neutropenia and also noted a significant association between BSI and severity of neutropenia (p = 0.01) (Mvalo et al., 2018).

Good nutritional status is important in the functioning of the immune system. Children on treatment for malignancies are often predisposed to the risk of malnutrition due to the catabolic nature of the disease and also the side effects of the

treatment that lead to poor nutritional intake. Diminished nutritional status can be a factor associated with decreased immune function (Bauer et al., 2011), predisposing patients to infections. According to a study in Columbia majority (85%) of patients with malignancy are malnourished (Hanzelina et al., 2022),.

In addition to this, a study by Oyuang et al noted that the risk of febrile neutropenia in children with malignancy was higher in those with malnutrition (Oyuang et al., 2013). Children with malnutrition are at increased risk of infections due to a depressed immune system. Furthermore, a study by Chaudhuri et al, they reported that haematological malignancies and chemotherapeutic interventions amplify the changes that occur in the immune system of malnourished children making them more susceptible to infections (Chaudhuri et al., 2016).

Another study done in India, found that the incidence of febrile neutropenia was significantly more in the group of children with severe malnutrition (p=0.001) (Roy et al., 2013). This was also supported by Hanzelina et al in Columbia (Hanzelina et al., 2022), who in their study found a significant association between malnutrition and febrile neutropenia. Moreover, in another study, it was noted that children with significant weight loss during the induction phase of ALL treatment had a higher risk of developing complications such as febrile neutropenia (Sneha et al., 2022).

In Malawi, a study noted that children with acute malnutrition at diagnosis had a higher rate of febrile neutropenia when compared to those who were not malnourished (Israëls et al., 2009).

CHAPTER THREE: METHODOLOGY

3.1 Study design

This was a descriptive cross-sectional study whereby patients in the oncology ward who developed a fever and neutropenia while undergoing treatment with chemotherapy were identified and were then recruited, in order to describe their clinical characteristics and identify the common bacterial organisms through blood cultures. The study was carried out for 10 months from June 2021 to April 2022.

3.2 Study site

The study site was the paediatric oncology ward in Shoe 4 Africa Paediatric Hospital at Moi Teaching and Referral Hospital. Moi Teaching and Referral Hospital (MTRH) is a level six public referral hospital located along Nandi Road in Eldoret town in Uasin Gishu County. It is the second largest national referral hospital in the country. It has a capacity of about 1000 beds and offers inpatient and outpatient services as well as specialized healthcare services that include oncology treatment.

The hospital serves a population of about 24 million people spread across at least 22 counties in the western part of Kenya. The hospital also receives patients from parts of Eastern Uganda and Southern Sudan.

The Shoe 4 Africa Children's hospital has a bed capacity of approximately 200 beds. It comprises both surgical and medical wards catering to patients with various conditions. On average 3000 patients are admitted per year at the Shoe 4 Africa Hospital with various diseases including malignancies. As per the hospital policy, only children more than one month of age to less than 15 years are admitted at Shoe 4 Africa.

The paediatric oncology ward in Shoe 4 Africa MTRH has a bed capacity of 27 beds that have been spread across six rooms. On average there are about 100 patients admitted to the oncology ward per month, with about 18 newly diagnosed patients admitted each month. Due to limited resources in terms of availability of bed space, the oncology ward experiences a high average bed occupancy each month of approximately 52 (192%) patients, leading to congestion in the wards further increasing the risk of infection transmission among the patients.

The ward is divided into two sub-units, with each sub-unit having three rooms. In each sub-unit, one of the rooms is reserved as an isolation unit for those with severe neutropenia. This is done to achieve infection prevention and control.

The unit is run by an able team that comprises of nurses trained in the management of oncology patients. It also has three registered clinical officers, one medical officer and two consultants.

Strict isolation is recommended for those with severe neutropenia in addition to other infection prevention measures, however, this is not possible due to the high number of patients and the limited amount of space in the unit. Emphasis is made on aseptic measures when handling patients through strict handwashing or the use of sanitizers between patients, with minimal handling of those in isolation rooms with severe neutropenia. However, patients with severe neutropenia often have to share rooms and amenities such as washrooms and bathrooms with the other patients due to the limited resources. Also, not every room and bed has sanitization facilities, due to the inconsistency in the availability of hand sanitisers. Each patient is required to be accompanied by only one caretaker as a measure of infection prevention and also in order to reduce congestion in the wards.

As per the MTRH Oncology management protocol, patients on chemotherapy routinely receive empiric antimicrobial prophylaxis during their course of treatment. All patients receive co-trimoxazole three times a week and in addition to this, those with AML receive ciprofloxacin and fluconazole on a daily basis. For those who develop a fever with or without neutropenia, blood and urine cultures are required to be drawn from them. For those with neutropenia, this is recommended prior to the initiation of antimicrobial treatment agents.

The initial therapy for patients with fever and neutropenia involves using antibiotics tailored to findings on patient history and physical examination. The choice of antibiotics is usually broad-spectrum targeting both gram-positive and gram-negative organisms.

The first line of treatment involves monotherapy with ceftriaxone and with cefepime or meropenem for those with AML or on induction chemotherapy for ALL. Combination therapy is usually with an aminoglycoside and antipseudomonal penicillin plus or minus a beta-lactamase inhibitor. If the patient continues to have a fever and clinical deterioration after 48 hours, an antibiotic covering anaerobes (metronidazole) is added. If the fever and clinical deterioration persist after 72 hours, an antifungal (fluconazole or amphotericin B if the former is unavailable) is added.

At MTRH, laboratories are organized according to the tests and specimens handled. This includes the biochemistry, haematology and microbiology lab. Blood culture samples collected from various parts of the hospital are usually analysed at the microbiology lab. The laboratory is ISO 15189:2012 certified and it received its accreditation certificate from Kenya Accreditation Service (KENAS) in December 2018. The personnel are all trained and qualified microbiologists who are capable of

handling highly infectious specimens. The tests done at the microbiology lab include blood, urine and stool cultures among others.

The personnel at the lab are responsible for receiving samples, recording them and ensuring the proper handling of the samples. Samples are also analysed and recorded before dispatching the results to the respective wards.

3.3 Target population

All children between the age of 2 months to 15 years, being treated for paediatric malignancies at MTRH SHOE 4 AFRICA paediatric oncology ward during the study period, were eligible for this study.

3.4 Study Population

All children between the age of 2 months and 15 years, admitted at the MTRH SHOE 4 AFRICA paediatric oncology ward, who developed a fever and neutropenia while on treatment with chemotherapy were recruited into the study.

3.4 Sample size calculation

We focused on the aetiology (blood culture isolates results) for sample size computation reasons. In order to be 95% sure that we estimated the true proportion of blood cultures that grew organisms within plus or minus 5% of the estimated value of 29%, from a study done in Egypt by (H. El-Mahallawy et al., 2005) we computed the sample size using a formula for finite population as described by Daniel's (1999).

$$n \geq \frac{N Z^2{}_{\alpha/2} P(1 - P)}{d^2(N - 1) + Z^2{}_{\alpha/2} P(1 - P)}$$

Where;

n was the minimum sample size

N was the estimated population size within the study period (N=110)

P was the estimated prevalence (P = 0.29 based on the proportion of blood cultures that grew organisms in a study done by (H. El-Mahallawy et al., 2005)

$Z_{\alpha/2}$ was the critical value for standard normal distribution at α-level of significance (α = 0.05, $Z_{\alpha/2}$ =1.96)

d is the margin of error (d = 0.05)

Using the formula and defined parameters, the minimum sample size calculated was 109.75 = 110 patients. Therefore, a total of 110 participants were needed to attain the study objectives.

3.5 Sampling technique

In order to get the sampling interval to recruit the participants, the estimated study population within the study period was divided by the sample size required; k=110/110=1

Given the above k of 1, all the participants who met the inclusion criteria were systematically enrolled until the sample size of 110 was reached.

3.6 Eligibility Criteria

3.6.1 Inclusion Criteria

Children admitted to the paediatric oncology ward, while on chemotherapy

- developed fever with a temperature of >38° sustained over one hour.
- had an ANC of <1000 cells/µL

3.6.2 Exclusion criteria

There were no exclusion criteria applicable to this study

3.7 Study Execution

3.7.1 Participant recruitment

The primary investigator (P.I.) recruited a research assistant (R.A.), who was a qualified clinical officer intern who was practising at MTRH Shoe 4 Africa hospital and trained her on the process of identification and recruitment of the study participants for the research study. The principal investigator then proceeded to introduce himself and the research assistant to the staff at the oncology ward. The principal investigator then sensitized the staff at the oncology ward on the study prior to commencing it.

As part of their clinical duty, the nurses in the oncology ward routinely check the vital signs of the admitted patients which include temperature checks every 8 hours and record them in a vitals chart book that is placed in the nursing station. In addition to their routine vital signs assessment, the nurses also check the temperatures of any patient whom the caretakers would report feeling hot to the touch. The nurses would also review the vitals of any patient noted to have a deterioration in their general condition.

For any patient who was found to have a fever, the primary clinician would order a Complete Blood Count (CBC) as part of the normal routine clinical practice, to identify the aetiology of the fever, together with either a blood or urine culture. Once the CBC results were available and the patient was noted to have neutropenia, the PI or the RA was then informed by the staff in the oncology ward to recruit them into the study. The research assistant or the PI also visited the paediatric oncology ward every day to check for patients with a fever from the nursing file chart that contains the patients' daily recorded vitals. After identifying those with a fever the research

assistant or the PI would then proceed to confirm the presence of neutropenia which we defined as an ANC of <1000 cells/µL, from a CBC in the patient's file.

Patients who met the inclusion criteria of fever with a temperature of > 38□C sustained over 1 hour and had an ANC of <1000 cells/µL while on treatment with chemotherapy or after treatment with chemotherapy, were recruited for the study. Informed consent was then sought from the parent or legal guardian and assent from those older than twelve years, to participate in the study.

3.7.2 Data Collection

The PI or RA proceeded to carefully explain to the patients and their parents/guardians the purpose of the study. The PI or RA then provided the parents/guardians with the consent form to go through and answered or explained any questions that they had arising from it prior to them signing it. This was done either at the bedside of the patient or in the procedure room in the paediatric oncology ward, prior to the collection of the blood sample. For those whose blood culture samples had been collected prior to being recruited into the study and were eligible for the study, the PI or RA would follow them up to recruit them.

The patients who were recruited had their clinical and demographic characteristics, which included age, sex, malignancy type and level of ANC extracted from their files and written down into a prepared data collection form by the PI or the RA.

The samples for blood culture were then collected from a peripheral venepuncture site which was either the antecubital fossa of the patient's arm or at the dorsum of the hand, after carefully disinfecting the area by applying an alcohol or 70% spirit swab. About 2-5mls of blood was drawn from the patients for blood culture using a 5cc syringe and a 23G size needle. This was usually done by the PI or RA within 1 hour of consenting or by the hospital phlebotomist. All the blood culture samples were

collected and transported to the MTRH laboratory in a thermostable carrier that maintained temperatures of $< 30^{\circ}$C.

The blood culture specimen collected was then put in the BACTEC Peds Plus blood culture specimen collection bottle, which requires between 1-3mL as per the manufacturer's recommendation and was then labelled. The antibiotics which the patient was on were indicated on the lab request form which was coded for study identification purposes.

The BACTEC Peds Plus culture contains specialised media that can accommodate small-volume samples (<3ml of blood), to optimize the detection of common paediatric pathogens. The reduced amount of broth optimizes the blood to broth ratio and improves the time to detection for the culture of small blood volumes. (Maager & Sally I, n.d.). In a US children's hospital, blood cultures done with blood collected in the BACTEC Peds Plus/F bottle detected organisms with volumes as low as 1 to 1.5 ml. Three millilitres appeared to suffice for the detection of microorganisms. (Lancaster, Friedman, Chiotos, & Sullivan, 2015).

The samples were then transported to the MTRH microbiology lab within 4 hours after collection where they were received by the microbiologist and their details entered in a records book before being incubated. According to the American Society for Microbiology (ASM) and the Clinical Laboratory Standards Institute (CLSI), a time interval of between 2 – 4 hours between blood culture collection and incubation can be considered optimal.

3.8 Blood Culture and Sensitivity Procedure.

3.8.1 Blood Culture Procedure

All the blood culture samples collected were analysed at the MTRH Microbiology lab. The blood culture samples that were received in the lab were incubated in the BACT/ALERT automated blood culture machine. While in the machine, if there is bacterial metabolism from the blood culture, a gas is produced which is sensed by the machine. Once the machine senses the gas a red flag indicator is produced by the machine, meaning the culture is positive for bacterial growth. The sample is then removed and inoculated on three media which are 'Blood agar', Chocolate agar' and MacConkey'. It is then incubated for 18-24 hours, after which the bacterial colonies from the plates were examined and gram staining was done to identify gram-positive and gram-negative bacteria colonies. These colonies were then directly inoculated into the VITEK 2 COMPACT MACHINE which uses specific antibiotic susceptibility testing (AST) and identification (ID) cards to identify the isolates at the species level.

3.8.2 Data Management and Analysis

The PI checked the data which was collected in paper form for completeness and accuracy. He then proceeded to key in and enter the raw data that was in paper form into Microsoft Excel @ database where it was cleaned by excluding all the patients' identifiers, including the name and inpatient number, for maintaining confidentiality and coded by using a generated study number for use. The data analysis was then carried out using STATA version 16. Passwords were utilized to prevent unauthorized access. Data backup was done on hard disks and the cloud (OneDrive).

Descriptive statistics were done to explore and summarize the variables. Categorical variables such as patient clinical and demographic characteristics, bacterial organisms isolates, antimicrobial sensitivity patterns and ANC levels were recorded as frequencies and percentages and plotted in tables to show the distribution.

Both Chi-Square and Fisher's exact test were used to test for association between the outcome variable which was the blood culture results and the patients 'clinical and demographic characteristics which include age, sex, diagnosis, ANC levels and nutritional status. To test for the association of severity of neutropenia (ANC level) with categorical variables, Chi-Square, Fischer's exact and t test were used. Fischer's exact test was used when the variable count was less than 5 and the t test was used when the variable was continuous. A p-value of < 0.05 in all analyses done was considered to be statistically significant.

3.9 Ethical considerations.

Ethical approval to conduct this study was sought and obtained from the Institutional Research Ethics Committee (IREC) of MTRH-Moi University (Appendix 2 and 3). Administrative approval was obtained from the MTRH Chief Executive Officer (CEO), prior to commencing the study (Appendix 1).

Consent was sought from the patients' parents or legal guardians and assent from subjects who are above twelve years of age. In the absence of parents, the patients' legal guardians were identified using the MTRH central form for admissions that is in the patient's file, where the details of the guardians that includes their names and phone numbers are recorded (Appendix 4 and 5).

Prior to obtaining the consent, the nature, reasons for enrolling the patient, benefits and risks of the study were explained in detail to the patients, their parents or

guardians. No incentives or coercion were done for one to take part in the study. None of the identified study participants declined to be enrolled into the study. The clinical care of the participants followed the treatment guidelines used in the unit. Confidentiality was maintained throughout the study. The results of the blood cultures were disseminated back to the primary clinician after documentation, for continuity of patient care.

The findings of the study will be shared with the MTRH management, primary clinicians of the patients at the Shoe 4 Africa paediatric oncology ward and with the Department of Child Health and Paediatrics, Moi University.

The findings of this research will be made available through publishing in journals for the benefit of the larger scientific community.

3.9.1 Ethical Principles Addressed

Respect for Autonomy

The study participants were made aware of their right not to participate or to withdraw from the study at any point that they wished to.

Confidentiality

The principal investigator kept the form that included the patient's identifiers discreet and only shared the coded sheet.

Beneficence

The results of the blood cultures were immediately made available to the primary clinician for prompt care.

Non-maleficence

To prevent or minimize the risk associated with blood culture sample collection, the principal investigator engaged the assistance of a phlebotomist from the MTRH laboratory when needed to assist in the collection of the blood samples.

Justice

Equal and fair treatment was accorded to all participants.

CHAPTER FOUR: RESULTS

In this chapter, the data collected from the study participants in the paediatric

oncology unit from the period of May 2021 to April 2022, is described in detail.

A total of 112 patients with fever and neutropenia who were admitted to the paediatric

oncology ward in S4A, MTRH were identified, and 110 were recruited into the study.

The two who were excluded from the study had either their parents or legal guardians

absent and were being looked after by caretakers who weren't the legally authorised

representatives.
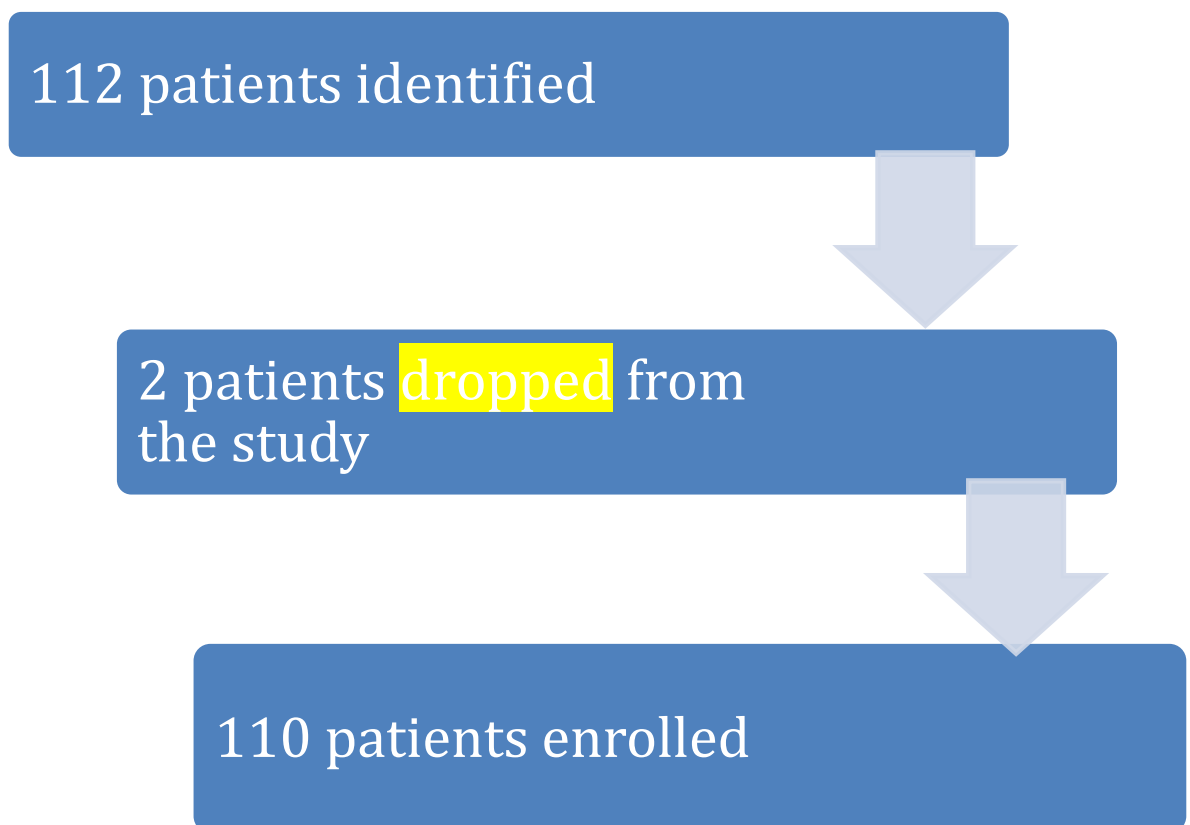
Figure 1: Sequence of Patient Recruitment

4.0 Participant characteristics

Out of the 110 participants who were recruited into the study males were more at 60% while 40% (n = 44) were female. The age of patients ranged from 6 months to 15 years with a mean of 6.3 (SD 3.7) years, (Table 1).

The majority of the patients were between the age bracket of 5 to 10 years at 52.7%. Seventy-one (64.5%) of the participants had haematological malignancies.

Table 1: Patient Characteristics

Characteristics	No. n = 110 (%)
Sex	
Male	66 (60%)
Female	55(40%)
Age category (years)	
0 - 4 years	26 (23.63%)
5 – 10 years	58 (52.7%)
11 – 15 years	26 (23.63%)
Malignancy type	
Haematological malignancies	71 (64.5%)
Solid tumours	39 (35.5%)
ANC	
< 500 cells/µL	85 (77.27%)
> 500 - <1000 cells/µL	25 (22.73%)
Weight-Height Z-score	
Normal (z-score > -2)	105 (95.45%)
Moderate malnutrition (-3 > z-score < -2)	3 (2.72%)
Severe malnutrition (z-score < -3)	2 (1.81%)

The most frequent cancer among study participants was Acute Myeloid Leukaemia (24.54%), followed by, nephroblastoma at (22.7%), Acute Lymphoblastic Leukaemia at (21.81%) and Burkitt lymphoma (15.4%) Table 2.

The majority of the patients in this study were residents from Uasin Gishu county at 13.01% while Kericho, Samburu and Nyamira each had one case. Among the four most common malignancies, 3 patients from Nakuru county had AML while 3 from Bungoma had Acute Lymphoblastic Leukaemia. The majority of the patients with haematological malignancies were from Uasin Gishu county while Busia had the most cases of solid tumours.
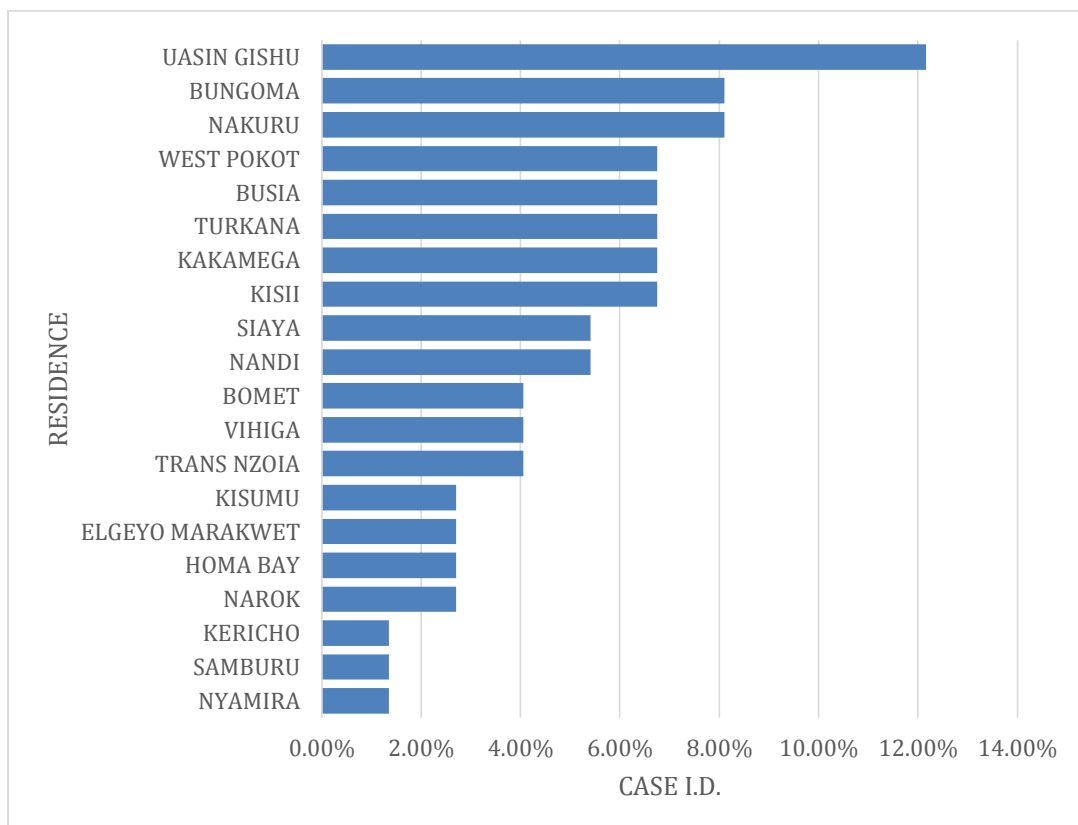
Figure 2: Distribution of malignancies according to the county of residence

Table 2: Distribution of malignancy type

Variable	Category	Frequency	Percentage
Diagnosis	Acute Myeloid Leukemia	27	24.5
	Nephroblastoma	25	22.7
	Acute Lymphoblastic Leukemia	24	21.8
	Burkitt lymphoma	19	17.3
	Retinoblastoma	3	2.7
	Rhabdomyosarcoma	3	2.7
	Nasopharyngeal carcinoma	2	1.8
	Germ cell tumours	2	1.8
	Osteosarcoma	2	1.8
	Ewing sarcoma	1	0.9
	Hodgkin Lymphoma	1	0.9
	Neuroblastoma	1	0.9

Other solid tumours included retinoblastoma and rhabdomyosarcoma each at 2.7% while Ewing sarcoma, Hodgkin lymphoma and neuroblastoma occurred in only one patient each.

Majority of the patients had severe neutropenia (77.27%) with ANC of < 500 cells /μL, those with malnutrition were only 5 with 2 patients having severe malnutrition (1.81%). In comparison between solid tumours and haematological malignancies, there was a significant association between the severity of neutropenia and the type of cancer diagnosis. Patients with haematological malignancies had significantly higher proportions of severe neutropenia (84.5%; p = 0.015) compared to patients with solid tumours Table 3.

Table 3: Level of ANC in relation to Patient Characteristics

| Variable | Category | ANC | | p-value |
		Non-severe	Severe	
Gender	Male	14 (21.1%)	52 (78.8%)	0.642[c]
	Female	11 (25%)	33 (75%)	
Diagnosis	Solid	14 (35.9%)	25 (64.1%)	0.015[c]
	Hematological	11 (15.5%)	60 (84.5%)	
Diagnosis	AML	1 (4.3%)	22 (95.7%)	0.028[c]
	ALL	6 (26.1%)	17 (73.9%)	
	Other Hematological	4 (16%)	21 (84%)	
	Solid tumours	14 (35%)	25 (64.1%)	
W-H z score	Normal	25(23.8%)	80 (76.2)	0.586[f]
	Malnourished	0	5 (100%)	
Bacteria	Gram positive	4(12.1%)	15(45.5%)	0.618[c]
	Gram negative	2(6%)	12(36.4%)	

[c] Chi square
[f] Fischer's Exact
[t] *t* test

When looking at the level of ANC in the different diagnoses, among the patients with AML, a majority of them (95.7%) had severe neutropenia, compared to the other malignancies. This was noted to be statistically significant at (p = 0.028). The majority 60% (n=5) of the undernourished patients were noted to be those with Burkitt lymphoma

4.2 Bacterial Isolates

Of the 110 blood cultures taken, 31 (28.18%); were positive for bacterial growth. Two of the cultures were polymicrobial while the rest were caused by a single bacterial isolate. A total of 33 microorganisms were grown from all the positive blood cultures. Out of the 33 isolates, 57.6% (n = 20) of the microorganisms were gram positive while the rest were gram negative. The most prevalent gram negative organisms were *Escherichia coli* 6 (18.18%) followed by *Klebsiella Pneumoniae* (9.1%). Staphylococcus aureus 5 (15.15%) was the most frequent for the gram-positive organisms, followed by *Enterococcus faecium* 4 (12.1%). Table 4.

Table 4: Bacterial Organisms Isolated

Organism	Species	Frequency	Percentage
Gram positive (20)			
	Staphylococcus aureus	5	15.15
	Enterococcus faecium	4	12.1
	Staphylococcus hominis	3	9.1
	Staphylococcus hemolyticus	3	9.1
	Staphylococcus epidermidis	3	9.1
	Streptococcus parasanguinis	1	3.03
	Enterococcus gallinarum	1	3.03
Gram negative (13)			
	Escherichia coli	6	18.18
	Klebsiella pneumoniae	3	9.1
	Acinetobacter lwoffii	1	3.03
	Pseudomonas aeruginosa	1	3.03
	Pseudomonas strutzei	1	3.03
	Raoultella ominithilyca	1	3.03
Total		**33**	

According to the total number of positive cultures (n = 31), the highest rates of blood stream infections were noted to be in those with ALL, AML and Burkitt lymphoma (25.8%, 19.35%; and 19.35% respectively) compared to those isolated among nephroblastoma (9.7%). Eight (34.8%) isolates were obtained from the total specimen (n = 24) taken from patients with Acute Lymphoblastic Leukaemia (Table 5).

Table 5: Distribution of Bacterial Cultures as per the diagnosis

Diagnosis	No growth	Growth	Total
Acute Myeloid Leukaemia	21 (77.8%)	6 (22.2%)	27
Nephroblastoma	22 (88%)	3 (12%)	25
Acute Lymphoblastic Leukaemia	16 (66.7%)	8 (33.3%)	24
Burkitt lymphoma	13 (68.4%)	6 (31.6%)	19
Retinoblastoma	2 (66.7%)	1 (33.3%)	3
Rhabdomyosarcoma	1 (33.3%)	2 (66.7%)	3
Nasopharyngeal carcinoma	0	2 (100%)	2
Germ cell tumours	2 (100%)	0	2
Ewing sarcoma	1 (100%)	0	1
Hodgkin Lymphoma	0	1 (100%)	1
Neuroblastoma	1 (100%)	0	1
Osteogenic sarcoma	0	2 (100%)	2

Among the blood cultures drawn from patients with solid tumours, the cultures drawn from patients with post-nasal space tumours and osteogenic sarcoma, were all positive for bacterial growth, while the two cultures from germ cell tumours and Ewing sarcoma did not have bacterial growth as shown above in Table 5.

Looking at patient characteristics in relationship to blood stream infections, out of all the 110 blood cultures that were taken, patients with haematological malignancies had more cases of blood stream infections (29.6%) compared to patients with solid tumours (25.6%). However, this was not statistically significant (p = 0.661). Table 6

Table 6: Patient characteristics in relation to Bacterial growth

Characteristics	Positive culture N = 31	Negative culture N = 79	p-value
Sex			
Male	21 (67.74%)	34 (43.04%)	0.020[c]
Female	10 (32.26%)	45 (56.96%)	
Cancer type			
Haematologic	21 (67.74%)	50 (63.29%)	0.661[c]
Solid tumours	10 (32.26%)	29 (36.71%)	
Age			
< 5 yrs.	5 (16.13%)	21 (26.58%)	0.154[c]
5-10 yrs.	15 (48.39%)	43 (54.43%)	
>10 yrs.	11 (35.48%)	15 (18.99%)	
ANC Levels			
< 500 cells/μL	25 (80.65%)	60 (75.95%)	0.597[c]
>500-<1000 cells/μL	6 (19.35%)	19 (24.05%)	
W-H Z score			
Normal	30 (28.6%)	75 (71.4%)	>0.99 [c]
Malnourished	1 (20%)	4 (80%)	

[c] Chi square

Univariate analysis demonstrated greater bacterial growth in the male participants compared to their female counterparts (67.74%; p = 0.02). The age bracket of 5-10 years also had the most growth rate 48.39%. There was no association seen between malnutrition and bacterial growth.

Table 7: Bacterial isolates in relation to patient diagnosis

Bacterial isolates	AML	Nephroblastoma	ALL	BL	RMS	Nasopharyngeal ca.	HL	Osteosarcoma	RB
Gram positive									
Staphylococcus aureus	1(14.3)		1(12.5)	1(14.3)		1(50)			1(100)
Enterococcus faecium		1(33.3)		1(14.3)	1(50)		1(100)		
Staphylococcus hominis			1(12.5)	1(14.3)	1(50)				
Staphylococcus hemolyticus	1(14.3)	1(33.3)	1(12.5)						
Staphylococcus epidermidis	1(14.3)	1(33.3)		1(14.3)					
Streptococcus parasanguinis			1(12.5)						
Enterococcus gallinarum	1(14.3)								
Gram negative									
Escherichia coli	3(42.9)		1(12.5)	1(14.3)				1(50)	
Klebsiella pneumoniae			1(12.5)	2(28.6)					
Pseudomonas aeruginosa						1(50)			
Pseudomonas strutzei			1(12.5)						
Acinetobacter lwoffii								1(50)	
Raoultella ominithilyca			1(12.5)						

ALL, Acute Lymphoblastic Leukaemia; AML, Acute Myeloid Leukaemia; BL, Burkitt Lymphoma;

From the table above, there is no specific diagnosis that we could point to be associated with a specific organism

4.2 Antimicrobial Sensitivity Patterns

All the cultured bacterial isolates were found to be resistant to benzylpenicillin and ampicillin at 100%. Most organisms were also noted to have high resistance to both Amoxicillin-clavulanic acid and ceftriaxone at 87.5% and 83.3% respectively. High resistance rates were also observed towards, levofloxacin (73.7%), ceftazidime (75%) and trimethoprim/sulfamethoxazole (87.5%)

However, all the bacterial species were found to be sensitive to both linezolid and vancomycin. High sensitivity was also observed towards meropenem with rates at 90.9%.

Table 8:Antimicrobial Sensitivity Patterns

Diagnosis	Sensitive	Resistant	Total
Ampicillin	0	12 (100%)	12
Benzylpenicillin	0	17 (100%)	17
Gentamicin	10 (35.7%)	18 (64.3%)	28
Levofloxacin	5 (26.3%)	14 (73.7%)	19
Linezolid	15 (100%)	0	15
Vancomycin	18 (100%)	0	18
Amikacin	7 (63.6%)	4 (36.4%)	11
Amoxiclav	1 (12.5%)	7 (87.5%)	8
Nitrofurantoin	16 (76.2%)	5 (23.8%)	21
Rifampicin	9 (75%)	3 (25%)	12
Clindamycin	6 (54.6%)	5 (45.4%)	11
Meropenem	10 (90.9%)	1 (9.1%)	11
Cefepime	3 (42.9%)	4 (57.1%)	7
Ceftriaxone	1 (16.7%)	5 (83.3%)	6
Ceftazidime	1(25%)	3(75%)	4
TMP/SMX	1(12.5%)	7(87.5%)	8
Piperacillin/tazobactam	2 (40%)	3 (60%)	5

Amoxiclav, amoxicillin-clavulanic acid; TMP/SMX, trimethoprim/sulfamethoxazole

The enterococci showed high resistance to all the antibiotics tested except linezolid and vancomycin. All the *Staphylococcus aureus* species were methicillin resistant. However, most of the gram-positive bacteria were sensitive towards nitrofurantoin with only *E. faecium* and *S. hemolyticus* having resistance rates of 50% and 33.3% respectively. The gram-positive organisms tested on rifampicin showed low resistance rates ranging from 25% to 50%.

As for the gram-negative bacteria, *E. coli* was resistant to all cephalosporins tested, whereas *Klebsiella pneumoniae,* showed resistance to ampicillin and gentamicin but was sensitive to amikacin, meropenem and cefepime. All were sensitive to linezolid and vancomycin. *Pseudomonas aeruginosa* was resistant to amikacin, meropenem and cefepime at 100% but was noted to be sensitive to gentamicin, linezolid and vancomycin.

Table 9: Summary of Antibiotic Sensitivity and Resistance

Bacterial organisms	Antibiotics	
	Sensitive	Resistant
E. coli	Linezolid; vancomycin; meropenem	Ampicillin; gentamicin; amikacin; amoxiclav; nitrofurantoin, piperacillin-tazobactam
K. pneumoniae	Linezolid, vancomycin, amikacin, meropenem, cefepime	Ampicillin; gentamicin; amoxiclav, nitrofurantoin; ceftriaxone; piperacillin-tazobactam
S. aureus	Linezolid, vancomycin, nitrofurantoin,	Benzylpenicillin, gentamicin, levofloxacin, rifampicin, clindamycin
E. faecium	Linezolid; vancomycin;	Ampicillin, benzylpenicillin; gentamicin; levofloxacin; nitrofurantoin
S. hominis	Linezolid; vancomycin; nitrofurantoin; rifampicin; clindamycin	Benzylpenicillin, gentamicin, levofloxacin,
S. hemolyticus	Linezolid, vancomycin	Benzylpenicillin; gentamicin; levofloxacin; nitrofurantoin; rifampicin; clindamycin

Table 10: Antimicrobial sensitivity as per organism

Organism	Ampicillin	Benzylpenicillin	Gentamicin	Levofloxacin	Linezolid	Vancomycin	Amikacin	Amoxiclav	Nitrofurantoin	Rifampicin	Clindamycin	Meropenem	Cefepime	Ceftriaxone	Piperacillin-tazobactam
E. coli (n=6)			3 (50%)				3 (50%)		3 (50%)			5/5 (100%)			1/3 (33.3%)
S. aureus (n=5)			2 (40%)	1 (20%)	4/4 (100%)	5 (100%)			4/4 (100%)	3/4 (75%)	1/4 (25%)				
E. faecium (n=4)					3 (100%)	4 (100%)			2 (50%)						
S. hominis (n=3)				1 (33.3%)	3 (100%)	3 (100%)			3 (100%)	3 (100%)	3 (100%)				
S. hemolyticus (n=3)			1 (33.3%)	1 (33.7%)	2/2 (100%)	3 (100%)			2 (66.7%)	2 (66.7%)	2 (66.7%)				
S. epidermidis (n=2)			1 (50%)	1 (50%)	2 (100%)	2 (100%)			2 (100%)	1 (50%)					
K. pneumoniae (n=2)							2 (100%)	1 (50%)				2 (100%)	2 (100%)		1 (50%)
A. lwoffii (n=1)				1 (100%)								1 (100%)	1 (100%)	1 (100%)	
E. gallinarum (n=1)					1 (100%)	1 (100%)									
P. aeruginosa (n-1)			1 (100%)												
P. strutzei (n=1)			1 (100%)				1 (100%)					1 (100%)			
R. ominithilyca (n=1)			1 (100%)				1 (100%)		1 (100%)			1 (100%)			

CHAPTER FIVE: DISCUSSION

This is the first study on bacterial isolates in children on treatment for cancer with febrile neutropenia in MTRH. The study set out to describe the clinical and demographic characteristics of children with febrile neutropenia on treatment for cancer at MTRH and to identify the common bacterial isolates associated with it.

5.1 Demographic and clinical characteristics of the population and Factors associated with febrile neutropenia.

Most of the patients in this study were below the age of 10. This was also observed in studies done in Yemen, Ethiopia and at MTRH in Kenya by Ba-Saddik, Mohammed and Mostert respectively (Ba-Saddik, 2013; Mohammed et al., 2019; Mostert et al., 2012). The bulk of the participants falling into the age bracket of less than 10 years may be attributed to the fact that the peak incidence for most malignancies such as acute leukaemias, lymphomas and nephroblastoma is usually below the age of 10 years.

In this study, it was also noted that bacterial infection occurred more among children below the age of 10 years. This was a similar finding to a study by Hanzelina, done in Indonesia by who noted that bacterial infection occurred more in patients below the age of 10 years (52%) (Hanzelina et al., 2022). The higher rate of BSI in this population may be due to the fact that this population comprised the majority of patients in our set up and the peak incidence for most leukaemias. The higher incidence of BSI in this population could be explained by the fact that leukaemias mainly affect the bone marrow and lead to early onset neutropenia and subsequently a higher rate infection.

This study noted that in children with febrile neutropenia, the most common malignancies were acute leukaemias (AML and ALL), nephroblastoma and Burkitt lymphoma, from the enrolled participants. This was similar to studies done in India by Babu et al, in South Africa by Mvalo et al and Uganda by Lubwama et al on children with febrile neutropenia, where the most common malignancies were acute lymphoblastic leukaemia, non-Hodgkins lymphoma, nephroblastoma and acute myeloblastic leukaemia (Kg. Babu et al., 2016; Lubwama et al., 2019; Mvalo et al., 2018). Haematological malignancies have more prevalence of neutropenia compared to solid tumours and this can be explained by the fact that in haematological malignancies, the underlying malignancy can directly invade the bone marrow leading to a disruption in the production of blood cells and components or cause the production of malignant cells. Thus, in this study, haematological malignancies were noted to be associated with severe neutropenia and consequently had more bacterial growth when compared to patients with solid tumours. Moreover, in this study, BSI were noted to occur more in patients with severe neutropenia when compared to those with mild and moderate neutropenia. This was supported by studies done in Turkey by Kara et al, that noted bacteraemia was associated with ANC levels of $< 100/\text{mm}^3$ and in a study in Uganda by Lubwama et al, that also reported that out of 23 cultures, 16 were from patients with ANC of $< 100\text{cells}/ \mu L$. (Kara et al., 2019; Lubwama et al., 2019). The disruption in the production of blood cells, including WBCs, which form an important part of cell-mediated immunity, predisposes the patients to infections due to a blunted immune response. Additionally, the leukocytes in patients with AML and ALL are dysfunctional since they are malignant and mostly blast cells (immature), hence are not able to respond adequately to bacterial invasion. This fact was also supported in a study by Davis & Wilson et al, which stated that the

haematological malignancies invade the bone marrow and cause chemotactic and phagocytic defects in neutrophils, impairing their ability to reach the site of infection and contain it (Davis & Wilson, 2020b). In this study, it was also noted that the most common malignancy type among those with febrile neutropenia was acute myeloid leukaemia. This could be due to the fact that the induction chemotherapy regimen for AML is more intense when compared to that of other malignancies. It involves two induction courses with cytarabine and doxorubicin which are associated with bone marrow suppression, compared to vincristine and L-asparaginase in ALL which are less myelosuppressive. Thus, leading to a higher incidence of febrile neutropenia in patients with AML. This fact was supported by Calitri et al, in a study which noted that haematological malignancies especially AML require more intensive myeloablative chemotherapy regimens that are associated with severe myelosuppression, leading to a disruption in the normal haematopoiesis (Calitri et al., 2018). Therefore, due to its intense induction treatment, AML is associated with severe and prolonged neutropenia when compared to other haematological malignancies.

5.3 The Bacterial isolates

From this study, the bacterial growth rate from the blood cultures collected was 28.18%. This is comparable to that of studies done in Colombia and India by Bello-Suarez et al and Bothra et al where the documented bacterial growth rate was 29.23% (92/315) and 27.8% from 155 blood culture samples collected respectively (Bello-Suárez AK et al., 2022; Bothra et al., 2013) and also from a study in Egypt by H. El-Mahallaway, that had a growth rate of 29% from 1135 blood cultures (H. El-Mahallawy et al., 2005). Our findings are comparable to the estimated bacterial growth rate according to a study by Feld et al, which reported that bloodstream infections (bacteraemia) account for approximately 25-30% of febrile episodes in patients with febrile neutropenia (Feld, 2008). This was also supported by the Infectious Disease Society of America (IDSA), which stated that bacteraemia occurs in 10-25% of patients with febrile neutropenia, with most infections occurring in the setting of severe neutropenia and by Klastersky et al in their study who stated that overall bacteraemia can be detected in about 20% of patients with febrile neutropenia (Klastersky et al., 2016). This could be due to the fact that not all episodes of febrile neutropenia are as a result of bacterial infection. The incidence of invasive fungal infections in patients with febrile neutropenia ranges from 2-36% while viraemia has been reported to range from about 15-49% in patients with FN and in some cases in the absence of a clinical or microbiological evidence of infection, FN is marked as a fever of unknown origin (Cennamo et al., 2021). However, the rate of bacteraemia in this study was more than what was observed in a study done by af Sanderberg et al in Sweden where they had a growth rate of 16% (40/251 blood cultures) (af Sandeberg

et al., 2017). The difference in the growth rates between the study in Sweden and this study could be due to the fact that in Sweden, empirical management of febrile neutropenia involved the use of cephalosporins and carbapenems as well as antiviral and antifungal which could explain the lower growth rate, since not every neutropenic episode is caused by bacteria.

Gram-positive bacteria were more frequently isolated than gram-negative bacteria in this study. This was also the case seen in different studies done in Jordan by al Omar et al, in Qatar by Al-Mulla et al and in South Africa by Mvalo et al in which all reported a predominance of gram positive bacteraemia compared to gram negative bacteria (50% vs. 20%; 55.2% vs. 48.2% and 49.1% vs. 41.6% respectively) (al Omar et al., 2013; Al-Mulla et al., 2014; Mvalo et al., 2018). Although gram negative bacteria were initially predominantly associated with bacteraemia in febrile neutropenic patients, it can be speculated that over time, the increase in the use of efficient antimicrobial prophylaxis with agents such as fluoroquinolones, targeting gram-negative bacteria has led to the emergence of gram positive bacteria as the dominant species associated with bacteraemia in febrile neutropenic patients. This was supported by a study done by Johannsen et al, that stated that the prophylactic use of sulfamethoxazole/trimethoprim and fluoroquinolones has led to the emergence of a more resistant gram positive flora (Johannsen et al., 2013b). Other reasons include severe neutropenia, the extensive use of indwelling invasive devices such as CVADs and mucosal barrier defects due to intensive chemotherapy regimens resulting in mucositis have been associated with increased risk of infection by gram-positive bacteria, that normally colonize the gastrointestinal tract and oropharyngeal mucosa and furthermore, according to another study *Streptococci* and Coagulase Negative Staphylococcus (CONS) reside in the mucosal barriers, therefore, chemotherapy

induced mucositis is associated with early onset gram positive bacteraemia (van Vliet et al., 2010). In addition to this, a study reported that 70% of the blood cultures that are positive in the setting of FN are reported to be gram positive bacteria (de Naurois et al., 2010).

From this study out of the 31 positive blood cultures, the most common gram positive organisms seen were *Staphylococcus aureus* at 15.15%, followed by *Enterococcus faecium*, while the most common gram negative bacteria were *E. coli* followed by *K. pneumoniae*. Similar to the findings in this study, studies done in India and Ghana, found that the most common gram-positive and gram-negative bacteria isolated were *Staphylococcus aureus* and *E. coli* (Kg. Babu et al., 2016; Bothra et al., 2013; Oberoi et al., 2017). This slightly differed from the findings in studies done in Uganda and South Africa which had the most common gram positive bacteria being CONS and Viridans group Streptococcus however, both found that the most common gram negative bacteria were similar to those in this study.

The frequency in the occurrence of bacterial organisms varies across different centres. However, literature from several studies conducted recently in different parts of the world has shown the most common gram positive organisms to be *Staphylococci* species (MRSA and CONS) while the most common gram negative species have been reported to *be E. coli* and *Klebsiella pneumoniae* (Kar et al., 2017).

These findings were also supported by a meta-analysis which reported findings from 17 different studies worldwide that showed *E. coli* was the dominant pathogen constituting a median of 21% of all BSI strains in the 17 studies. It was followed by *Klebsiella pneumoniae* with a median of 11%. The common gram positive species were *Staphylococci* species with the rate of *S. aureus* varying from 1-13% and that of CONS ranging from 2-42% (Blennow & Ljungman, 2016a).

Most of the gram-negative organisms showed high resistance to cephalosporins which are usually the first line treatment for patients with febrile neutropenia in accordance with the paediatric oncology protocol in our set up which recommends the use of cefepime or ceftazidime as monotherapy. However, they showed great sensitivity towards carbapenems, which is similar to what was observed in Uganda and South Africa in studies by (Mvalo et al., 2018) and (Lubwama et al., 2019).

The increasing resistance to cephalosporins seen in this study was also observed in a study in Lebanon whereby 29.3% of the total blood stream infections were caused by third generation cephalosporin resistant gram-negative bacteria (Moghnieh et al., 2015). Additionally, another study stated that many centres no longer considered the use of ceftazidime a third generation cephalosporin as a suitable monotherapy in patients with FN due to its low activity against many gram-positive microorganisms such as streptococci (Virizuela et al., 2015).

The reason could be due to the frequent or overuse of cephalosporins as first line treatment for infections due to their broad spectrum antibiotic coverage. According to a study in Egypt, it was stated that increased consumption of broad spectrum antibiotics; namely extended-spectrum cephalosporins, beta-lactam-beta-lactamase inhibitor combinations, carbapenems, fluoroquinolones, and aminoglycosides led to a significant rise in multidrug resistant organisms (Hadir A. El-Mahallawy et al., n.d.).

In this study, Meropenem, Vancomycin and Linezolid were all shown to have the least resistance with high sensitivity levels of 90.9%, 100% and 100% respectively. This is probably due to the fact that they are usually reserved for second line use and are mostly indicated in cases of severe infections pending blood culture results.

A multiple drug resistant (MDR) isolate is defined as an organism that is resistant to at least one antibiotic in three or more antimicrobial classes, an extensively drug resistant (XDR) isolate is defined as being resistant to one agent in all but two or fewer antimicrobial categories and a pan-drug resistant isolate is one that is resistant to all agents in all antimicrobial categories (Magiorakos et al., 2012).

Most of the organisms in our study were noted to be multiple drug resistant including the ESKAPE pathogens (*E. faecium, S. aureus, K. pneumoniae, A. baumannii, P. aeruginosa and Enterobacter spp*). Despite most of the organisms being multi-drug resistant and all the *Staphylococcus spp* being methicillin resistant, all were found to be susceptible to Linezolid, Vancomycin and Rifampicin. In Iran, a study also noted that all of the *Staphylococcus* organisms were resistant to methicillin (Karimi et al., 2018).

In this study, most bacteria were found to have resistance to levofloxacin with high resistance seen with *E. faecium* and *E. gallinarum* and also with *S. aureus*, *S. hominis* and *S. hemolyticus*. A study done in Jordan recommended the use of piperacillin-tazobactam as an empirical monotherapy for patients with febrile neutropenia since it was noted that none of the gram negative bacteria was resistant to it. However, in this study, it was noted that both *E. coli* and *Klebsiella* were resistant to piperacillin-tazobactam (Ahmed Hussein et al., 2016).

CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATION

6.1 Conclusions

I. Majority of the study participants were between the age of 5 and 10 years, and the most common malignancies among those with febrile neutropenia were AML (25.54%,) Nephroblastoma (22.7%) and ALL (21.81%).

II. Haematological malignancies especially, AML, was noted to be associated with febrile neutropenia and BSI. Age, nutritional status and sex were not found to be significantly associated with febrile neutropenia.

III. Gram positive bacteria were more commonly isolated than gram negative bacteria. The most common organisms isolated were; *E. coli* followed by *Staph aureus* and *E. faecium*; with high resistance rates to benzylpenicillin, ampicillin and cephalosporins. All isolates demonstrated sensitivity to linezolid, vancomycin and meropenem.

6.2 Recommendations

- Empirical antimicrobial management of febrile neutropenia should target gram positive bacteria; first line treatment should be with meropenem as monotherapy or in combination with an aminoglycoside such as amikacin; linezolid or vancomycin should be reserved for second line treatment indicated in patients with meropenem resistant organisms or if blood culture results show sensitivity towards them.

- Early initiation of appropriate antimicrobial treatment, supportive care, with emphasis on aggressive infection prevention strategies such as isolation, and strict hand washing are recommended for patients with haematological malignancies, especially those with AML.

6.3 Study limitations

There was a lack of standardization of disks used in the antibiotic sensitivity test. Different antibiotic disks were tested for different isolates.

In some instances, there would be a delay in the incubation of the collected blood samples from the time of collection in the Oncology ward, however, they were all stored in a thermostable specimen collection box and kept at room temperature of < 30°C after collection.

6.4 Study strengths

This being a pioneer study looking at bacterial aetiology of febrile neutropenia at the MTRH paediatric oncology centre, it sets a precedence for further research on febrile neutropenia in children on treatment for cancer.

REFERENCES

af Sandeberg, M., Johansson, E., Wettergren, L., Björk, O., Hertting, O., & Nilsson, A. (2017). Antibiotic use during infectious episodes in the first 6 months of anticancer treatment—A Swedish cohort study of children aged 7–16 years. *Pediatric Blood and Cancer*, *64*(7). https://doi.org/10.1002/pbc.26397

Ahmad, M. N., Pillinger, K. E., & Shahid, Z. (2019). Prophylaxis and management of infectious complications after hematopoietic cell transplantation. *Hematopoietic Cell Transplantation for Malignant Conditions*, 349–367. https://doi.org/10.1016/B978-0-323-56802-9.00025-0

Ahmed Hussein, A., Al-Antary, E. T., Najjar, R., Al-Zaben, A., & Frangoul, H. (2016). Incidence and risk factors of bacterial infections in children following autologous hematopoietic stem cell transplantation: Single-center experience from Jordan. *Pediatr Transplantation*, *20*, 683–686. https://doi.org/10.1111/petr.12727

al Omar, S., Nazer, L., & Alkayed, K. (2013). A Prospective Study of Febrile Neutropenia in Pediatric Cancer Patients in Jordan. *Journal of Pediatric Hematology/Oncology*, *35*(8), 614–617. https://doi.org/10.1097/MPH.0b013e31829f3480

Al-Mulla, N., Elshafie, S. S., Janahi, M., Al-Nasser, A., Chandra, P., & Taj-Aldeen, S. J. (2014). Bacterial bloodstream infections and antimicrobial susceptibility pattern in pediatric hematology/oncology patients after anticancer chemotherapy. *Infection and Drug Resistance*, *7*, 289–299. https://doi.org/10.2147/IDR.S70486

Alp, S., & Akova, M. (2013). Management of febrile neutropenia in the era of bacterial resistance. *Therapeutic Advances in Infectious Disease*, *1*(1), 37. https://doi.org/10.1177/2049936113475610

Andersen, C. L., Tesfa, D., Siersma, V. D., Sandholdt, H., Hasselbalch, H., Bjerrum, O. W., Felding, P., Lind, B., Olivarius, N. de F., & Palmblad, J. (2016). Prevalence and clinical significance of neutropenia discovered in routine complete blood cell counts: a longitudinal study. *Journal of Internal Medicine*, *279*(6), 566–575. https://doi.org/10.1111/JOIM.12467

Babu, K. G., Lokanatha, D., Lakshmaiah, K. C., Babu, M. C. S., Jacob, L. A., Bhat, G. R., Vardhana, H., Sinha, M., Vijaykumar, B. R., Sumati, B. G., & Jayshree, R. S. (2016). Bloodstream infections in febrile neutropenic patients at a tertiary cancer institute in South India: A timeline of clinical and microbial trends through the years. *Indian Journal of Medical and Paediatric Oncology : Official Journal of Indian Society of Medical & Paediatric Oncology*, *37*(3), 174. https://doi.org/10.4103/0971-5851.190352

Babu, Kg., Lokanatha, D., Lakshmaiah, K., Suresh Babu, M., Jacob, L., Bhat, G., Vardhana, H., Sinha, M., Vijaykumar, B., Sumati, B., & Jayshree, R. (2016). Bloodstream infections in febrile neutropenic patients at a tertiary cancer institute in South India: A timeline of clinical and microbial trends through the years. *Indian Journal of Medical and Paediatric Oncology*. https://doi.org/10.4103/0971-5851.190352

Badr, M., Hassan, T., Sakr, H., Karam, N., Rahman, D. A., Shahbah, D., Zakaria, M., & Fehr, S. (2016). Chemotherapy-induced neutropenia among pediatric cancer patients in Egypt: Risks and consequences. *Molecular and Clinical Oncology*, *5*(3), 300–306. https://doi.org/10.3892/MCO.2016.957

Bansal, D., Davidson, A., Supriyadi, E., Njuguna, F., Ribeiro, R. C., L Kaspers, G. J., & Gertjan L Kaspers, C. J. (n.d.). *Pediatric Blood & Cancer SIOP PODC*

adapted risk stratification and treatment guidelines: Recommendations for acute myeloid leukemia in resource-limited settings. https://doi.org/10.1002/pbc.28087

Ba-Saddik, I. A. (2013). Childhood cancer in Aden, Yemen. *Cancer Epidemiology*, *37*(6), 803–806. https://doi.org/10.1016/J.CANEP.2013.10.001

Bauer, J., Jürgens, H., & Frühwald, M. C. (2011). Important Aspects of Nutrition in Children with Cancer 1. *Adv. Nutr*, *2*, 67–77. https://doi.org/10.3945/an.110.000141

Blennow, O., & Ljungman, P. (2016a). The challenge of antibiotic resistance in haematology patients. *British Journal of Haematology*, *172*(4), 497–511. https://doi.org/10.1111/BJH.13816

Blennow, O., & Ljungman, P. (2016b). The challenge of antibiotic resistance in haematology patients. *British Journal of Haematology*, *172*(4), 497–511. https://doi.org/10.1111/BJH.13816

Boccia, R., Glaspy, J., Crawford, J., & Aapro, M. (2022). Chemotherapy-Induced Neutropenia and Febrile Neutropenia in the US: A Beast of Burden That Needs to Be Tamed? *The Oncologist*, *27*(8), 625. https://doi.org/10.1093/ONCOLO/OYAC074

Bos, M. M. E. M., Smeets, L. S., Dumay, I., & de Jonge, E. (2013). Bloodstream infections in patients with or without cancer in a large community hospital. *Infection 2013 41:5*, *41*(5), 949–958. https://doi.org/10.1007/S15010-013-0468-1

Bothra, M., Seth, R., Kapil, A., Dwivedi, S. N., Bhatnagar, S., & Xess, I. (2013). Evaluation of predictors of adverse outcome in febrile neutropenic episodes in pediatric oncology patients. *Indian Journal of Pediatrics*, *80*(4), 297–302. https://doi.org/10.1007/S12098-012-0925-3

Calitri, C., Ruberto, E., & Castagnola, E. (2018). Antibiotic prophylaxis in neutropenic children with acute leukemia: Do the presently available data really support this practice? In *European Journal of Haematology* (Vol. 101, Issue 6). https://doi.org/10.1111/ejh.13162

Cecinati, V., Principi, N., Brescia, L., & Esposito, S. (2014). Antibiotic prophylaxis in children with cancer or who have undergone hematopoietic cell transplantation. *European Journal of Clinical Microbiology & Infectious Diseases : Official Publication of the European Society of Clinical Microbiology*, *33*(1), 1–6. https://doi.org/10.1007/S10096-013-1932-7

Cennamo, F., Masetti, R., Largo, P., Argentiero, A., Pession, A., & Esposito, S. (2021). *children Update on Febrile Neutropenia in Pediatric Oncological Patients Undergoing Chemotherapy*. https://doi.org/10.3390/children8121086

Chan, A., Lee, C. P., Chiang, J., & Ng, R. (2013). Breakthrough febrile neutropenia and associated complications among elderly cancer patients receiving myelosuppressive chemotherapy for solid tumors and lymphomas. *Supportive Care in Cancer : Official Journal of the Multinational Association of Supportive Care in Cancer*, *21*(8), 2137–2143. https://doi.org/10.1007/S00520-013-1768-9

Chaudhuri, J., Biswas, T., Datta, J., Sabui, T. K., Chatterjee, S., Ray, S., Raychaudhuri, D., Mandal, K., Chatterjee, K., & Chakraborty, S. (2016). *Evaluation of malnutrition as a predictor of adverse outcomes in febrile neutropenia associated with paediatric haematological malignancies*. https://doi.org/10.1111/jpc.13233

Classen, A. Y., Henze, L., von Lilienfeld-Toal, M., Maschmeyer, G., Sandherr, M., Durán Graeff, L., Alakel, N., Christopeit, M., Krause, S. W., Mayer, K., Neumann, S., Cornely, O. A., Penack, O., Weißinger, F., Wolf, H.-H., Jörg, &, & Vehreschild, J. (n.d.). *Primary prophylaxis of bacterial infections and*

Pneumocystis jirovecii pneumonia in patients with hematologic malignancies and solid tumors: 2020 updated guidelines of the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology (AGIHO/DGHO). https://doi.org/10.1007/s00277-021-04452-9/Published

Cristina Stefan, D. (2015). Patterns of distribution of childhood cancer in Africa. *Journal of Tropical Pediatrics*, *61*(3), 165–173. https://doi.org/10.1093/TROPEJ/FMV005

Davis, K., & Wilson, S. (2020a). Febrile neutropenia in paediatric oncology. In *Paediatrics and Child Health (United Kingdom)* (Vol. 30, Issue 3, pp. 93–97). Churchill Livingstone. https://doi.org/10.1016/j.paed.2019.12.002

Davis, K., & Wilson, S. (2020b). Febrile neutropenia in paediatric oncology. *Paediatrics and Child Health*, *30*(3), 93–97. https://doi.org/10.1016/J.PAED.2019.12.002

de Naurois, J., Novitzky-Basso, I., Gill, M. J., Marti, F. M., Cullen, M. H., & Roila, F. (2010). Management of febrile neutropenia: ESMO Clinical Practice Guidelines. *Annals of Oncology*, *21*(SUPPL. 5), v252–v256. https://doi.org/10.1093/annonc/mdq196

DeBraud, F., Munzone, E., Nolè, F., de Pas, T., Biffi, R., Brienza, S., & Aapro, M. S. (1998). Synergistic activity of oxaliplatin and 5-fluorouracil in patients with metastatic colorectal cancer with progressive disease while on or after 5-fluorouracil. *American Journal of Clinical Oncology: Cancer Clinical Trials*, *21*(3), 279–283. https://doi.org/10.1097/00000421-199806000-00015

Egan, G., Robinson, P. D., Martinez, J. P. D., Alexander, S., Ammann, R. A., Dupuis, L. L., Fisher, B. T., Lehrnbecher, T., Phillips, B., Cabral, S., Tomlinson, G., & Sung, L. (2019). Efficacy of antibiotic prophylaxis in patients with cancer and hematopoietic stem cell transplantation recipients: A systematic review of randomized trials. *Cancer Medicine*, *8*(10), 4536. https://doi.org/10.1002/CAM4.2395

El-Mahallawy, H. A., Hassan, S. S., El-Wakil, M., & Moneer, M. M. (2016). Bacteremia due to ESKAPE pathogens: An emerging problem in cancer patients. *Journal of the Egyptian National Cancer Institute*, *28*(3), 157–162. https://doi.org/10.1016/j.jnci.2016.05.002

El-Mahallawy, H., Sidhom, I., Ali El-Din, N. H., Zamzam, M., & El-Lamie, M. M. (2005). Clinical and microbiologic determinants of serious bloodstream infections in Egyptian pediatric cancer patients: a one-year study. *International Journal of Infectious Diseases*, *9*, 43–51. https://doi.org/10.1016/j.ijid.2003.11.010

Fedhila, F., Ahmed, S. ben, Jbebli, E., Mezghani, F., Haddad, S., Rhayem, S., & Khemiri, M. (2022). Neutropénie fébrile chimio-induite dans une unité d´oncologie pédiatrique tunisienne. *PAMJ. 2022; 42:34*, *42*(34). https://doi.org/10.11604/PAMJ.2022.42.34.28176

Feld, R. (2008). Bloodstream infections in cancer patients with febrile neutropenia. *International Journal of Antimicrobial Agents*, *32*(SUPPL. 1), S30–S33. https://doi.org/10.1016/J.IJANTIMICAG.2008.06.017

Freifeld, A. G., Bow, E. J., Sepkowitz, K. A., Boeckh, M. J., Ito, J. I., Mullen, C. A., Raad, I. I., Rolston, K. v., Young, J. A. H., & Wingard, J. R. (2011). Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. *Clinical Infectious Diseases*, *52*(4). https://doi.org/10.1093/CID/CIR073

Gentile, R. C., Shukla, S., Shah, M., Ritterband, D. C., Engelbert, M., Davis, A., & Hu, D. N. (2014). Microbiological spectrum and antibiotic sensitivity in endophthalmitis: A 25-year review. *Ophthalmology*, *121*(8), 1634–1642. https://doi.org/10.1016/j.ophtha.2014.02.001

Girmenia, C., Bertaina, A., Piciocchi, A., Perruccio, K., Algarotti, A., Busca, A., Cattaneo, C., Maria Raiola, A., Guidi, S., Paola Iori, A., Candoni, A., Irrera, G., Milone, G., Marcacci, G., Scimè, R., Musso, M., Cudillo, L., Sica, S., Castagna, L., … San Matteo, P. (n.d.). Rozzano and 19 Fondazione IRCCS Istituto Nazionale dei Tumori, University of Milan. *Humanitas Cancer Center*, *18*. https://doi.org/10.1093/cid/cix690

Gupta, S., Howard, S. C., Hunger, S. P., Antillon, F. G., Metzger, M. L., Israels, T., Harif, M., & Rodriguez-Galindo, C. (2015). Treating Childhood Cancer in Low- and Middle-Income Countries. *Disease Control Priorities, Third Edition (Volume 3): Cancer*, 121–146. https://doi.org/10.1596/978-1-4648-0349-9_CH7

Hadir A. El-Mahallawy, M., 1, * Mohamed El-Wakil, M., 2, ** Manar M. Moneer, M., & 3 and Lobna Shalaby, M. (n.d.). *Antibiotic Resistance Is Associated With Longer Bacteremic Episodes and Worse Outcome in Febrile Neutropenic Children With Cancer*. Retrieved October 14, 2019, from https://scholar.cu.edu.eg/sites/default/files/medial_sector/files/22926_ftp.pdf

Hanzelina, H., Widnyana, A. A. N. K. P., Windiani, I. G. A. T., Karyana, I. P. G., Ariawati, N. K., & Mahalini, D. S. (2022). Malnutrition as Risk Factor for Febrile Neutropenia in Children with Acute Lymphoblastic Leukemia. *Open Access Macedonian Journal of Medical Sciences*, *10*(B), 681–685. https://doi.org/10.3889/oamjms.2022.8448

Hughes, W. T., Armstrong, D., Bodey, G. P., Bow, E. J., Brown, A. E., Calandra, T., Feld, R., Pizzo, P. A., Rolston, K. V. I., Shenep, J. L., & Young, L. S. (2002). 2002 Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer. *Clinical Infectious Diseases*, *34*(6), 730–751. https://doi.org/10.1086/339215

Irene, M., & Peter, M. (n.d.). *Acta Scientific PAEDIATRICS (ISSN: 2581-883X)*. https://doi.org/10.31080/ASPE.2020.03.0272

Islas-Muñoz, B., Volkow-Fernández, P., Ibanes-Gutiérrez, C., Villamar-Ramírez, A., Vilar-Compte, D., & Cornejo-Juárez, P. (2018). Bloodstream infections in cancer patients. Risk factors associated with mortality. *International Journal of Infectious Diseases*, *71*, 59–64. https://doi.org/10.1016/J.IJID.2018.03.022

Israëls, T., Kambugu, J., Kouya, F., El-Mallawany, N. K., Hesseling, P. B., Kaspers, G. J. L., Eden, T., Renner, L., & Molyneux, E. M. (2013). Clinical trials to improve childhood cancer care and survival in sub-Saharan Africa. *Nature Reviews Clinical Oncology 2013 10:10*, *10*(10), 599–604. https://doi.org/10.1038/nrclinonc.2013.137

Israels, T., Mbah Afungchwi, G., Klootwijk, L., Njuguna, F., Hesseling, P., Kouya, F., Paintsil, V., Landman, L., Chitsike, I., Chagaluka, G., Sung, L., Molyneux, E., & Molyneux con-tributed equally, E. (2021). *Pediatric Blood & Cancer Fever and neutropenia outcomes and areas for intervention: A report from SUCCOUR-Supportive Care for Children with Cancer in Africa*. https://doi.org/10.1002/pbc.29224

Israëls, T., van de Wetering, M. D., Hesseling, P., van Geloven, N., Caron, H. N., & Molyneux, E. M. (2009). Malnutrition and Neutropenia in Children Treated for Burkitt Lymphoma in Malawi. *Pediatr Blood Cancer*, *53*, 47–52. https://doi.org/10.1002/pbc.22032

Jawass, M. A., Al-Ezzi, J. I., Gouth, H. S. B., Bahwal, S. A., Bamatraf, F. F., & Ba'amer, A. A. (2016). Pattern of malignancies in children <15 years of age reported in Hadhramout Cancer Registry, Yemen between 2002 and 2014. *Saudi Medical Journal*, *37*(5), 513. https://doi.org/10.15537/SMJ.2016.5.14954

Johannsen, K. H., Handrup, M. M., Lausen, B., Schrøder, H., Sci, M., & Hasle, H. (2013). High Frequency of Streptococcal Bacteraemia During Childhood AML Therapy Irrespective of Dose of Cytarabine. *Pediatr Blood Cancer*, *60*, 1154–1160. https://doi.org/10.1002/pbc.24448

Juárez-Ocaña, S., González-Miranda, G., Mejía-Aranguré, J. M., Rendón-Macías, M. E., del Carmen Martínez-García, M., & Fajardo-Gutiérrez, A. (2004). *Frequency of cancer in children residing in Mexico City and treated in the hospitals of the Instituto Mexicano del Seguro Social (1996-2001)*. https://doi.org/10.1186/1471-2407-4-50

Kar, Y. D., Özdemir, Z. C., & Bör, Ö. (2017). Evaluation of febrile neutropenic attacks of pediatric hematology-oncology patients. *Turk Pediatri Arsivi*, *52*(4), 213–220. https://doi.org/10.5152/TurkPediatriArs.2017.5312

Kara, S. S., Tezer, H., Polat, M., Cura Yayla, B. C., Bedir Demirdağ, T., Okur, A., Fettah, A., Kanik Yüksek, S., Tapisiz, A., Kaya, Z., Özbek, N., Yenicesu, İ., Yarali, N., & Koçak, Ü. (2019). Risk factors for bacteremia in children with febrile neutropenia. *Turkish Journal of Medical Sciences*, *49*(4), 1198–1205. https://doi.org/10.3906/SAG-1901-90

Karimi, F., Ashrafi, F., Moghaddas, A., & Derakhshandeh, A. (2018). Management of Febrile Neutropenia: A Description of Clinical and Microbiological Findings by Focusing on Risk Factors and Pitfalls. *Journal of Research in Pharmacy Practice*, *7*(3), 147. https://doi.org/10.4103/JRPP.JRPP_18_16

Klastersky, J., de Naurois, J., Rolston, K., Rapoport, B., Maschmeyer, G., Aapro, M., Herrstedt, J., & on behalf of the ESMO Guidelines Committee. (2016). Management of febrile neutropaenia: ESMO clinical practice guidelines. *Annals of Oncology*, *27*, v111–v118. https://doi.org/10.1093/ANNONC/MDW325

Lam, C. G., Howard, S. C., Bouffet, E., & Pritchard-Jones, K. (2019). Science and health for all children with cancer. *Science (New York, N.Y.)*, *363*(6432), 1182–1186. https://doi.org/10.1126/SCIENCE.AAW4892

Libuit, J., Whitman, A., Wolfe, R., & Washington, C. S. (2014). Empiric Vancomycin Use in Febrile Neutropenic Oncology Patients. *Open Forum Infectious Diseases*, *1*(1). https://doi.org/10.1093/OFID/OFU006

Lubwama, M., Phipps, W., Najjuka, C. F., Kajumbula, H., Ddungu, H., Kambugu, J. B., & Bwanga, F. (2019). Bacteremia in febrile cancer patients in Uganda. *BMC Research Notes*, *12*(1), 4–9. https://doi.org/10.1186/s13104-019-4520-9

Marin, M., Gudiol, C., Ardanuy, C., Garcia-Vidal, C., Calvo, M., Arnan, M., & Carratalà, J. (2014). Bloodstream infections in neutropenic patients with cancer: Differences between patients with haematological malignancies and solid tumours. *Journal of Infection*, *69*(5), 417–423. https://doi.org/10.1016/J.JINF.2014.05.018

Michalski, A. M., Richardson, S. D., Browne, M. L., Carmichael, S. L., Canfield, M. A., Vanzutphen, A. R., Anderka, M. T., Marshall, E. G., & Druschel, C. M. (1997). *Sex Ratios Among Infants with Birth Defects*. https://doi.org/10.1002/ajmg.a.36865

Moghnieh, R., Estaitieh, N., Mugharbil, A., Jisr, T., Abdallah, D. I., Ziade, F., Sinno, L., Ibrahim, A., & Matar, G. M. (2015). *Third generation cephalosporin resistant Enterobacteriaceae and multidrug resistant gram-negative bacteria*

causing bacteremia in febrile neutropenia adult cancer patients in Lebanon, broad spectrum antibiotics use as a major risk factor, and correlation with poor prognosis. https://doi.org/10.3389/fcimb.2015.00011

Mohammed, H. B., Yismaw, M. B., Fentie, A. M., & Tadesse, T. A. (2019). Febrile neutropenia management in pediatric cancer patients at Ethiopian Tertiary Care Teaching Hospital. *BMC Research Notes*, *12*(1). https://doi.org/10.1186/S13104-019-4569-5

Molyneux, E., Scanlan, T., Chagaluka, G., & Renner, L. (2017). Haematological cancers in African children: progress and challenges. *British Journal of Haematology*, *177*(6), 971–978. https://doi.org/10.1111/BJH.14617

Montassier, E., Batard, E., Gastinne, T., Potel, G., & de La Cochetière, M. F. (2013). Recent changes in bacteremia in patients with cancer: a systematic review of epidemiology and antibiotic resistance. *European Journal of Clinical Microbiology & Infectious Diseases 2013 32:7*, *32*(7), 841–850. https://doi.org/10.1007/S10096-013-1819-7

Mostert, S., Njuguna, F., Kemps, L., Strother, M., Aluoch, L., Buziba, G., & Kaspers, G. (2012). Epidemiology of diagnosed childhood cancer in western kenya. *Archives of Disease in Childhood*, *97*(6), 508–512. https://doi.org/10.1136/ARCHDISCHILD-2011-300829

Mueller, E. L., Croop, J., & Carroll, A. E. (2016). Fever and neutropenia hospital discharges in children with cancer: A 2012 update. *Http://Dx.Doi.Org/10.3109/08880018.2015.1102998*, *33*(1), 39–48. https://doi.org/10.3109/08880018.2015.1102998

Murphy-Alford, A. J., Prasad, M., Slone, J., Stein, K., & Mosby, T. T. (n.d.). *Perspective: Creating the Evidence Base for Nutritional Support in Childhood Cancer in Low-and Middle-Income Countries: Priorities for Body Composition Research*. https://doi.org/10.1093/advances/nmz095

Mvalo, T., Eley, B., Bamford, C., Stanley, C., Chagomerana, M., Hendricks, M., van Eyssen, A., & Davidson, A. (2018). Bloodstream infections in oncology patients at Red Cross War Memorial Children's Hospital, Cape Town, from 2012 to 2014. *International Journal of Infectious Diseases*, *77*, 40–47. https://doi.org/10.1016/j.ijid.2018.09.012

Nesher, L., & Rolston, K. V. I. (2014). The current spectrum of infection in cancer patients with chemotherapy related neutropenia. *Infection*, *42*(1), 5–13. https://doi.org/10.1007/S15010-013-0525-9

Neumann, S., Krause, S. W., Maschmeyer, G., Schiel, X., & von Lilienfeld-Toal, M. (2013). Primary prophylaxis of bacterial infections and Pneumocystis jirovecii pneumonia in patients with hematological malignancies and solid tumors : guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Annals of Hematology*, *92*(4), 433–442. https://doi.org/10.1007/S00277-013-1698-0

Nguah, B. S. (2015). Pattern of Childhood Cancers Presenting to the Paediatric Cancer Unit of a Tertiary Hospital in Kumasi, Ghana. *Journal of Cancer Prevention & Current Research*, *Volume 3*(Issue 3). https://doi.org/10.15406/JCPCR.2015.03.00083

Obeng-Nkrumah, N., Labi, A. K., Acquah, M. E., & Donkor, E. S. (2015). Bloodstream infections in patients with malignancies: Implications for antibiotic treatment in a Ghanaian tertiary setting. *BMC Research Notes*, *8*(1), 1–10. https://doi.org/10.1186/S13104-015-1701-Z/TABLES/5

Oberoi, S., Das, A., Trehan, A., Ray, P., & Bansal, D. (2017). Can complications in febrile neutropenia be predicted? Report from a developing country. *Supportive Care in Cancer 2017 25:11*, *25*(11), 3523–3528. https://doi.org/10.1007/S00520-017-3776-7

Rondinelli, P. I. P., Ribeiro, K. D. C. B., & de Camargo, B. (2006). A proposed score for predicting severe infection complications in children with chemotherapy-induced febrile neutropenia. *Journal of Pediatric Hematology/Oncology*, *28*(10), 665–670. https://doi.org/10.1097/01.MPH.0000212996.94929.0B

Roy, A., Saha, A., Chakraborty, S., Chattopadhyay, S., & Sur, P. (2013). Effects of pre-existing undernutrition on treatment-related complications and treatment outcomes in children with acute lymphoblastic leukemia: A tertiary care center experience. *Clinical Cancer Investigation Journal*, *2*(2), 143. https://doi.org/10.4103/2278-0513.113637

Siddaiahgari, S., Manikyam, A., Anand Kumar, K., Rauthan, A., & Ayyar, R. (2014). Spectrum of systemic bacterial infections during febrile neutropenia in pediatric oncology patients in tertiary care pediatric center. *Indian Journal of Cancer*, *51*(4), 403–405. https://doi.org/10.4103/0019-509X.175367

Siddiqui, B., Azmat, R., Tikmani, S. S., Rafi, S., Syed, B., Khan, M. T., Rehman, H., & Paracha, S. (2018). Frequency of bloodstream infection in febrile neutropenic patients, experience from a developing country. *Annals of Medicine and Surgery*, *34*, 71–74. https://doi.org/10.1016/J.AMSU.2018.09.004

Sneha, L. M., Sakthikumar, L., Kadiyala, A., Scott, J., & Jayaraman, D. (2022). Implications of undernutrition in children with acute lymphoblastic leukaemia during induction therapy-experience from a developing country. *Mal J Nutr*, *28*(1), 79–086. https://doi.org/10.31246/mjn-2020-0131

Steliarova-Foucher, E., Colombet, M., Ries, L. A. G., Moreno, F., Dolya, A., Bray, F., Hesseling, P., Shin, H. Y., Stiller, C. A., Bouzbid, S., Hamdi-Cherif, M., Hablas, A., Chirpaz, E., Buziba, N., Chesumbai, G. C., Manraj, S. S., Reynders, D., Wabinga, H. R., Chokunonga, E., … Masuyer, E. (2017). International incidence of childhood cancer, 2001-10: a population-based registry study. *The Lancet. Oncology*, *18*(6), 719–731. https://doi.org/10.1016/S1470-2045(17)30186-9

Stergiotis, M., Ammann, R. A., Droz, S., Koenig, C., & Abayie Agyeman, P. K. (2021). Pediatric fever in neutropenia with bacteremia-Pathogen distribution and in vitro antibiotic susceptibility patterns over time in a retrospective single-center cohort study. *PloS One*, *16*(2). https://doi.org/10.1371/JOURNAL.PONE.0246654

Tamma, P. D., Han, J. H., Rock, C., Harris, A. D., Lautenbach, E., Hsu, A. J., Avdic, E., & Cosgrove, S. E. (2015). Carbapenem therapy is associated with improved survival compared with piperacillin-tazobactam for patients with extended-spectrum β-lactamase bacteremia. *Clinical Infectious Diseases*, *60*(9), 1319–1325. https://doi.org/10.1093/cid/civ003

Tandon, S., Moulik, N. R., Kumar, A., Mahdi, A. A., & Kumar, A. (2015). Effect of pre-treatment nutritional status, folate and vitamin B12 levels on induction chemotherapy in children with acute lymphoblastic leukemia. *Indian Pediatrics*, *52*(5), 385–389. https://doi.org/10.1007/S13312-015-0642-X

van Vliet, M. J., Harmsen, H. J. M., de Bont, E. S. J. M., & Tissing, W. J. E. (2010). The Role of Intestinal Microbiota in the Development and Severity of Chemotherapy-Induced Mucositis. *PLOS Pathogens*, *6*(5), e1000879. https://doi.org/10.1371/JOURNAL.PPAT.1000879

van Weelderen, R. E., Njuguna, F., Klein, K., Mostert, S., Langat, S., Vik, T. A., Olbara, G., Kipng'etich, M., & Kaspers, G. J. L. (2021a). Outcomes of pediatric acute myeloid leukemia treatment in Western Kenya. *Cancer Reports*, e1576. https://doi.org/10.1002/CNR2.1576

van Weelderen, R. E., Njuguna, F., Klein, K., Mostert, S., Langat, S., Vik, T. A., Olbara, G., Kipng'etich, M., & Kaspers, G. J. L. (2021b). Outcomes of pediatric acute myeloid leukemia treatment in Western Kenya. *Cancer Reports*, e1576. https://doi.org/10.1002/CNR2.1576

Vanderpuye, V., Yarney, J., & Beecham, K. (2011). Management of Febrile Neutropenia in Patients receiving Chemotherapy for Solid Tumors: A Retrospective Study of Twenty Cases from the Radiotherapy Centre, Accra, Ghana. *West African Journal of Medicine*, *29*(5). https://doi.org/10.4314/wajm.v29i5.68249

Vehreschild, J. J., Böhme, A., Cornely, O. A., Kahl, C., Karthaus, M., Kreuzer, K. A., Maschmeyer, G., Mousset, S., Ossendorf, V., Penack, O., Vehreschild, M. J. G. T., & Bohlius, J. (2014). Prophylaxis of infectious complications with colony-stimulating factors in adult cancer patients undergoing chemotherapy-evidence-based guidelines from the Infectious Diseases Working Party AGIHO of the German Society for Haematology and Medical Oncology (DGHO). *Annals of Oncology : Official Journal of the European Society for Medical Oncology*, *25*(9), 1709–1718. https://doi.org/10.1093/ANNONC/MDU035

Virizuela, J. A., Carratalà, J., Aguado, J. M., Vicente, D., Salavert, M., Ruiz, M., Ruiz, I., Marco, F., Lizasoain, M., Jiménez-Fonseca, P., Gudiol, C., Cassinello, J., Carmona-Bayonas, A., Aguilar, M., Cruz, J. J., Carratalà, J., María Aguado, J., Salavert, M., Marco, F., … Transl Oncol, C. (2094). Management of infection and febrile neutropenia in patients with solid cancer. *Clinical and Translational Oncology*. https://doi.org/10.1007/s12094-015-1442-4

Viscoli, C., Varnier, O., & Machetti, M. (2005). Infections in Patients with Febrile Neutropenia: Epidemiology, Microbiology, and Risk Stratification. *Clinical Infectious Diseases*, *40*(Supplement_4), S240–S245. https://doi.org/10.1086/427329

von Allmen, A. N., Zermatten, M. G., Leibundgut, K., Agyeman, P., Ammann, R. A., & Characteristic Homo sapiens, S. (2018). Data Descriptor: Pediatric patients at risk for fever in chemotherapy-induced neutropenia in Background and Summary. *Nature Publishing Group*. https://doi.org/10.1038/sdata.2018.38

Williams, L. A., Richardson, M., Marcotte, E. L., Poynter, J. N., & Spector, L. G. (2019). Sex-ratio among childhood cancers by single-year of age. *Pediatric Blood & Cancer*, *66*(6), e27620. https://doi.org/10.1002/PBC.27620

Zembower, T. R. (2014). Epidemiology of infections in cancer patients. *Cancer Treatment and Research*, *161*, 43–89. https://doi.org/10.1007/978-3-319-04220-6_2/TABLES/4

Zimmer, A. J., & Freifeld, A. G. (2019). Optimal management of neutropenic fever in patients with cancer. *Journal of Oncology Practice*, *15*(1), 19–24. https://doi.org/10.1200/JOP.18.00269

APPENDICES

Appendix 1: Administration Approval

An ISO 9001:2015 Certified Hospital

MOI TEACHING AND REFERRAL HOSPITAL

Telephone :(+254)053-2033471/2/3/4
Mobile: 722-201277/0722-209795/0734-600461/0734-683361
Fax: 053-2061749
Email: ceo@mtrh.go.ke/directorsofficemtrh@gmail.com

Nandi Road
P.O. Box 3 – 30100
ELDORET, KENYA

Ref: ELD/MTRH/R&P/10/2/V.2/2010

16th April, 2020

Dr. Samuel K. Kipchumba,
Moi University,
School of Medicine,
P.O. Box 4606- 30100,
ELDORET-KENYA.

APPROVAL TO CONDUCT RESEARCH AT MTRH

Upon obtaining approval from the Institutional Research and Ethics Committee (IREC) to conduct your research proposal titled:-

"Bacterial Aetiology of Febrile Neutropenia in Children on Treatment for Cancer Admitted at the Moi Teaching and Referral Hospital".

You are hereby permitted to commence your investigation at Moi Teaching and Referral Hospital.

DR. WILSON K. ARUASA, MBS
CHIEF EXECUTIVE OFFICER
MOI TEACHING AND REFERRAL HOSPITAL

cc - Senior Director, (CS)
     - Director of Nursing Services (DNS)
     - HOD, HRISM

All correspondence should be addressed to the Chief Executive Officer
Visit our Website: **www.mtrh.go.ke**
TO BE THE LEADING MULTI-SPECIALTY HOSPITAL FOR HEALTHCARE, TRAINING AND RESEARCH IN AFRICA

Appendix:2 Institutional Research and Ethics Committee (IREC) Approval

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

Reference: IREC/2019/294
Approval Number: 0003587

2nd April, 2020

Dr. Samuel Kipkemoi Kipchumba
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

Dear Dr. Kipchumba,

BACTERIAL AETIOLOGY OF FEBRILE NEUTROPENIA IN CHILDREN ON TREATMENT FOR CANCER ADMITTED AT MOI TEACHING AND REFERRAL HOSPITAL.

This is to inform you that **MU/MTRH-IREC** has reviewed and approved your above research proposal. Your application approval number is **FAN:0003587.** The approval period is **2nd April, 2020 – 1st April, 2021.**

This approval is subject to compliance with the following requirements;

i.   Only approved documents including (informed consents, study instruments, MTA) will be used.
ii.   All changes including (amendments, deviations, and violations) are submitted for review and approval by **MU/MTRH-IREC**.
iii.   Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to **MU/MTRH-IREC** within 72 hours of notification.
iv.   Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to **MU/MTRH-IREC** within 72 hours.
v.   Clearance for export of biological specimens must be obtained from relevant institutions.
vi.   Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii.   Submission of an executive summary report within 90 days upon completion of the study to **MU/MTRH-IREC.**

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://oris.nacosti.go.ke and also obtain other clearances needed.

Sincerely,

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc	CEO	-	MTRH	Dean	-	SOP	Dean	-	SOM
	Principal	-	CHS	Dean	-	SON	Dean	-	SOD

Appendix: 3 Continuing IREC Approval

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET
Tel: 33471/2/3
2nd April, 2021

Reference: IREC/2019/294
Approval Number: 0003587

Dr. Samuel Kipkemoi Kipchumba,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET- KENYA.

Dear Dr. Kipchumba,

RE: CONTINUING APPROVAL

The Institutional Research and Ethics Committee has reviewed your request for continuing approval to your study titled:-

"Bacterial Aetiology of Febrile Neutropenia in Children on Treatment for Cancer Admitted at Moi Teaching and Referral Hospital"

Your proposal has been granted a Continuing Approval with effect from 2nd April, 2021. You are therefore permitted to continue with your study.

Note that this approval is for 1 year; it will thus expire on 1st April, 2022. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

INSTITUTIONAL RESEARCH &
ETHICS COMMITTEE
0 2 APR 2021
APPROVED
P.O. Box 4606-30100 ELDORET

**PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE**

cc: CEO   -   MTRH
     Principal -   CHS
     Dean   -   SOM
     Dean   -   SPH
     Dean   -   SOD

Appendix 4: Consent Form
Name.……………………… Hospital No………………………

Study Title: BACTERIAL AETIOLOGY OF FEBRILE NEUTROPENIA IN CHILDREN ADMITTED FOR CANCER AT MOI TEACHING AND RFERRAL HOSPITAL AND THEIR CHARACTERISTICS

Investigator: Dr Kipchumba Samuel (Resident in Paediatrics and child Health) Tel Number: - 0723-936516.

Supervisors: Professor Winstone Nyandiko

Dr Njuguna Festus

Introduction: The purpose of this study is to define the bacterial aetiology of febrile neutropenia among paediatric cancer patients admitted at MTRH and their characteristics. This study seeks to identify the most common organisms isolated in the blood stream infection of paediatric cancer patients with febrile neutropenia and their sensitivity patterns.

The procedure to be undertaken in this study will be: Taking of blood samples for culture and sensitivity, to identify the bacterial microorganisms associated with febrile neutropenia in paediatric cancer patients.

Participation: Enrolment in the study will be on voluntary basis. There will be no financial rewards to you for participating in the study. One is free to participate or withdraw from the study at any point. Refusal to participate will not compromise your child's care in any way.

Risks: No invasive procedures carried out in the study will harm your child. However, there may be minimal risks such as pain and bleeding and development of hematomas at the venepuncture site. Refusal to participate will in no way interfere with the treatment of your child.

Confidentiality: The information obtained about you, your child and your family will be kept in strict confidence. No specific information regarding you, your child or your family will be released to any person without your written permission. We will, however, discuss general overall findings regarding all children assessed but nothing specific will be discussed regarding your child's condition. We will also, not reveal the identity of you or your child in these discussions.

Problems or Questions: If you have any questions about the study or about the use of the results, contact the principal investigator, Dr Kipchumba Samuel on Tel No.0723-936516.

Questions about your rights as a research subject: You may contact Institutional Review Ethics Committee (IREC) 053 33471 Ext.3008. IREC is a committee that reviews studies for safety and to protect the rights of study subjects.

I ……………………………………………………………………….having received adequate information regarding the study research, risks hereby AGREE / DISAGREE (Cross out as appropriate) to participate/ for my child to participate in the study.

I understand that our participation is fully voluntary and that I am free to withdraw at any time. I have been given adequate opportunity to ask questions and seek clarification on the study and these have been addressed satisfactorily.

Participant / Guardian's Signature: ……………………… Date……………………….

I ……………………………………………………………………declare that I have adequately explained to the above participant/ guardian, the study procedure, risk and given him /her time to ask questions and seek clarification regarding the study. I have answered all the questions raised to the best of my ability.

Investigator's   Signature……………………………

Date……………………………...

Appendix 5: Fomu ya makubaliano ya kushiriki katika utafiti huu kwa washiriki walio chini ya umri wa miaka kumi na nane:

Mada ya Utafiti: Etiolojia ya bakteria kwenye futi ya neutropenia kwa watoto wanaotibiwa ugonjwa wa Saratani katika hospitali kuu ya rufaa ya MTRH pamoja na sifa zao.

Mtafiti: Daktari Samuel Kipchumba (mwanafunzi katika chuo kikuu cha Moi katika idara ya maabara na afya ya watoto). Nambari ya simu 0723936516

Wasimamizi: Profesa Winstone Nyandiko

Daktari Njuguna Festus

Utangulizi: Lengo la utafiti huu ni kufahamu etiolojia ya bakteria kwenye ugonjwa wa futi ya neutropenia kwa watoto wanaotibiwa ugonjwa wa saratani katika hospitali kuu ya MTRH pamoja na sifa zao. Utafiti huu vilevile unalenga kutambua viumbe vilivyo vya kawaida sana vya bakteria katika maambukizi ya ukondo wa damu kwa watoto waanaougua ugojwa wa saratani na mwelekeo wao wa unyeti.

Utaratibu utakaofuatwa katika utafiti huu ni: sampuli za damu kutolewa kusudi kufanyiwa utafiti wa utaratibu na unyeti ili kutambua viumbe vya kawaida sana vya bakteria vinavyohusikana na ugonjwa wa futi ya neutropenia katika watoto wanaougua ugonjwa wa saratani.

Ushiriki: uandikishaji wa kushiriki katika utafiti huu ni kwa hiari ya mshiriki pekee. Ana uhuru wa kushiriki au kujiondoa kutoka utafiti huu kwa wakati wowote katika uendeshaji wa utafiti huu. Walakini kunaweza kuwa na hatari ndogo kama maumivu na kutokwa na damu na pia kutokea kwa hematoma kwenye sehemu ya kuteka damu, yote haya hayana madhara kwa mtoto wako.Kutoshiriki hautaathiri huduma kwa mtoto wako kwa njia yoyote.

Madhara ya kushiriki: hakuna utaratibu wowote ambao utatahadharisha afya ya mtoto wako, katika utafiti huu. Walakini kunaweza kuwa na hatari ndogo kama vile

maumivu na kutokwa na damu na kutokezwa kwa hematoma kwenye sehemu patakapo tolewa damu.

Hakuna gharama yoyote itakayotokana kwa ajili ya kushiriki katika utafiti huu. Hakuna malipo yoyote utakayopata katika kushiriki katika utafiti huu.

Siri: habari zote za utafiti huu yatatunzwa kwa siri na kutumika katika utafiti tu. Utambulisho wako hautawekwa bayana katika makaratasi yoyote. Makaratasi yote yatawekwa katika kabati lililofungwa na kifunguu kuwekwa na mtafiti mkuu. Tarakilishi itatumika kuimarisha siri. Maswali ya dodoso yatajibiwa katika chumba ambacho kitakuwa kimetafutwa na mtafiti kwa usaidizi wa wahudumu wa afya kitachoshughulukia mambo ya siri. Majibu yako hayatapatiwa kwa mzazi/mlezi wako.

Lawama au maswali: Iwapo utakuwa na swali lolote au lawamakuhusu utafiti huu, tafadhali wasiliana na, Daktari Samuel Kipchumba kupitia numbari ya simu ya rununu 0723936516.

Baada ya kusoma na kuelezwa kwa kina mambo yanayohusiana na utafiti huu;

Mimi…………………………………………………………………………………natoa idhini yangu kushiriki katika utafiti huu. Nafahamu kuwa naweza kusitisha kushiriki kwangu katika utafiti huu wakati wowote bila madhara yoyote.

Sahihi ya mshiriki…………………………Tarehe………………………..

Sahihi ya mtafiti mkuu ………………………Tarehe……………………….