PATTERNS OF ANTIBIOTIC PRESCRIPTION DURING FEBRILE EPISODES IN PAEDIATRIC PATIENTS WITH CANCER AT THE KENYATTA NATIONAL HOSPITAL

A research proposal submitted to the Department of Pediatrics and Child Health in the School of Medicine in partial fulfillment for the award of the degree of Masters of Medicine (M.MED) in Pediatrics and Child Health, University of Nairobi (UON).

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DECLARATION

I, Maureen Muchela, hereby declare that this is my original work and has not been presented for the award of a degree in any other university.

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ABBREVIATIONS

KNH-	Kenyatta National Hospital
HCA-I –	Health care associated infection
CDI-	Clinically documented infection
BSI-	Blood stream infection
HAUTI-	Health care associated urinary tract infection
CDC/NHSN-	Centers of Disease Control and prevention /National Health and Safety Network
NETs-	Neutrophil Extracellular Traps
DAMPs-	Damage associated molecular patterns
PAMPs-	Pathogen associated molecular patterns
NADPH-	Reduced form of nicotinamide adenine dinucleotide phosphate (NADP)
SSI-	Surgical site infection
IDSA-	Infectious Diseases Society of America
AMC-	Absolute Monocyte Count
ANC-	Absolute Neutrophil Count
ESR-	Erythrocyte Sedimentation Rate
CRP-	C **- reactive protein**
FBC/WBC/CBC-	Full Blood Count/ whole blood count /complete blood count
UEC-	Urea /Electrolyte /Creatinine
ESKAPE-	*(Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter spp.)*
CONS-	Coagulase negative staph. Aureus

OPERATIONAL DEFINITIONS

Fever – A**xillary** temperature of greater than 37.8^{o}C (Kasili's Synopsis of the management of Paediatric cancers in Kenya)

Febrile neutropenia- Fever (as defined above) and an absolute neutrophil count (ANC) of $<0.5 \times 10^{9}$/l (Kasili's synopsis of the management of paediatric cancers in Kenya)

Febrile episode- a period of time during which there was documented fever as defined above. Resolution of a febrile episode was defined as the absence of fever for more than 48 hours. (Kasili's Synopsis suggests stoppage of antibiotics after 2 days fever free with evidence of marrow recovery. Only resolution of fever for 48 hours was used in the study)

Microbiologically documented infection (MDI) – Neutropenic fever with a clinical focus of infection and an associated pathogen (Immunocompromised host society definition).

Clinically documented infection (CDI) –Neutropenic fever with a clinical focus (e.g., cellulitis, pneumonia), but without the isolation of an associated pathogen (Immunocompromised host society definition)

Unexplained fever – Neutropenic fever with neither a clinical focus of infection nor an identified pathogen (Immunocompromised host society definition)

Febrile non-neutropenic episode- a period of time which there was fever as defined above and an absolute neutrophil count (ANC) of $>0.5 \times 10^{9}$/l (fever definition as in (Kasili's synopsis of the management of paediatric cancers in Kenya)

Empiric antibiotic therapy- Antibiotic treatments given in case of suspected infection before microbiology results are available. The first antibiotic prescription after the start of a febrile episode was considered empiric in the study.

Suspected cancer- a diagnosis of cancer by a medical practitioner that includes the use of specific terms synonymous with cancer (cancer, .malignant carcinoma, sarcoma, leukemia, lymphoma) (CDC National Notifiable Disease Surveillance System 2010 case definition)

Confirmed cancer - laboratory confirmed cases with positive histology, cytology or other positive microscopic confirmation. (CDC National Notifiable Disease Surveillance System 2010 case definition)

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ABSTRACT

Background: Children with cancer have increased vulnerability to infections. Prompt initiation of empiric antibiotics for fever episodes as guided by local antimicrobial sensitivity patterns is therefore recommended. However, irrational use of antibiotics, has been demonstrated even in the presence of clinical guidelines. This study aims to describe the patterns of antibiotic prescription during febrile episodes among pediatric oncology patients at the Kenyatta National Hospital (KNH).

Objectives: To describe the antibiotic prescription patterns during febrile episodes in children 1-15 years of age with suspected or confirmed cancer, to describe the clinical and laboratory evaluation of febrile illness in children with cancer at the KNH.

Methodology: A retrospective study was done. Paediatric patients with cancer and febrile episodes in KNH fulfilling the inclusion criteria were recruited into the study and data collected for the most recent febrile episode from October 2018 to September 2019.

Data analysis: Descriptive statistics were performed to generate frequencies, percentages, means and medians. Inferential statistics was conducted through the Chi-Square test of independence as well as binary logistics regression. Analysis was done using IBM SPSS Version 25.

Results: 139 most recent febrile episodes were included. Median age was 6 years (IQR 3-9years), 58.3% were males, and the most common underlying malignancies were solid tumors in 43.7%, and 64.4% of the study participants had received chemotherapy. Non-neutropenic febrile episodes were predominant (69.4%), febrile neutropenic episodes consisted 30.6%. Mean temperature was 38.5^0C ($\pm 0.67^0$C), mean duration of febrile episode was 5days (±3 days), median length of admission prior to the febrile episodes was 28 days (IQR 6-75 days).

Antibiotics were prescribed in 86.2% of the febrile episodes. A significant association was noted between the type of febrile episode and the antibiotic therapy prescribed, X^2 ($p=0.017$) with antibiotic monotherapy prescription more likely for non-neutropenic febrile episodes while combination antibiotics more likely for neutropenic episodes. Antibiotic combination prescription containing 3rd generation cephalosporins was most frequent in neutropenic febrile episodes (33.3%) and antibiotic monotherapy prescription containing 3rd generation cephalosporins was the most frequent (54.8%) for non-neutropenic febrile episodes. Mean antibiotic duration was 9days (SD 5 days) and in 42.4% of the febrile episodes had recent antibiotic use, with a higher proportion among neutropenic febrile episodes.

Conclusion:

There is a varied pattern of antibiotic prescription for both neutropenic and non neutropenic fever episodes, with 3rd generation- cephalosporin- based-combination therapy most frequently prescribed for neutropenic febrile episodes, and ceftriaxone monotherapy most frequently prescribed for non neutropenic febrile episodes.

Recommendations;

We recommend developing local clinical practice guidelines for the management of febrile non neutropenic episodes in pediatric oncology patients and judicious antibiotics use for febrile episodes in paediatric oncology patients at the KNH.

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1.0 CHAPTER ONE: INTRODUCTION

Children with cancer have increased vulnerability to infections in the period prior to start of anti-cancer treatment, during cancer treatment and several months after successful cancer treatment(1,2). The innate and adaptive arms of the immune system are both affected in several ways, leaving the pediatric cancer patient immune-compromised, vulnerable to different pathogens. The phenomenon best described has been fever in the setting of neutropenia, febrile neutropenia, which has been associated with infections in this vulnerable population(3). Febrile neutropenia is an oncologic emergency, as affected individuals often have no other manifestation of illness apart from fever and require prompt assessment and initiation of empiric antibiotics. Thus guidelines have recommended the baseline evaluation in the setting of febrile neutropenia, as well as empiric antibiotics as guided by the local antibiotic sensitivity patterns(4–7).

Within the Kenyan setting, the Kasili's synopsis was the first guideline to be launched specifically for use among pediatric cancer patients treated in the public sector which contained specific guidelines for the management of febrile neutropenia. In early 2018 the Kenyatta National Hospital (KNH) antimicrobial guide for therapy was launched and although not specific for cancer patients, provided empiric antibiotic guidelines as per the most recent antimicrobial sensitivity data from the cultures done at the hospital. The recommendations for the categories among which cancer patients fall bear similarities to the international guidelines for the empiric management of febrile neutropenia. Less described however, is fever that occurs in non-neutropenic pediatric cancer patients, with fewer studies documenting the antibiotic management of this subset of febrile cancer patients.

We set to describe the antibiotic prescription patterns, the clinical and laboratory evaluation received by febrile pediatric cancer patients (for the most recent febrile episode), and describe the antimicrobial sensitivity patterns of organisms grown on cultures from pediatric cancer patients.

1.1 Problem statement

As is already known, pediatric cancer patients are vulnerable to infections, and often need to be treated empirically while the clinical and laboratory evaluations are ongoing. The decision of the type of antibiotic to be prescribed should be guided by the local resistance patterns in this sub-population. Clinical practice guidelines have been developed for this, to guide the primary clinician on the empiric prescription. In the local setting, there are multiple guidelines that address the empiric prescription, and this still poses a challenge to the primary

clinicians on the choice of empiric antibiotic. Large variations of empiric antibiotic prescription have also been described elsewhere, suggesting that even in the presence of clinical practice guidelines, irrational use of antibiotics may still occur.

Antibiotic use has been directly linked to antimicrobial resistance, an emerging problem that if left unchecked predisposes the already vulnerable population to difficult-to-treat multi drug resistant bacterial infections. This increases the cost of health care, morbidity and mortality among the pediatric cancer patients.

Description of the antibiotic prescription patterns is an important initial step towards antimicrobial stewardship and improving antibiotic prescription practices among the clinicians taking care of these patients

2.0 CHAPTER TWO: BACKGROUND AND LITERATURE REVIEW

The burden of cancer among children in low and middle income countries has been rising throughout the decade (8–10). In addition to this, mortality from cancer in children in low and middle income countries is comparatively high(8).Although most of the children with cancer die from the cancer itself(11), infection is an important cause of morbidity and mortality in children with cancer(11–13).Children with cancer are known to be immune-suppressed before starting chemotherapy, during chemotherapy and even after successful treatment using chemotherapy and radiotherapy .Febrile neutropenia has been recognized as an oncologic emergency, occurring typically after administration of chemotherapeutic agents(5). In a study conducted by Pizzo *et al*, a prospective review of 1001 febrile episodes, 79% of the fever among pediatric and young adults with cancer was diagnosed in neutropenic patients(14).While fever in neutropenia has been extensively studied, less data exists for fever in non-neutropenic cancer patients, among whom at least 40% of the fever episodes may be infectious in origin(14).The case fatality of febrile neutropenia from single centre studies in low and middle income countries ranges from 6-13%(15–17). A study conducted in Nigeria by Brown *et al* on mortality records of pediatric cancer patients reported infections as the immediate cause of death in 39% of the deaths(11). However, in this study more than 80% of the pediatric cancer patients had progressive disease at the time of death. In a study conducted in Canada, a decade long study of deaths of pediatric cancer patients, infections were directly responsible for 22% of treatment related mortality, coming second after respiratory illness(18). Over 60% of those respiratory illnesses were concurrent with infections(18).

With infections playing a large part in the influencing the outcomes of pediatric cancer patients, guidelines for empiric antibiotics were developed, especially for the treatment of febrile neutropenia(4,19). Prompt and timely administration of antibiotics has become the standard of care for febrile neutropenia and indeed sepsis in pediatric patients. Empiric antibiotics cover the most probable cause of infection as per the local antibiograms. Guidelines have been shown to improve antibiotic utilization in pediatric cancer patients by reducing delay and suboptimal prescription and reducing hospital stay and excessive durations of antimicrobial therapy(20). Fisher et al in their study however demonstrated large variations in prescription of antibiotics for febrile neutropenia (even in the presence of clinical practice guidelines), that had no association with severity of illness(21).

Within the Kenyatta National hospital setting, there are several guidelines that may be used to guide the antibiotic decisions among pediatric oncology patients with fever: the Kasili's synopsis for the management of pediatric cancers, the clinical practice guideline for pediatric oncology patients, was the first of its kind in the public sector and recommends the empiric use of crystalline penicillin and gentamicin for febrile neutropenia, with additions of anaerobic cover when GI infection is suspected, The Basic Pediatric Protocol, which was developed for use for community acquired infections and emergency care for the sick child, does not explicitly cover febrile neutropenia but suggests the use of high dose ceftriaxone (100mg/kg/day) for sepsis. This protocol has widespread use as it is printed and distributed widely and in large numbers from the ministry of health. The Kenyatta National Hospital guide to antimicrobial therapy was launched recently in response to antibiogram of the hospital. The recommendations therein are summarized elsewhere in the text (table 3 and 4). The effort was directed towards antimicrobial stewardship in the hospital. The recommendations therein for the category 2 and 3 are similar in some aspects to the international guidelines, which recommend an anti-pseudomonal beta-lactam or a carbapanem as empiric antibiotic therapy. These guidelines are for use all throughout the hospital, as they were not developed specifically for fever in pediatric oncology patients. It suggests the use of the basic pediatric protocol to guide antibiotic choices in patients below the age of five. The multiplicity of guidelines is hypothesized to be a challenge (for pediatric residents /medical officers) in timely selection of empiric antibiotic for the management of fever in pediatric oncology patients.

Description of antibiotic utilization in this subset of patients has, to the best of our knowledge, not been done in the local setting, especially in the setting of multiplicity of guidelines for empiric antibiotic choices. Furthermore, there is a paucity of data on antibiotic treatment of non-neutropenic fevers from our setup. In the ever increasing risk of development of antimicrobial resistance, it is imperative to audit the local practice in order to provide background information for future antimicrobial stewardship activities in this subset of patients.

2.1 Increased Vulnerability to Infections

Children and adolescents with cancer are known to have an increased vulnerability to infections. Infections are a major cause of morbidity and mortality among pediatric cancer patients(5,22,23) There are several factors that interact to make the pediatric cancer patient increasingly vulnerable to infection. Disruption of normal mechanical barriers on the skin and

the various mucosal surfaces in the respiratory, gastrointestinal tract (GIT) and genitourinary tract may occur, causing a breech in the first line of defense, the innate immune system. This disruption follows tumor invasion to epithelial surfaces leading to disruption of normal anatomic structures, surgery- which results in anatomic variations and wounds providing local sites for pathogen entry, during administration of chemotherapy agents especially in the GIT mucosa, following radiation and from indwelling/surgically implantable ports, which provide direct access of skin flora to blood and subcutaneous tissue.(5,22,23). Shifts in the usual colonizing microbial flora following prolonged antibiotic use and chemotherapy predispose the patients to colonization and infection by resistant organisms(22).

Another mechanism which predisposes these children with cancer to infection is the dysfunction of the cellular immune system. Most commonly affected are the neutrophils, monocytes and lymphocytes.

The association between neutropenia and increased risk of infections has been described (14,22), and in different subsets of pediatric cancer patients, prolonged periods of neutropenia have been associated with more serious infection(24). The depth and duration of neutropenia is an important determinant to susceptibility to bacterial and fungal infections. The number of circulating neutrophils can be affected by the underlying malignancy through infiltration of the marrow by the malignant cells or bone marrow aplasia, or by chemotherapeutic agents which may cause bone marrow suppression(5,22). Functional neutropenia also may result when the neutrophil microbicidal activity is interfered with as a result of underlying malignancy or as a result of steroid therapy(22). Steroid therapy results in impaired neutrophil chemotaxis and killing, as such the patient is left vulnerable to infections despite normal peripheral neutrophil counts.

In the review by Segel, infections that are to be anticipated at different levels of neutropenia are described(25). Lower level of neutropenia predispose the affected individuals to more invasive infections(25).Segel however noted that in a subset of individuals of African descent(3%-5%), the ranges of absolute neutrophil count are below 1500/microliter, which is included in the definition of levels of neutropenia(25).

According to the Infectious Diseases Society of America (IDSA) guidelines of 2010, neutropenia is defined as an absolute neutrophil count (ANC) of less than 500 cells/mm3 or an absolute neutrophil count that is expected to decrease to 500 cells/mm3 during the next 48 hours. Profound neutropenia is defined ANC of less than 100 cells/mm3; a manual reading of the blood smear is required to confirm this degree of neutropenia(6)

The National Cancer institute documents four grades of neutropenia that can be graded as an adverse event of cancer therapy /hematologic toxicity:

Grade 1: Neutrophils <Lower limit of normal for age to 1500 cells/mm3

Grade 2:1000 to 1500 cells/mm3 – mild neutropenia

Grade 3:500 to 1000cells/mm3 –moderate neutropenia

Grade 4 <500 cells/mm3 – severe neutropenia

The association of a reduced monocyte count with a heightened risk of infection has been suggested from various studies that sought to identify the risk factors for infection in febrile neutropenic pediatric patients(26–28). A higher absolute monocyte count predicted low risk of significant bacteremia, and this could be explained physiologically by the observed pattern of monocytes preceding the neutrophils during marrow recovery after chemotherapy(26,28). The absolute monocyte count may be affected by the underlying disease or by the chemotherapeutic agents used in the treatment of cancer.

Depletion of lymphocytes also occurs following administration of anti-neoplastic agents and it occurs in a mainly dose and intensity related fashion(1). T-cell depletion is particularly associated with immune-suppression and increased vulnerability to opportunistic infections in recipients of anti-neoplastic chemotherapy(1). The CD4 + subset of T lymphocytes was shown to be depleted more than the other T-cell subsets(2). Opportunistic infections that arose were similar to those that occur following CD4 lymphocyte depletion in HIV(1,2). Cyclophosphamide and the purine nucleoside analogs (e.g. fludarabine) have been associated with marked lymphocyte depletion following their administration(1). The recovery from lymphocyte depletion has been described to be slower (compared to the neutrophils), and therefore the risk of OIs in the recipients of antineoplastic therapy still persists a few months after the completion of chemotherapy(1,29). Steroid therapy is also associated with impaired T cell function. High dose prolonged steroid use is associated with increased risk of invasive fungal disease such as Aspergillus and Cryptococcus. B cells also are depleted following antineoplastic therapy, and reductions in IgA and IgM have been recorded in literature, with only modest reductions in IgG (1,29).Lymphocytes are also affected by the underlying disease e.g. in chronic lymphocytic leukemia in which is more often than not complicated with hypogammaglobulinemia, leaving the patient susceptible to encapsulated bacteria(22).

2.2 Repeated or Prolonged Admissions

Besides the cancer and treatment related predisposition to infection, pediatric cancer patients often have repeated and /or prolonged admissions due to chemotherapy or chemotherapy

related complications. Febrile neutropenia, a well-recognized complication of cancer treatment, typically necessitates admission and treatment with parenteral antibiotics for the pediatric oncology patients(4,5). Due to prolonged and repeated contact with the health care system and or health care workers, pediatric oncology patients are at increased risk of health care associated infections.

A health care associated infection (HCAI) is an infection occurring in a patient during the process of care in a health care facility which was not present or incubating at the time of admission, and includes infections acquired in the hospital, appearing after discharge and occupational infections among the staff working at that facility (15,16). The true burden of HCAIs is unknown, particularly for developing countries, however the consequences of health care associated infections are well recognized(30). Prolonged hospital stay, increased mortality, increased resistance of microorganisms to antibiotics, and a high financial cost to both health systems and patients with their families are recognized consequences of HCAIs(30,32,33). HCAIs necessitate prolonged admissions therefore further predisposing the already immune-suppressed pediatric oncology patients to infection by antibiotic resistant organisms.

There are four main types of health care associated infections: surgical site infection (SSI), blood stream infection (BSI), health care associated urinary tract infection (HA-UTI), and health care associated pneumonia(31). Pediatric oncology patients are predisposed to BSIs as they typically have central venous access devices that can act as potential portals of entry to disease causing organisms if not properly managed. BSIs represent the most common type of health care associated infection in many centers(32,34–36).The use of indwelling urinary catheters predisposes these patients to health care associated urinary tract infections. Surgical site infections may occur after incisional or excisional biopsies done as part of diagnosis or treatment of various malignancies. As noted above, these procedures cause a breach in the skin which acts as the first line of defense against microorganisms, and infections may ensue. Case definitions for these HCAIs are outlined in the CDC/NHSN surveillance definitions document(31). The definitions seem to be similar for immune competent and immune suppressed patients except health care associated pneumonia definition, which includes definition of HCA pneumonia among the patients who are immune-suppressed. However for blood stream infection, the definition requires the growth of organisms on culture and excluding the ‘normal flora’. It has been noted that positive blood cultures occur in less than 50% of the blood cultures in febrile neutropenic patients, and often ‘normal flora’ is obtained from this cultures(14,15,37,38) .

2.3 Infection related morbidity and mortality in pediatric cancer patients

Infection in cancer patients is a major contributor to treatment related mortality(39,40). Treatment related mortality(TRM) is defined as the absence of progressive (malignant) disease at death(41). Infection related mortality is more in the developing countries than in developed countries contributing to poor outcomes in pediatric cancer(39). Factors contributing to infection related mortality are not well described, but from single centre experiences and cumulative data comparative to general population, ethnicity (42), chromosomal abnormalities like Down's Syndrome (12), female gender (12,43), and the intensity of the treatment protocol and those who received total body irradiation (12,43), older age at diagnosis (>15 years)(43) have been associated with higher infection related mortality among subsets of pediatric cancer patients and survivors. Infections may occur in the pediatric cancer patients in both non-neutropenic periods and in neutropenic periods(14). Fever occurring in pediatric cancer patients in the setting of neutropenia is considered an oncologic emergency. Since the individuals are already immune-suppressed, fever may be the only sign of a life threatening infection.

Febrile neutropenia is generally defined as an oral temperature of >38.3°C or two consecutive readings of >38.0°C for 2 h and an absolute neutrophil count (ANC) of $<0.5 \times 10^9$/l, or expected to fall below 0.5×10^9/l within the next 48 hours(6,7). The Kasili's synopsis for the management of paediatric cancers however defines fever as a temperature greater than 37.8^{o}C of (axillary) temperature(5), but recommends starting antibiotic if a temperature of 38 degrees Celsius is sustained for more than 4 hours, or a single temperature of more than 38.5 degrees Celsius for neutropenic patients.

Typically for febrile neutropenia episodes, the yield of the septic screen is low even in countries with advanced laboratory capacity and expertise, and it has remained low throughout the years, ranging from 13%-36.5% of microbiologically documented infection among pediatric cancer patients with fever and neutropenia(14–16,37,38,44). The International Immuno-compromised Host Society has classified initial neutropenic fever syndromes into three categories;

- **Microbiologically documented infection** – Neutropenic fever with a clinical focus of infection and an associated pathogen.
- **Clinically documented infection** – Neutropenic fever with a clinical focus (e.g., cellulitis, pneumonia), but without the isolation of an associated pathogen.

- **Unexplained fever** – Neutropenic fever with neither a clinical focus of infection nor an identified pathogen.

Febrile neutropenia is still associated with morbidity and mortality in pediatric cancer patients(3,15). From data in high income countries, the overall incidence of febrile neutropenia is low and the mortality from febrile neutropenia has been decreasing through the years, a change attributed to improved management of neutropenic episodes(37,45). However, more recently, in one centre in a developed country, the incidence of febrile neutropenia has been noted to increase through the years in children with ALL(46).Case fatality of febrile neutropenia in children ranges from 6% to 13.2%(15–17).

Non neutropenic fever syndromes on the other hand are less well described but generally from existing literature are defined according to the localized signs found or unexplained fever" which is fever without localizing signs.

2.4 Empiric Antibiotic Guidelines

Empiric antibiotic guidelines have therefore been developed especially for the management of febrile neutropenia, based on the anticipated micro-organisms that may cause infection. The empiric antibiotic guidelines are mainly for febrile neutropenia, non neutropenic fevers are not emphasized upon in these guidelines. The table below summarizes the recommendations from the existing febrile neutropenia guidelines. Comparison is made between the institutional guideline to some of the existing guidelines for management of febrile neutropenia.

Table 1 Recommendations for treatment and investigations of febrile neutropenia

Recommendation	**International Pediatric Fever and Neutropenia guideline 2012**(4)	**European Society of Medical Oncology**(7)**(adult guidelines)**	**Kasili's Synopsis of the management of pediatric cancers in Kenya**(5)
Risk stratification	Yes, recommended Not specified	Yes, MASCC score	Yes, recommended Based on duration of neutropenia.
Evaluation	Blood culture(2 sites) Urine culture CXR in symptomatic	FBC/UEC/LFT Blood culture(2 sites) Coagulation screen CXR Urine/sputum/stool cultures if infection focus found	Septic screen- blood cultures Urine, stool, secretions, wound swabs, throat swabs, rectal swabs, nasal swabs LFTs, U/E, Blood Sugar, TBC+ESR, Blood film and Malaria parasites
Empiric antibiotic high risk	Monotherapy with antipseudomonal B-lactam or carbapanem Addition of 2nd gram negative agent/glycopeptides in clinically unstable	Monotherapy with antipseudomonal B lactam or carbapanem Specific antibiotic depending on clinical presentation	Crystalline penicillin and gentamicin Addition of metronidazole if diarrhea present
Empiric antibiotic low risk	Oral medication with amoxicillin clavulanate/ fluoroquinolone	Outpatient oral medication amoxicillin clavulanate/ fluroquinolone	IV Crystalline penicillin and gentamicin as initial antibiotic

Modification	-In all Negative culture-stop double gram negative coverage/glycopeptides at 24-72 hrs. -Escalate if fever persistent to anaerobic cover plus Gram positive and gram negative agent -Persistent fever with clinical stability-modification for broad spectrum coverage	-In all Negative culture stop antibiotics at 48 hrs. -fever + clinical instability-Escalate and consult further on appropriate choice	-Stop antibiotics in all only after resolution of neutropenia for 2 days -if neutropenia and fever persist beyond 14 days, stop antibiotics and manage expectantly
Cessation of antibiotics	-Negative blood culture at 48 hrs. -Afebrile for 24hrs with evidence of marrow recovery -Stop at 72hours if negative blood culture, afebrile for~ 24 hrs. in low risk neutropenic patient	-In all Negative culture stop antibiotics at 48 hrs. -In the afebrile and neutropenic continues antibiotics for 5-7days	Stop antibiotics in all only after resolution of neutropenia for 2 days -if neutropenia and fever persist beyond 14 days, stop antibiotics and manage expectantly
Antifungal treatment addition	Start after 96 hours in high risk patients	Start at 3-7 days	Add antifungal on day 5 in those with persistent fever

A Table illustrating recommendations for management of febrile neutropenia among pediatric oncology patients. Adult guidelines are included for comparison revealing very minimal differences in approach to management. Kasili's synopsis is the local clinical practice guideline that includes management of pediatric febrile neutropenia.

The guidelines' recommendations appear very similar, with subtle differences in risk stratification, management of low risk neutropenic patients, and in the type and duration of antibiotic treatment for febrile neutropenic episodes. The Kasili's Synopsis includes co-trimoxazole as antibiotic prophylaxis in neutropenic cancer patients, for pneumocystis pneumonia prevention. The overarching theme, however , seems to emphasize the empirical coverage of gram positive , gram negative organisms with the addition of other antibiotic that may be deemed necessary by the patients' underlying presentation and the organisms identified.

The treatment of febrile neutropenia, as outlined in the guidelines above, require a thorough examination of the febrile neutropenic patient to identify the possible focus of infection, and to collect the appropriate specimen for the identification of the responsible organisms. The local guideline is adapted for a malaria endemic setting, with the inclusion of blood slide for malarial parasites among the investigations required for a febrile neutropenic patient. The risk stratification is done after the initial 5 day course of antibiotic with low risk denoting the neutropenic fevers that have resolved and those that persist are denoted as high risk. There is currently no internationally validated risk scoring system for pediatric patients with cancer and febrile neutropenia. The recommended empiric antibiotic combination for treatment of febrile neutropenia in the local guideline is crystalline penicillin and gentamicin, for duration of 7-14 days depending on the risk stratification of the febrile episode. Addition of an empiric antifungal agent is recommended after 5 days of persistent neutropenic fever. The local guideline also recommends continuing of the course of antibiotics until the severe neutropenia resolves, even though the patient is afebrile.

In international febrile neutropenia guidelines however, in neutropenic fevers that have abated for more than 48 hours in the presence of negative cultures, stoppage of the antibiotic course is recommended(4). This may not be practical for the local set up for which the turn-around time for culture reports from the laboratory may take longer than 48 hours.

The antibiotic management of 'low risk' neutropenic fevers in children with cancer is shifting from mandatory inpatient management to successful outpatient management and early discharge of those found with low risk. This however requires careful risk stratification in order to identify those children with a probability of having complications following the febrile episodes. Several centers have proposed and validated within their setting various scores to predict those at risk of complications during their febrile neutropenic episodes. The table below summarized the various components of the risk prediction scores identified in different centers.

Table 2 : Components of risk prediction scores from various studies

Study	Components suggested as predictors of risk
PICCNIC study(47)	tumor type, temperature, clinical description of being 'severely unwell' hemoglobin concentration, total white cell count Absolute monocyte count.
Amman (48)	Chemotherapy more intensive than ALL maintenance Hemoglobin WBC count platelet count
Alexander (49)	AML Burkitts Lymphoma ALL in induction Progressive or relapsed disease with bone marrow involvement Hypotension Tachypnea/ hypoxia New infiltrate in CXR Altered mental status Mucositis requiring IV narcotics Vomiting/abdominal Pain
Klaassen(26)	Absolute monocyte count Presence of co morbidity Abnormal CXR
Baorto score(27)	AMC value>or =155per mm3

Table 2; illustrates the components of risk prediction scores from different studies. None of these have been validated for use in the local setting.

The performance of acute phase reactants e.g. C reactive protein (CRP) and procalcitonin in prediction of bacteremia in pediatric oncology patients has been mixed. In one study among pediatric oncology patients, CRP levels were found to be higher in those with

microbiologically defined infection than in CDIs and unexplained fevers(15). Another study done to compare the diagnostic test properties of both CRP and procalcitonin among children with cancer with blood stream infections revealed a high negative predictive value (94.67%) for procalcitonin. CRP had a comparably lower negative predictive value(90.6%) at the set cut off values in the study (50). The study recommended the use of procalcitonin for the exclusion of bacteremia in pediatric oncology patients. A systematic review of the two acute phase reactants was inconclusive on the use any acute phase reactant in predicting the risk of bacteremia in pediatric oncology patients(51) .

The empiric antibiotic guidelines recommended would therefore be developed to suit local antimicrobial resistance patterns, and should be periodically revised for the best clinical outcomes of infections among pediatric oncology patients.

2.5The KNH Guide to Empiric Antimicrobial Therapy

The Kenyatta National Hospital recently launched a guide to antimicrobial therapy among all patients who seek healthcare services in the hospital. This was done in the spirit of antimicrobial stewardship. The guide was developed after careful study of local antimicrobial resistance patterns. The guide has a major focus on adult patients and patient above the age of five, and recommends the management of community acquired infections among children under the age of five to be as per the basic pediatric protocol, a clinical practice guideline already in use among the pediatric population for the most common community acquired infections in our setting.

2.5.1 Risk Stratification of Infections among Patients

The risk stratification in the KNH guideline categorizes patients suspected to have infections according to their presentation and the type of microorganism that is likely to be causing the infection. This ranges from those who are suspected to have infections caused by susceptible community acquired microorganisms to those who may have infections caused by multi-drug resistant microorganisms.

The KNH empiric antimicrobial guideline recommends the risk stratification of patients into four major treatment categories;

- Category 1- for patients who have had no contact with the health care system or antibiotics use in the last 90 days, with no co-morbidities or organ failure.
- Category 2- for patients who have had a recent hospital admission, recent antibiotic exposure, or has had any invasive procedure done.

- Category 3- for long hospitalized patients with invasive procedures done, severe neutropenia, recent multiple antibiotic therapies used
- Category 4- patients unresponsive to antibacterial agents, with multi drug resistant microorganisms.

It then recommends the identification of the site of infection, whether bloodstream, intra-abdominal, lower respiratory, in order to guide the choice of empiric antibiotic to be used after appropriate specimens have been taken for evaluation. De-escalation is also recommended after susceptibility report is available.

Pediatric oncology patients in our facility would typically fall under category two and three risk categories, even at initial admission before a cancer diagnosis is made, as they come typically as referrals from peripheral hospitals, have had recent antibiotic use, have co-morbidities at presentation and later on, most will have invasive procedures done as part of the cancer diagnosis and or treatment, and some may have severe neutropenia at presentation.

2.5.2 Anticipated Organisms

The anticipated organisms for different sites of infection as outlined in the KNH guidelines are summarized in the table below as per the site of infection and the risk category. The risk categories are as described in sectioned 2.5.1 above

Table 3: Anticipated microorganisms per risk stratification in the KNH antibiotic guideline

Risk category / Site of infection	Category 1	Category 2	Category 3
Bloodstream infections	Staph.aureus CONS E. coli	E.coli Klebsiella Proteus	Pseudomonas* E.coli* Klebsiella* Enterobacter* Citrobacter* Acinetobacter *
Pneumonia	S. pneumonia, Staph. spp,	E.coli Klebsiella	Pseudomonas spp* Klebsiella pneumo.* Acinetobacter*
Urinary tract infection	E. coli Staph. saprophyticus	E.coli Klebsiella Staph. Spp Proteus enterococci	E.coli Klebsiella Staph. Spp. Proteus spp. Enterococci Pseudomonas spp.
Skin and soft tissue infection	Staph. aureus streptocoocus	Staph.spp Enterobacteriaceae	Pseudomonas spp. Enterobacteriaceae

*Multidrug resistant organisms

The table above illustrates the anticipated organisms in each category that determine the empiric antibiotic that is to be used for the most common type of infections encountered.

It is however to be noted that the yield for microorganisms during fever in immune-suppressed cancer patients is low, up to 36%(14–16,37,38,44). In the setting of immune-

suppression, the organisms that have low virulence have a potential of causing serious disease in pediatric oncology patients with febrile neutropenia.

The epidemiology of organisms associated with febrile neutropenia is region specific and has been changing in the same regional patterns(52). In some developed countries, a predominance of gram negative organisms was reported initially, then a shift towards gram positive predominance after the introduction of antibiotic prophylaxis for low risk neutropenic patients, and more recently an increase in gram negative and poly-microbial organisms implicated in febrile neutropenia(15,52,53). In some developing and developed countries, the predominance of gram negative organisms in pediatric febrile neutropenia has not changed from the reported epidemiological data(52,54). Attention has been drawn to some of the most threatening bacterial pathogens in existence, summarized in the acronym ESKAPE(53,55), which are multi drug resistant(53,55). There has been a universal increase in antibiotic resistance among cancer patients, and this has had an effect on the choice of empiric antibiotics in febrile neutropenia.

The KNH guideline recommends mandatory infectious disease consultation for patients identified to have multidrug resistant organisms, or unresponsive to antibacterial agents.

2.5.3 Empiric Antimicrobial Treatment

The table below summarizes the empiric antibiotics to be used in blood stream infections, pneumonia, UTI, and skin and soft tissue infection from the KNH guideline. The treatment for category one is not included as the pediatric oncology patient typically fall into categories 2/3/4. The guideline recommends the basic pediatric protocol for antibiotic choices for those below 5 years of age for the different sites of infection mentioned above. In the basic pediatric protocol, specific recommendations for pneumonia, malaria, diarrhea, meningitis but no specific guidelines for urinary tract infection, skin and soft tissue infection.

Table 4: Empiric antibiotic choices per the KNH antibiotic guideline

Risk category / Site of infection	Category 2	Category 3	Basic pediatric protocol (56)
Bloodstream infections	Piperacillin/tazobactam + amikacin OR Ceftazidime+amikacin OR Ertapenem	Imipenem/meropenem + amikacin OR Piperacillin/tazobactam + amikacin OR Cefepime +amikacin	Ceftriaxone 50mg/kg 12hrly
Pneumonia	Piperacillin/tazobactam Or ceftazidime + amikacin	Imipenem cilastatin Or meropenem Or Piperacillin/tazobactam Or cefepime+ amikacin (vancomycin teicoplanin/linezolid if MRSA suspected)	High dose amoxicillin crystalline penicillin + gentamicin Add flucloxacillin if Staph aureus suspected
Urinary tract infection	Nitrofurantoin Or Ertapenem or Piperacillin/tazobactam	Imipenem/meropenem + amikacin OR Piperacillin/tazobactam + amikacin	*No explicit reference in guideline
Skin and soft tissue infection	Clindamycin or ceftriaxone Or tigecycline	Piperacillin/tazobactam + amikacin OR Cefepime +amikacin	*No explicit reference in guideline

2.6 Challenges in Selection of Initial Choice of Antibiotic

In the local set-up pediatric oncology patients are typically long stay in-patients. Prolonged hospital stay has been linked to development of hospital acquired infections, and predisposes the individuals to antimicrobials that are more resistant to the commonly used empiric antibiotics. Antibiotic resistance in turn is linked to increased health care costs(more expensive antibiotics, prolonged hospital stay) and increased mortality from febrile episodes(32,33,54). Patients referred from peripheral facilities may have antibiotic resistant organisms (resulting from prolonged contact with a hospital environment) and hence complicate initial antibiotic choices.

Antibiotic resistance has been described in pediatric cancer patients to increase over the years. In a study in Egypt, ESKAPE pathogens accounted for 24% of the total number of blood stream infections evaluated during the 6 month period of the study. 74% of the ESKAPE pathogens were multidrug resistant, defined in that study as non-susceptibility to at least one agent in three or more antimicrobial classes. The duration of illness and mortality due to ESKAPE infections were higher than the CONS related infections. CONS accounted for 40% of the total number of blood stream infections. 41.5% of the CONS identified were multidrug resistant with a majority (58.5%) remaining sensitive to empiric antibiotic regimens(55).

There are multiple institutional guidelines for empiric antibiotic choices in the hospital. The basic pediatric protocol which gives guidelines for common community acquired infection for children under the age of five years, the KNH guideline to empiric antibiotic therapy described above, and the Kasili's Synopsis of management of pediatric cancers which gives specific guidelines for the management of febrile neutropenia. All the above guidelines have different empiric antibiotic choices for pediatric patients who present with fever, whether neutropenic or non-neutropenic. For example, the Kasili's synopsis suggests crystalline penicillin and gentamicin for treatment of neutropenic fevers, the basic pediatric protocol suggests use of ceftriaxone at 100mg/kg /day for sepsis (comparable definition to blood stream infection in pediatric cancer patients), and the KNH guide recommends the use of piperacillin / tazobactam in combination with amikacin for category 2 patients in which most pediatric oncology patients would fall. The multiplicity of guidelines thus not only complicates empiric antibiotic choice for the primary clinician, but also promotes poor antimicrobial stewardship in this subset of patients.

The minimum quality of evaluation that a pediatric cancer patient should receive in the setting of febrile neutropenia has been outlined in several clinical practice guidelines. Guidance is provided to the clinician on the empirical choice of antibiotic and later escalation or de-escalation of the empiric choice. These minimum standards of evaluation are defined in the existing clinical practice guidelines and are summarized in table 1 above.

The Kasili's synopsis, which is the local guideline, recommends extensive evaluation in the setting of febrile neutropenia. The synopsis recommends the careful clinical evaluation of a pediatric cancer patient who develops fever especially in the setting of neutropenia. Blood cultures to be taken once the temperature is above 38^{o}C, in addition to urine and stool cultures and other specimens as mentioned above (see table 1) and should be re-cultured every 24 hr. period if the temperature remains above 38^{o}C. Antibiotics may also be started in those who despite being afebrile are 'looking unwell'. While these evaluations are important, the laboratory turn-around time especially for cultures in the local setup is comparatively long, and may not support the timely decisions on escalation or de-escalation of antibiotics.

2.7 Theoretical and Conceptual Framework

The conceptual framework used in this study is based on a theoretical model of factors that determine antibiotic prescribing suggested by Parker et al(57). This theoretical model is mapped onto the theoretical behavior change wheel, which was developed to assist in understanding factors that determine behavior change in order to be able to design effective intervention strategies. The utility of this study is to eventually form a basis for future interventions in antimicrobial stewardship, and the variables in this study form part of the centre of the wheel. According to the behavior change wheel, three factors interact that determine a certain behavior, a good example being antimicrobial prescribing behavior. The three factors include capability, motivation and opportunity, the COM-B model, as suggested by Michie et al(58).

Capability in the COM-B model was described as an individual's possession of psychological and physical capacity to engage in the concerned activity, i.e. having the necessary knowledge and skill. Opportunity described all factors that lie outside of the individual that either prompt the behavior or make it possible, while motivation described brain processes that energize or direct behavior including habitual processes, emotional responding and analytical decision making(58).

This model was applied in the study by Parker et al describing determinants of antimicrobial prescribing among hospital doctors in England, in which the COM-B model was modified for the conceptual framework in that study. Capability was mapped onto autonomy in antimicrobial prescribing among the doctors, and opportunity was mapped onto antimicrobial guidelines adherence, and motivation was mapped onto antibiotic awareness. Autonomy was defined as the ability of the doctor to prescribe or alter antibiotic prescriptions without consultation of other colleagues. Antibiotic awareness which was mapped into motivation for prescription of antibiotics included the knowledge of antibiotics as a limited resource and the knowledge of existence of antibiotic resistance. Opportunity was attributed or mapped onto the adherence of physicians to antibiotic guidelines. The theoretical framework suggested and utilized by Michie et al(58) and Parker et al above(57) is illustrated below.

Illustration depicting the relationship of the factors that determine behavior-(COM-B) theory and its application to an antimicrobial prescription study

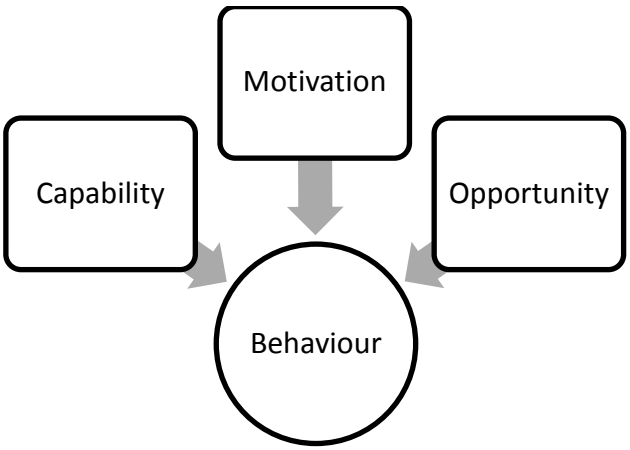

Figure 1; an illustration depicting the relationship of factors that determine behavior COM-B theory

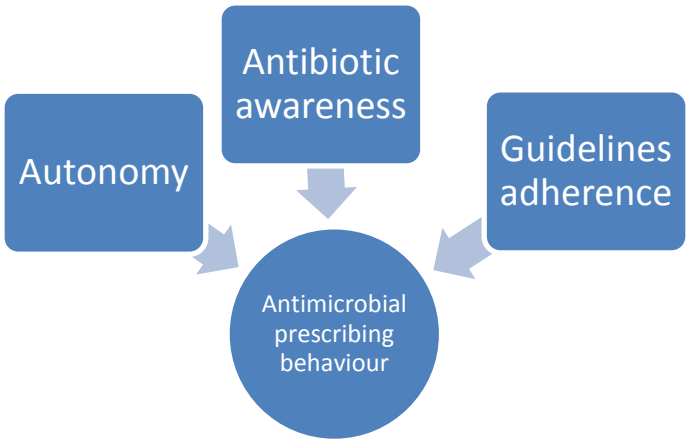

Figure 2: the application of COM-B theory to an antimicrobial prescription study

The 'motivation' factor as outlined and explained in the COM-B model is further elucidated by the Drug Choice model, which is a cognitive prescribing model related to Vroom's expectancy theory, a management theory that is used to explain motivation at work. The Drug choice Model suggests that a practitioner's drug choice is based upon beliefs that the likelihood that certain outcomes will occur when the drug is used and the value that the

practitioner places on those outcomes. The six (6) outcomes identified to be important to practitioners are: 1.

Control of the disease, 2. Patient compliance 3. Side effects 4.Cost 5.Satisfying patient demand 6.Criticism from colleagues. The Drug Choice model partially explains the motivation factor in the COM-B model, which was defined as brain processes that energize or direct behavior including habitual processes, emotional responding and analytical decision making(58).

In the proposed study, antimicrobial prescribing patterns for pediatric cancer patients for the most recent febrile episode will be retrospectively studied. The variables for the proposed study will be mapped into the determinants of behavior as suggested by Michie et al and as applied by Parker and colleagues(57,58). The Kenyatta National Hospital setting is a tertiary hospital with several cadres of practitioners. In regards to the pediatric cancer wards, the primary doctor is typically a pediatric resident, or a medical officer, who are supervised by hemato-oncologists once or twice weekly in order to make clinical decisions regarding cancer patients. There is also an infectious disease team that should be consulted (as per the KNH antimicrobial guide) in case of multidrug resistant infections. The study design, being retrospective, will not be fully able to assess the capability and/or autonomy of empiric antibiotic choices as potential respondents cannot be contacted to respond to the autonomy of their prescription decisions.

Guideline adherence will however be assessed in comparison to three local existing guidelines that could have potentially informed empiric antibiotic prescriptions during fever episodes among pediatric cancer patients. These include the Kasili's synopsis of management of pediatric cancers, the GOK basic pediatric protocol 2016, and the KNH guide to empiric antimicrobial therapy second edition 2018. Clinical practice guidelines are typically known to inform the most recent best practice for management of specific conditions. The extent of influence of guidelines on prescription of empiric antibiotics will be brought under focus.

In this study motivation will depict and attempt to decipher the reasoning behind each antibiotic prescription. The characteristics of patients that are prescribed with antibiotics will be described and patterns that arise from the prescriptions will be documented. The patients demographics, type of cancer and its staging, cycle of chemotherapy, status of underlying cancer (whether relapsed or in remission), presence of localized or disseminated infection are some of the variables that will be documented to describe the pattern of antibiotic prescription among pediatric cancer patients with fever.

The relationship between the patient's hematologic characteristics and the risk stratification has been derived from the studies that predicted the risk of bacteremia or serious illness in pediatric cancer patients with febrile neutropenia. The presence of neutropenia with attendant monocytopenia, low hemoglobin and low platelet count have been associated in several studies as to predict severe illness in pediatric cancer patients with neutropenia(26–28,48,49)

The conceptual framework to be utilized for this study is as depicted below.

Fig 3 Conceptual framework for the proposed study

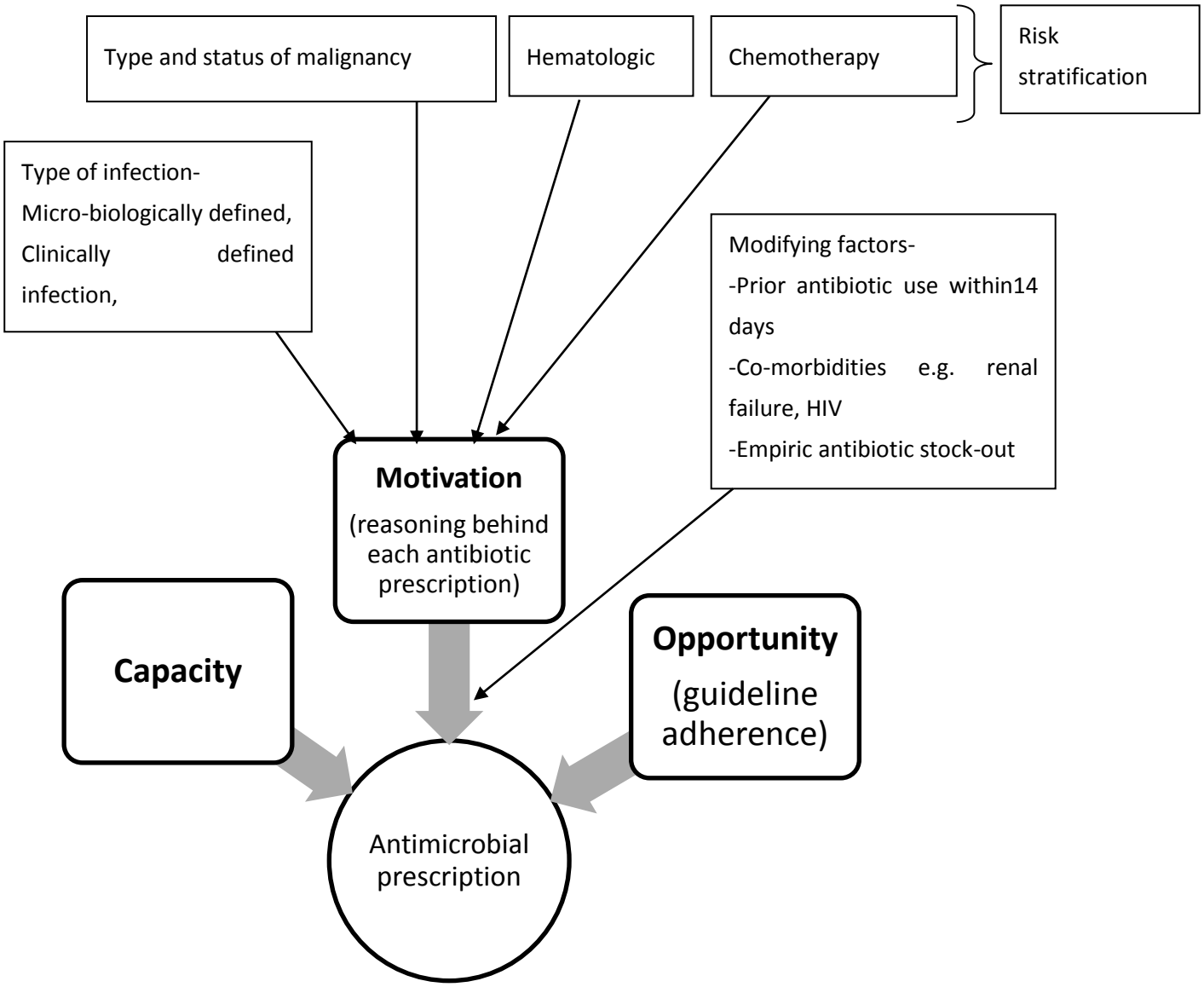

Figure 3; the conceptual framework for the proposed study

2. 8 Justification and Utility

Antibiotic management in pediatric cancer patients with febrile episodes has not been described in our setting. In view of the increasingly problematic issue of antimicrobial resistance, the knowledge of the choice of empiric antibiotics in pediatric cancer patients in the setting of multiple guidelines will begin the journey towards proper antibiotic stewardship. The recently launched KNH guideline for antimicrobial therapy provided a background for an audit of the antibiotic management of the febrile episodes.

Quality evaluation of febrile illness in paediatric cancer patients forms a basis for antibiotic prescription, as it would enable proper classification of febrile illness in pediatric cancer patients(particularly those immune suppressed)and hence the recommended antibiotic given. The study provides insight into the quality of evaluation received by pediatric cancer patients during febrile episodes as compared to the recommended care in the Kasili's synopsis- the institutional clinical practice guideline for pediatric cancer patients.

In addition, there is a paucity of studies on antibiotic utilization among pediatric oncology patients in sub-Saharan Africa, and such studies would add knowledge to the subject.

The results from this study avails baseline data for future interventions to improve the antimicrobial use among oncology patients and stimulate further research in antimicrobial resistance patterns in pediatric oncology patients and its routine surveillance in our hospital.

2. 9 Research Question and Study Objectives

What is the antibiotic management for febrile episodes in children 1-15 years with cancer at the Kenyatta National Hospital from1st October 2018 to 30th September 2019?

2.9.1Primary Objective

To describe the pattern of antibiotic prescription for febrile episodes in children 1-15 years of age with cancer at the Kenyatta National Hospital.

2.9.2 Secondary Objectives

To describe the clinical and laboratory evaluation of febrile illness in children with cancer at the Kenyatta National Hospital.

To describe the pattern of microbes grown and their sensitivity to the empiric antibiotics.

3.0 CHAPTER THREE: METHODOLOGY

3.1 Study Design

This is a retrospective observational study that involved review of medical charts febrile containing febrile episodes of children between the ages of 1-15 years seen within Kenyatta National Hospital who have suspected or confirmed diagnosis of any malignancy.

3.2 Study Site

The study was conducted within the Kenyatta National Hospital, a tertiary government hospital, one of the largest public hospitals that offer comprehensive cancer care at an affordable cost. It is located in Kenya's capital city, Nairobi, and it serves as a teaching and referral hospital. It has a total bed capacity of 1800 beds and is also one of the oldest hospitals in Kenya.

The setting was within the pediatric specialized oncology unit which is a 28 bed capacity unit and is an isolated unit within the hospital, general pediatric wards, in which children with suspected and confirmed malignancy are admitted; specialized wards in which children have been admitted with various malignancies(inclusive of but not limited to pediatric eye unit, ENT department, general surgical ward and orthopedic ward), the adult specialized oncology ward where children with suspected or confirmed cancer beyond 13 years of age are admitted; and in the gynecological ward for children with reproductive tract tumors. The setting also included the outpatient oncology clinic, which runs on Mondays, through which paediatric oncology patients are admitted into the various wards.

3.3 Study Population

The study population was of children between the ages of 1-15 years seen within Kenyatta National Hospital who have suspected or confirmed diagnosis of any malignancy and have

medical charts containing febrile episodes. The antibiotic management of the febrile episodes must have been started and completed in Kenyatta National Hospital.

The study participants included those admitted in the specialized pediatric oncology ward with a bed capacity of 28 (twenty eight) beds, within which children with both solid tumors and hematological tumors are treated. A fraction of children with confirmed cancer who were admitted within the pediatric general wards in special partitions within the wards were included, while those with suspected cancer prior to diagnosis were admitted with other pediatric patients until diagnosis was confirmed or until definitive treatment for cancer was instituted e.g. neoadjuvant chemotherapy for nephroblastoma. Some children initially were admitted in specialized wards due to their presentation and were admitted later on to the general pediatric wards once a diagnosis was made and were due for cancer chemotherapy or radiotherapy. For example, children with eye cancers were admitted within the specialized ophthalmology ward where they received their full treatment. For those presenting in the orthopedic, general surgical, otolaryngology, neurosurgical departments, chemotherapy and radiotherapy was coordinated from either the pediatric specialized oncology unit or the pediatric general wards. This means that after surgical excision or incisional biopsy, the patients were admitted to the various medical units for continued chemotherapy or radiotherapy and supportive care during their treatment.

Children above 13 years of age were admitted in the adult medical wards prior to a definitive diagnosis being made, and transferred to a specialized adult oncology ward when ready for definitive treatment for the particular type of cancer. These were also followed up in the hemato-oncology clinic which runs on Mondays and readmissions for subsequent chemotherapy sessions were also done from there.

In the proposed study period,, the Kenyatta National Hospital had 307 admissions of children less than 1-15 years of age with a cancer diagnosis from 1stOct 2018 to 30thSeptember 2019 This number includes only one admission per an individual patient.

3.3.1 Inclusion Criteria

Children 1-15 years of age with malignancy (suspected and confirmed) with most recent febrile episodes in children managed at Kenyatta National Hospital from 1st Oct 2018 to 30th September 2019.

3.3.2 Exclusion Criteria

Children 1-15years of age with suspected or confirmed cancer with most recent febrile episodes managed in the intensive care unit.

Febrile episodes occurring in children with suspected malignancy who received a final diagnosis other than a malignancy discovered during the period of study.

3.4 Sampling Size and Sampling Procedure

3.4.1 Sample Size Calculation

307 cases of malignancies admissions reported between1st October 2018 and 31st September 2019 at KNH for children aged 1 to 15 years. (Source: KNH health records department)

Sample size formula for a single population proportion

A baseline antibiotic use survey done by the Ministry of Health (Kenya) in 2003 revealed a prevalence of antibiotic use of 78% in our general population. We assume a proportion of 0.78 for the prevalence of use of antibiotics for fever episodes.

$$n_0 = \frac{Z_{\frac{\propto}{2}} * p(1-p)}{e^2}$$

Where: -

$\propto$ - Level of significance (estimated as 0.05); probability of type I error.

$Z_{\frac{\propto}{2}}$ – The critical value associated with significance level

p – Proportion estimate

e - Margin of error (acceptable random sampling error)

$$n_0 = \frac{1.96^2 * 0.78 * 0.22}{0.05^2}$$

$$= 263.68 \cong 264$$

$$\frac{264}{307} * 100 = 86\%$$

Finite Population Correction (FPC) Factor formula

We apply the FPC factor because the sample is a significant proportion of the population.

$$n = \frac{n_0 * N}{n_0 + (N - 1)}$$

$$n = \frac{264 * 307}{264 + 306}$$

$$= 142.2 \cong 142$$

The sample size for the study was 142 medical records.

3.4.2 Sampling Procedure

Consecutive sampling was used for the study. Children 1-15 years of age with suspected or confirmed cancer with fever episodes that meet the inclusion criteria were included in the study until the sample size calculated is reached.

Although the sites from where potential participants were recruited were many, the outcome of greatest interest is the occurrence of fever among this group of patients, which is rare from existing literature(37). Therefore, the very specific inclusion criteria were set to minimize the effect of missing data. The records of the potential participants were studied for potential to be included based on the criteria set.

To ensure that all potential records had a chance to be included in the study, recruitment was done on selected days for different study sites. On Monday and Fridays, recruitment of participants from outpatient oncology clinic was done, Tuesdays from pediatric specialized oncology unit, Wednesdays for participants from the surgical wards, Thursdays for the general paediatric wards, Fridays for participants from the adult oncology wards. Consecutive sampling was thereafter done in the specific study sites on the medical records of the patients

that were already in the wards or were being evaluated for admission into the ward at the outpatient clinic (active records). The days were selected after the pilot phase of the study as the days on which maximum number of files would be retrieved as only active records were used in the study, or when use of the records would not interfere with the day to day usage of the files for patient care.

This recruitment strategy was proposed because stratification by department of admission was difficult as the patient care is not centered in one unit only, for example, a child with nephroblastoma would initially be admitted to the pediatric general ward for neo adjuvant chemotherapy, be transferred to pediatric surgical wards for nephrectomy, after which will be transferred back to the pediatric wards for continuation of chemotherapy and subsequent radiotherapy.

Stratification by tumor type to divide between hematological or solid tumors produced unequal strata, with the population with solid tumors making up around 75% of the admissions in 2017(Source: KNH records department), yet in risk prediction studies, hematologic malignancies and their treatment are associated more with febrile episodes compared to solid tumors(28). This created a unique problem of probability of excluding potential participants as a result of stratification during recruitment.

Consecutive sampling on different sites on the different days was used across the study sites, as the hospital stay of paediatric oncology patients was typically lengthy, therefore nearly all potential charts meeting the inclusion criteria were included .This method was selected because childhood cancer in itself is rare(9), and incidence of fever episodes among children with cancer with is low as well(37). The active records in the study sites were also be easily accessible and this was found to be practical keeping in mind the short duration of the proposed study and the limited budget of the proposed study(59).

3.5 Recruitment and Consenting Procedures

A waiver of consent was obtained in order to study potential participants' medical records for eligibility into the study. This was done to be able to find the febrile episodes documented in the file that were eligible for inclusion in the study. Information that was obtained included: current age and sex of the child, diagnosis /suspected diagnosis (laboratory documents) and any fever episode from 1stOct 2018 to 30thSeptember 2019 in the study settings.

Only active records (medical records of patients that were already in the wards or were being evaluated for admission into the ward at the outpatient clinic) were used for this study. A waiver of consent was obtained for the study of active records to be able to identify the potential study participants for recruitment**.** Active records were proposed for use as they were deemed to be well preserved and would have the record of most recent febrile episode within the defined study period. In the specific study sites, active records were accessed; after introducing the data abstractor to the in charge in the specific site, displaying a copy of the approval letter from KNH/UON- ERC, and administrative permissions and first identifying potential participants from the admission book. The information obtained was then used to retrieve the files from the area where they are kept within the study site. The files were then perused for suitability to the inclusion criteria. The files with suitable febrile episodes were used in the data abstraction. The use of active records for the study did not interfere with the patient care. The timing of use of these records was scheduled for afternoons when most of the clinical use of the files was complete. The medical records were studied to identify, between the specified dates, the most recent febrile episodes from the clinician notes. A febrile episode with documented temperature and that fit the inclusion criteria was considered eligible for inclusion in the study. Only the most recent febrile episode in the selected records within the defined study period was carefully recorded. A waiver of consent was obtained from UON-ERC to allow for the use of the medical records in the study as consenting process for this minimal risk study was deemed to introduce a selection bias in the recruitment.

Recruitment was done by the principal investigator.

3.6 Data Collection Procedures

3.6.1 Data abstraction procedures

Data collection was done using a data abstraction tool that was designed (see appendix 1) and piloted for use in the study. During the pilot phase, the challenges in obtaining the consent for data abstraction were noted and a protocol amendment was made, in order to allow for the complete waiver of consent and was approved by the KNH-UON ERC (ref; KNH-ERC/Mod&SAE/381.

Medical files of participants in who fit the inclusion criteria were carefully studied to note the recording of febrile episodes; after the temperature chart was carefully studied to identify the most recent febrile episode and its duration, clinician review notes were studied next, then nurses records and then the laboratory records in that order. In case of differences between the nurse's records and clinician's record, the higher record of temperature was recorded for the most recent febrile episode. Once the temperature is recorded the other variables were filled out in the data abstraction tool.

The clinical findings were recorded according to the general and systemic findings as documented in the patients file. The findings were recorded as normal or abnormal as determined by from the participating records. The vital signs were included as part of the general examination and as such all the fever episodes had abnormal general examination due to the inclusion of the abnormal temperature in the general examination findings.

Documentation of findings of the systemic examination in the various systems was inclusive of both subjective and objective findings. In the pilot phase it was noted that documentation of the clinical findings was not complete as to fit into the definitions of clinical syndromes e.g. pneumonia, meningitis etc. as defined in the basic pediatric protocol. Therefore any documentation of subjective and or objective findings for the various systems was taken as

examination of the particular system. For example if only subjective history of dysuria was documented, it would be counted as though the genitourinary system was examined.

Laboratory investigations at admission were those done within 24 hours of admission while those at fever episode were investigations that were done at any time during the particular fever episode.

Empiric antibiotics were documented if the date they were prescribed on the treatment sheet was similar to the date of the start of the febrile episode or if they were started at any time during the febrile episode. Antibiotic duration was documented as the total number of days the particular antibiotic was administered, regardless of whether or not they were administered appropriately (in terms of frequency of administration). Prior use of antibiotics was documented as those administered within the last 14 days before the febrile episode; this period was chosen as documentation (as opposed to recent antibiotic use of 90 days) due to ease of obtaining the records of antibiotic usage within 14 days of start of the most recent febrile episode.

Older volumes of the files were requested for retrieval from the specific site health and information officer for further information that would have been missing from the current volume of medical record in use.

A new data abstraction tool was filled for each febrile episode that was identified as eligible as per the study criteria. Other missing variables were indicated by the dash symbol (-).These variables were coded differently during the analysis.

Only the principle investigator did the data abstraction.

3.6.2 Data collection

A small pilot study was conducted prior to the study to troubleshoot difficulties that would be experienced with the tool during data collection and analysis during the study. The pilot was conducted as an internal pilot, where information for other episodes (aside from the most

recent episode) was collected. The sample size for the pilot study was 10% of the calculated sample size i.e.15 records. To ensure adequate representation from each of the study sites, days for collection of data were assigned for the different study areas. Challenges in the consenting process were identified, which led to the protocol amendment as stated above.

Data was collected onto the data collection tool by the principal investigator from the medical records in the study sites. The review and use of medical records was scheduled so as not to interfere with the care the participant was receiving.

Suitable medical records available at the study sites were identified by the principal investigator and one research assistant. The inclusion and exclusion criteria were applied to find suitable febrile episodes for study.

The data was checked for completeness at the end of each day by the principal investigator, weekly by the statistician.

3.7 Study Variables

3.7.1 Dependent Variable

- Prescription of antibiotic

3.7.2 Independent variables

- Patient's age in years
- Patient's sex
- Diagnosis staging and status of malignancy
    - Hematologic malignancies
        - not in remission
        - in remission
        - relapsed
    - Lymphomas- confirmed and suspected
    - Solid tumors-confirmed and suspected

- Site /type of infection-as documented
- Hematologic characteristics
    - Absolute neutrophil count
    - Absolute monocyte count
    - Hemoglobin level
    - Platelet count
- Specimen type and culture results
    - Gram positive organisms
    - Gram negative organisms

3.7.3 Confounding variables

- Prior antibiotic use within 14 days prior to the fever episode
- Administrative factors e.g.
    - Pharmacy stock outs of prescribed empiric antibiotic (denoted in the treatment sheet as o.s.)
- Co morbidities- documented only in patients where these are present)
    - Renal failure(documented by the clinician and supported by results of deranged urea and creatinine)
    - Liver failure (documented by the clinician and supported by results of deranged liver enzymes)
    - HIV status

3. 8 Ethical Considerations

Approval for the study was sought initially from the department of Pediatrics and Child Health, University of Nairobi, then from the KNH/UON Ethics and Research Committee. Copies of the data collection tool the consent form as well as subsequent modifications to either document were presented to the above committee prior to commencement and continuation of the of the study after amendments made. Once approval was obtained, study data was collected and analyzed while maximum patient confidentiality was maintained. The data was fully anonymized during data entry and analysis.

Strict confidentiality was observed throughout the entire study period. The filled data collection forms were stored by the principal investigator in a locked cabinet with only the principal investigator with access. Data was entered into a computerized data base and codified. Access passwords were only given to the principle investigator and statistician.

This was a non-invasive study with minimal risks of harm. A waiver of consent was granted for the use of medical records of the potential participants. Being a retrospective study, the standard of care that the participants received remained as per the Kenyatta National Hospital's expected standards, and they were not interfered with in any way.

3.9 Data Management and Analysis

The filled in data collection forms were stored in a locked cabinet in the statistician's office during data entry. None of the participants' forms that had information that could directly identify the participants, only the serial numbers were used. The computers used for data entry and analysis were password protected.

The filled individual participant data collection tools were crosschecked for completion and proper filling by the principle investigator. Data collected was entered into a records form and the contents of the data base and the hard copy folders will be compared to identify any

errors. Data was, entered, cleaned and coded in a computerized database. The coded data was stored and analyzed.

All statistical analysis was done using IBM SPSS Version 25 - International Business Machines, Statistical Products and Service Solutions (Formerly Statistical Package for Social Sciences. Descriptive statistics were performed to generate frequencies, means, medians and standard deviations. In addition, inferential statics to determine whether there was a significant association between variables was conducted through Chi-square test of independence and binary logistic regression.

The results of the analyses are presented in frequency tables, figures and graphs with brief write-ups to describe the results and the interpretation derived from the results.

3.9.2 Management of missing data

Being a chart review, the medical records may be having incomplete/ missing data as they were recorded for clinical use and not for study purposes. The exclusion criteria covered those charts with lack of variables recorded in the chart (e.g. temperature defining fever), and presence of confounding co-morbidities that affected the outcome variable under study; the prescription of antibiotics. For example charts with febrile episodes managed in ICU were excluded.

Missing data at the level of analysis was managed by case deletion, so that for each variable only the complete charts regarding that variable were analyzed (complete case analysis). This assumed that the data was missing completely at random, so no biases were introduced at this level.

Data Dissemination

The overall study findings will be availed to the staff of the specialized pediatric oncology unit, pediatric residents working in the oncology rooms within the pediatric wards, KNH staff working in the pediatric wards in the overall aim of improving antimicrobial prescription

practices among the staff working in the Hospital. The study finding will also be presented to the University of Nairobi Department of Pediatrics and Child Health staff and residents as a fulfillment of the requirements of the M.Med program.

CHAPTER 4: RESULTS

4.0 Introduction

In the 1 year study period, 139 most recent febrile episodes from 139 pediatric patients with a suspected or confirmed diagnosis of any malignancy fulfilling the inclusion criteria were evaluated. All the data was retrospectively abstracted from active patient records using a data abstraction tool.

4.1 Patient characteristics

The patients' characteristics whose febrile episodes were included in the study are documented in the table below

Table 5: Clinical characteristics of paediatric patients with cancer and with febrile episodes at the KNH

Patient Characteristic(n=139)	**Frequency**	**Percentage**
Age (years)	**Median (IQR)6 (3-9)**	
1-<5	57	41
5 -10	63	45.3
>10	19	13.7
Gender (n=139)		
Male	81	58.3
Female	58	41.7
Underlying Diagnosis(n=139)		
Solid tumor	59	43.7
Leukemia	46	34.1
Lymphoma	30	22.2
Chemotherapy started(n=137)		
Yes	87	64.4
No	47	34.8

Three (3) patients died during the study period due to all-cause mortality, they all had progressive disease at the time of death. There were 139 most recent febrile episodes from 139 medical records of participants included in the study. Only one febrile episode was included per study participant. The median age at diagnosis of the most recent febrile episode

was 6 years (IQR 3 years-9 years). 81 (58.3%) were of male gender. The most common underlying cancer diagnosis were solid tumors 59(43.7%), but acute lymphoblastic leukemia was the most frequent actual cancer diagnosis (29%), followed by lymphomas (23%), then nephroblastomas (21%). Most of the fever episodes occurred among those who had already started their chemotherapy for their underlying malignancy. Table 5 above illustrates these findings.

4.1.1 Febrile episode characteristics

Fever was defined using the institutional definition, with a febrile episode being defined as a period of time during which there is documented fever. Resolution of a febrile episode was defined as the absence of fever for more than 48 hours. Fever episodes with a single temperature of $\geq 37.8^{o}C$ were included in the analysis. The institution mode of temperature measurements were mainly axillary thermometers and by digital non-contact thermometers. The characteristics of the febrile episodes are summarized in the table 6 below.

Table 6: Characteristics of febrile episodes in children with cancer in KNH

Variables	Frequency	Percent
Febrile Episodes characteristics (n=139)		
Temperature (Mean, SD);	38.54 (0.67)	
Duration of fever (days) (Mean, SD);	5 (3)	
Duration of fever episodes (days)		
≤5	95	68.3
>5	44	31.7
Time since admission(days) (n=139)		
Median (IQR)	28(6-75)	
Time since last chemotherapy (days) (n=84)		
Time from last chemo dose (days) Median (IQR)	5 (2-13)	
Neutropenia (n=111)		
<0.5	34	30.6
≥0.5	77	69.4

The mean temperature for the febrile episodes was 38.5^0C. The median duration in length of stay prior to febrile episode was 28 days (IQR 6-75 days). The mean duration of the febrile episodes was 5 days, with 68.3% of the febrile episodes lasting ≤5 days. The majority of the fever episodes (69.4%) were non-granulocytopenic, while 30.6% had febrile neutropenic episodes. Median duration of time since last dose of chemotherapy was 5 days (IQR 5-12 days). The chemotherapy regimens used were as documented in the Kasili's synopsis of management of pediatric cancers, the institutions clinical practice guideline.

4.1.2 Febrile neutropenic episodes: Characteristics

Table 7 below illustrates the distribution of neutropenic and non neutropenic febrile episodes in paediatric patients with various diagnoses of cancer.

Table 7: Distribution of neutropenic and non neutropenic febrile episodes in pediatric patients with cancer

Underlying cancer diagnosis	n=139(%)	Neutropenia	
		<0.5	≥0.5
Diagnosis (n=111)			
Solid tumor	40 (36.0)	5 (12.5)	35 (87.5)
Leukemia	42 (37.8)	23 (54.8)	19 (45.2)
Lymphoma	29 (26.1)	6 (20.7)	23 (79.3)
Total	139 (100%)	34 (30.6%)	77 (69.4%)

In the febrile episodes with documented absolute neutrophil count (ANC), majority 23(67.6%) of children with neutropenic episodes had leukemia as the underlying cancer diagnosis, with solid tumor least presenting 5 (14.7%). The mean temperature of the neutropenic febrile episodes was 38.6^0C (SD 0.7 degrees Celsius).

4.1.3 Febrile non-neutropenic episodes: Characteristics

The mean temperature for the non neutropenic fever episodes was 38.5^{O}C (SD 0.6^{O}C). Among the non neutropenic febrile episodes, majority 35 (45.5%) of patients had a diagnosis of solid tumor as the underlying cancer as illustrated in table 7 above.

4.2 Empiric antibiotics prescribed for the febrile episodes

For the 139 febrile episodes under study, in one febrile episode the source document for the antibiotics prescription was missing. Of the 138 febrile episodes, 19 (13.8%) of them did not have any antibiotics that were prescribed during the febrile episodes including 4 episodes that lasted more than 5 days. Of the 119 episodes that had an antibiotic prescription, 68(57.1%) had antibiotic monotherapy prescribed, while combinations of antimicrobials were prescribed in 51 (42.9 %) of the fever episodes. The mean duration of antibiotics was 9days (SD 5 days). In 54 (47%) episodes, antibiotic duration exceeded 7 days. Table 8 below illustrates these aspects of general antibiotic prescription during the febrile episodes

Table 8: General antibiotic prescription characteristics

Variables	Frequency	Percent
Antibiotic prescribed? (n=138)		
Not prescribed	19	13.8
Antibiotics prescribed	119	86.2
Episodes with antibiotic prescription (n=119)		
Antibiotic monotherapy prescribed	68	57.1
Combined antimicrobial therapy	51	42.9
Antibiotic monotherapy prescribed (n=68)		
3rd & 4th Generation Cephalosporins	30	44.1
Penicillins	20	29.4
2nd Generation Cephalosporins	5	7.4
Carbapanems	4	5.9
Other	9	13.2
Antibiotic combined therapy prescribed (n=51)		
3rd Generation Cephalosporins	19	37.3
Penicillins	11	21.6
2nd Generation Cephalosporins	3	5.9
Carbapanems	3	5.9
Other	15	29.4
Antibiotic duration (n=115)		
Mean duration of antibiotics(SD)(days)	9(5)	
≤4 days	21	18.3
5-7days	40	34.8
>7 days	54	47

4.2.1 Empiric antibiotic therapy for neutropenic febrile episodes.

34 febrile episodes were neutropenic with ANC levels less than 500 cells/mm3 and these constituted 30.6 % of the febrile episodes that had a full blood count done during the fever episode. This is illustrated in table 6 above.

Table 9 below summarizes the antibiotic regimens prescribed during febrile neutropenic and non-neutropenic episodes.

Table 9 Antibiotic regimens prescribed during neutropenic and non neutropenic febrile episodes

Antibiotic regimens	Episodes with documented (WBC) (n=96)	Neutropenic episodes(n=31)	Non neutropenic episodes(n=65)
Monotherapy	**n (%)**	**n (%)**	**n (%)**
3rd and 4th gen. Cephalosporins	27(28.1)	4(12.9)	23(37.1)
Penicillins	15(15.6)	5(16.1)	10(16.1)
2nd generation cephalosporin	5(5.2)	1(3.2)	4(6.5)
Others	4(4.2)	0	4(6.5)
Carbapanems	3(3.2)	2(6.5)	1(1.6)
Total	**54 (56.25%)**	**12 (38.7%)**	**42 (64.6%)**
Combination therapy			
Penicillin containing regimens	12(11.6)	3(10)	9(13.4)
3rd gen. cephalosporins regimens	20(21.1)	9(33.3)	11(16.9)
2nd generation cephalosporin	2(2.1)	2(6.7)	0
Carbapanem regimens	5(5.3)	4(13.3)	1(1.5)
Others	3(3.1)	1(3.3)	2(3.1)
Total	**42 (43.75%)**	**19 (61.3%)**	**23 (35.4%)**

Neutropenic episodes had both single and combined antimicrobial therapy as empiric antibiotic prescription. Penicillins and 3rd generation cephalosporins were the most frequently used antibiotic monotherapy in the neutropenic fever episodes. Antibiotic monotherapy was prescribed in 12 (38.7%) while combined antibiotic therapy was prescribed for 19(61.3%) of the total number of neutropenic fever episodes documented in the study. The most frequently prescribed empiric antibiotic regimens for neutropenic febrile episodes were regimens that contained 3rd generation cephalosporins. Notably 3/34 (8.8%) of febrile neutropenic episodes include in the study had no antibiotic prescription.

A Chi-square test for independence indicated a significant association between the type of febrile episode and the antibiotic therapy prescribed, X^2 (1, n=96) =5.72, p=0.017. Specifically, it was likely to prescribe a monotherapy among children with non neutropenic febrile episodes whereas the neutropenic children were likely to be prescribed for combined

therapy. A further Chi-square test of independence wasn't possible to identify the specific antibiotic regimens for neutropenic episodes as 60% of the counts were less than 5.

4.2.1.1 Duration of empiric antibiotic prescription for febrile neutropenic episodes

The Kasili's synopsis guideline suggests a risk stratification strategy of febrile neutropenic patients into low risk (neutropenia resolves in less than 5 days after antibiotic initiation) and high risk (neutropenia for > 5 days), and this determines the duration of antibiotic prescription. The duration of neutropenia thus determines the duration of empiric antibiotic administration.

Table 10 below shows the duration of antibiotics prescribed in neutropenic and non neutropenic episodes

Table 10: duration of empiric antibiotic prescription in neutropenic and non-neutropenic febrile episodes

Duration of antibiotic prescription	**Episodes with neutrophil count (n=94)**	
	<0.5	**≥ 0.5**
≤ 4 days	3(10.3)	15(23.1)
> 4 days	26(89.7)	50(76.9)
Totals	29	65

The proportion of febrile episodes with antibiotic duration of 5 days or more was higher in the neutropenic fever episodes (89.7%) compared to non neutropenic fever episodes (76.9%). A Chi-square test for independence was conducted indicated that there was no a significant association between the type of febrile episode and the duration of antibiotic therapy prescribed, X^2 (1, n=94) =2.100, p=0.147.

4.2.2 Empiric antibiotic therapy for non- neutropenic febrile episodes

There were 77(69.4%) children presenting with non neutropenic febrile episodes in the study, of these 11/77(14.3%) had no antibiotics prescribed. Among the non neutropenic fever episodes that had an antibiotic prescription, 42/65(64.6%) were antibiotic monotherapy prescription while 23/65 (35.4%) were combined antimicrobials prescription. Third and fourth generation cephalosporins were the most frequently prescribed 23/62 (37.1%) monotherapy antibiotics among the non- neutropenic fever episodes, unlike neutropenic fevers among which penicillins were the most frequent antibiotic monotherapy prescribed. Table 9 above illustrates these findings.

4.2.2.1 Duration of empiric antibiotic prescription for febrile non neutropenic episodes

There are virtually non-existent clinical practice guidelines for duration of empiric antibiotic prescription for febrile non neutropenic episodes in pediatric oncology patients. The local pediatric oncology guideline has no explicit reference to this subject; however, the KNH guide to antimicrobial therapy suggests that the duration of empiric antibiotic therapy should not exceed 5 days.

The proportion of non neutropenic fever episodes with antibiotic duration of 5 days and more was 76.9%. Table 10 above illustrates the duration of empiric antibiotic prescription in non neutropenic and neutropenic fever episodes.

4.2.3 Prior use of antibiotics before the febrile episodes

In 59/139 (42.4%) of the febrile episodes in the study, there was recent antibiotic use within 14 days prior to the febrile episode. 14 day period of recent antibiotic use was chosen due to ease of obtaining the treatment records within the period compared to the standard definition of recent antibiotic use (90 days).

The table 11 below illustrates the antibiotic regimens used within 14 days of the beginning of the most recent febrile episodes in the study.

Table 11: Antibiotic regimens used prior to the febrile episodes

Antibiotic regimens	**Episodes with prescription(n=59) n(%)**
Monotherapy	
Penicillins	11(7.9)
3rd and 4th gen. cephalosporins	9(6.5)
Carbapanems	3(2.2)
2nd generation cephalosporin	2(1.4)
Others	7(5.0)
Combination therapy	
Penicillin containing regimens	16(11.5)
3rd gen. cephalosporins regimens	8(5.8)
2nd generation cephalosporin	1(0.7)
Carbapanems	2(1.4)
Others	0

Penicillin monotherapy and penicillin containing antibiotic combination therapy were the most frequently used antibiotic regimens prior to the most recent febrile episodes.

Prior antibiotic use was also reported in the study for both neutropenic and non neutropenic febrile episodes. Table 12 below illustrates the proportion of fever episodes with prior antibiotic use in both neutropenic and non neutropenic febrile episodes.

Table 12 Frequency of prior antibiotic use in neutropenic and non neutropenic febrile episodes

Prior antibiotic use (n=111)	**Neutrophil count**		**Total**
	<0.5	**≥ 0.5**	
Episodes with prior antibiotic use	18(52.9)	31(40.3)	49(44.1)
Episodes with no prior antibiotic use	16(47.1)	46(59.7)	62(55.9)
Total	34	77	111

Neutropenic fever episodes had a higher proportion of febrile episodes with prior antibiotic prescription 18/34(52.9%) compared to non neutropenic febrile episodes 31/77(40.3%).

However, this difference was not significant based on the Chi-square test of independence conducted, X2 (1, n=111) =1.538, p=0.215.

4.2.4 Antibiotics prescribed for febrile episodes with presumed localized infections and adherence to clinical guidelines

The documentation of clinical findings was often inadequate to conclude the actual locus of infection for the specific febrile episodes. Antibiotic prescription patterns in this study were therefore loosely attributed to the febrile episodes that had been documented to have abnormal findings in the various systems. For instance, febrile episodes that had abnormal findings in multiple systems empiric antibiotics choices may represent only the system with the most morbidity to the patient. Table 13 below summarizes the antibiotic regimens prescribed for febrile episodes with presumed local infections in the respiratory, central nervous and urinary tract systems

Table 13: Antibiotic regimens prescribed for febrile episodes with presumed local infections.

Antibiotics prescription	Episodes with abnormal respiratory tract findings n=14 n (%)
Antibiotic regimens(respiratory tract)	
Monotherapy	
Penicillins	2(14.3)
3rd generation cephalosporins	3(21.4)
Macrolides	1(7.1)
Combined antibiotic therapy	
Penicillin combinations	3(21.4)
3rd gen. Cephalosporins+ other antimicrobials	4(28.6)
Meropenem, (+ antimalarial agent)	1(7.1)
Antibiotic regimens(central nervous system)	**Episodes with abnormal central nervous system findings n=8**
Monotherapy	n (%)
Penicillins	1(12.5)
Ceftriaxone	4(50)
Carbapenem	1(12.5)
Combination therapy	
Carbapenem (combination therapy)	1(12.5)
Penicillin combination therapy	1(12.5)
Antibiotic regimens	**Episodes with abnormal genitourinary tract findings n=5**
Ceftriaxone monotherapy	1
Combined antibiotics	
Penicillin based combination	1
Cephalosporin based combinations	2
Carbapenem regimens	1

For febrile episodes with abnormal respiratory tract findings, 3rd generation cephalosporin mono-therapy and also in combination with other antimicrobials were the most frequently prescribed (50%) for presumed respiratory tract infections.

There were 9 febrile episodes with documented abnormal CNS findings, and antibiotics prescribed for 8 episodes with abnormal CNS findings with ceftriaxone monotherapy prescribed most frequently (50%) in febrile episodes with presumed CNS infection.

There were 5 febrile episodes in the study with presumed urinary tract infections. The antibiotic prescription was varied for the few episodes recorded with presumed urinary tract infection.

Table 14 below shows the antibiotics prescription adherence to the locally available guidelines for empiric treatment of respiratory tract infections.

Table 14: Antibiotic regimens prescribed according to preexisting guidelines for presumed respiratory tract infections

Antibiotics prescription	Episodes with prescription n (%)	Episodes with abnormal Clinical findings	Guideline adherence
Antibiotic monotherapy (n=6)			
Amoxicillin clavulanic	7 (21.2)	2 (14.3)	3
Ceftazidime	3 (9.1)	1 (7.1)	4
Ceftriaxone	17 (51.5)	2 (14.3)	1
Erythromycin	1 (3.0)	1 (7.1)	4
Combined antibiotics therapy(n=8)			
Amikacin, Artesunate, Piperacillin/Tazobactam	1 (3.2)	1 (7.1)	3
Ceftriaxone, Fluconazole	4 (12.9)	1 (7.1)	1
Amoxicillin/clavulanic, Erythromycin	1 (3.2)	1 (7.1)	4
Ceftazidime, Acyclovir	1 (3.2)	1 (7.1)	4
Ceftriaxone, Vancomycin	1 (3.2)	1 (7.1)	4
Ceftriaxone, Acyclovir	1 (3.2)	1 (7.1)	1
Crystalline penicillin, Gentamicin	2 (6.5)	1 (7.1)	1,2
Meropenem, Artesunate	2 (6.5)	1 (7.1)	3

Guidelines 1.Basic pediatric protocol 2.Kasilis 3 KNH guide to antimicrobial therapy 4. No guidelines adherence

In 5/14(35.7%) of the episodes empiric antibiotic prescribed for presumed respiratory infections did not conform to any of the existing guidelines when only the antibacterial agents were considered. 4/14(28.6%) febrile episodes had empiric prescriptions conforming to the recently launched KNH guide to antimicrobial therapy.

The basic pediatric protocol is the only guideline that gives explicit guidance on empiric antibiotic treatment of presumed CNS infections, while the KNH guide to empiric antibiotic is the only guideline (among the three) that gives explicit advice on empiric antibiotics for urinary tract infection. Ceftriaxone monotherapy was used in 50 % of those with suspected CNS infections in adherence to the basic pediatric protocol, however only one combination prescription for urinary tract infection was in adherence to the recommendations in the KNH guide.

Clinical evaluation for the febrile episodes was largely incomplete for most of the febrile episodes, and a diagnosis of "unexplained fever" or "fever without a focus" could also not be made with certainty. Only 7(22.6%) neutropenic episodes had the prescription of a carbapanem or an antipseudomonal beta-lactam which are considered appropriate for empiric treatment of febrile neutropenia according to international guidelines.

4.2.5 Febrile episodes with no antibiotic prescribed

There were 19/138 (13.8%) fever episodes with no antibiotic prescribed. A majority of the episodes with no antibiotic prescribed had no documented focus of infection; only 2 febrile episodes with abnormal findings had no antibiotic prescription. Table 15 below illustrates the clinical characteristics of febrile episodes that had no antibiotic prescription.

Table 15 : Clinical characteristics of febrile episodes with no antibiotic prescribed

Variables	Total n (%)	Episodes with no antibiotics prescribed
Fever episodes (days) (n=138)		
≤5	94 (68.1)	15 (78.9)
>5	44 (31.9)	4 (21.1)
Age (Years) (n=138)		
<5	56 (40.6)	6 (31.6)
5 - 10	63 (45.7)	12 (63.2)
>10	19 (13.8)	1 (5.3)
Underlying Diagnosis (n=138)		
Solid tumor	58 (42.0)	8 (42.1)
Leukemia	48 (34.8)	6 (31.6)
Lymphoma	32 (23.2)	5 (26.3)
Chemotherapy (n=137)		
Yes	86 (62.8)	13 (68.4)
No	51 (37.2)	6 (31.6)
Neutropenia (n=110)		
<0.5	34 (30.9)	3 (21.4)
≥0.5	76 (69.1)	11 (78.6)

Of the 19 febrile episodes with no antibiotic prescription, 15 febrile episodes (78.9%) lasted less than 5 days. 13(68.4%) of these febrile episodes occurred in children who had already started their chemotherapy, and 11 febrile episodes with no antibiotic prescription occurred when the children were non-neutropenic.

4.2.5.1 Did different temperature defining fever thresholds influence withholding of antibiotics?

The temperature defining fever in this study was different from that suggested in the international fever and neutropenia guidelines. In an attempt to explore the possible reasons antibiotics were withheld, we hypothesized that the temperature threshold of the reported fever influenced antibiotic withholding. Table 16 below illustrates the effect of different temperature defining fever thresholds on the diagnosis of febrile episodes

Table 16 : Fever diagnosis at different temperature defining fever thresholds in episodes with no antibiotic prescription

Temperature at diagnosis of febrile episode		Episodes with no antibiotic prescription n=19
Temperature threshold 38^{o}C	<38^{o}C	3(15.8)
	≥38^{o}C	16(84.2)
Temperature threshold 38.4^{o}C	≤38.3^{O}C	12(63.2)
	>38.3^{O}C	7(36.8)

Using a temperature threshold of 38 degrees Celsius, 16(84.2%) of febrile episodes with no antibiotics prescribed had a temperature more than 38^{o}C (the threshold at which antibiotics should be started according to the local treatment guideline). When the temperature threshold of >38.4^{0}Cwas used, only 7 (36.8%) febrile episodes with no antibiotics prescribed surpassed this threshold.

4.3 Clinical evaluation during febrile episodes

Clinical evaluation of the fever episodes was extracted from the patients' medical records from the free text written by their primary clinician during the fever episode. This objective was heavily dependent on the accurate documentation of the findings of the clinical examination during the febrile episode. The first documented clinical examination following the day that the fever was noted was extracted. Clinical findings were interpreted as normal or abnormal based on the interpretation of the data abstractor (principal investigator).

The clinical evaluation of the fever episodes was not well documented for at least a half of the febrile episodes. The vital signs were for the purposes of analysis included in the general examination findings, and as such all were considered to have abnormal general examination findings due to the abnormal temperature that identified the fever episode.

Table 17: Clinical evaluation for febrile episodes with and without antibiotic prescription

Clinical findings	n	Antibiotic prescription	
		No	Yes
Respiratory (n=74)			
Normal	58 (78.4)	9 (100)	49 (75.4)
Abnormal	16 (21.6)	0	16 (24.6)
Central Nervous System (n=63)			
Normal	54 (85.7)	7 (87.5)	47 (85.5)
Abnormal	9 (14.3)	1 (12.5)	8 (14.5)
Gastrointestinal (n=75)			
Normal	38 (50.7)	6 (75.0)	32 (47.8)
Abnormal	31 (41.3)	1 (15.5)	30 (44.8)
Tumor	6 (8.0)	1 (15.5)	5 (7.5)
Genitourinary (n=10)			
Normal	4 (40.0)	1 (100)	3 (33.3)
Abnormal	5 (50.0)	0	5 (55.6)
Tumor	1 (10.0)	0	1 (11.1)
Skin (n=19)			
Normal	2 (10.0)	1 (100)	1 (5.6)
Abnormal	17 (90.0)	0	17 (94.4)

Of the 139 patients, 75 (53.9 %) had documented clinical findings in the respiratory system. Among these with documented respiratory findings, 16(21.3%) had abnormal findings. Among those with documented central nervous system findings, 75 (53.9%) of 139 fever episodes, only 9(14.1%) had abnormal clinical findings. Only 10/139 patients were clinically evaluated for a possible urinary tract infection, among these, only 5/10 had abnormal findings suggestive of an infection. Only 20/139 had documented findings on the skin, among whom 18(90%) had abnormal findings suggestive of an infection. In the gastrointestinal system,

76(54.7%) had documented clinical findings, of these 31(40.8%) had abnormal findings suggestive of an infection.

At least 79 fever episodes with foci of infection were documented.

It is curiously noted that in two (2) episodes with abnormal findings (gastrointestinal and central nervous), no antibiotic was prescribed.

4.3.2 Clinical evaluation in neutropenic and non-neutropenic episodes

Clinical evaluation for the neutropenic and non neutropenic febrile episodes that had documented clinical findings is summarized as below in table 18.

Table 18 Clinical evaluation findings in neutropenic and non neutropenic febrile episodes

Clinical evaluation	frequency	Neutrophil count	
		<0.5	≥0.5
Respiratory (n=60)			
Normal	48 (80.0)	16 (88.9)	32 (76.2)
Abnormal	12 (20.0)	2 (11.1)	10 (23.8)
Central Nervous System (n=52)			
Normal	44 (84.6)	14 (93.3)	30 (81.1)
Abnormal	8 (15.4)	1 (6.7)	7 (18.9)
Gastrointestinal (n=62)			
Normal	28 (45.2)	12 (66.7)	16 (36.4)
Abnormal	28 (45.2)	6 (33.3)	22 (50.0)
Tumor	6 (8.0)	0	6 (13.6)
Genitourinary (n=8)			
Normal	3 (37.5)	1 (50.0)	2 (33.3)
Abnormal	4 (50.0)	1 (50.0)	3 (50.0)
Tumor	1 (12.5)	0	1 (16.7)
Skin (n=14)			
Normal	2 (14.3)	1 (16.7)	1 (12.5)
Abnormal	12 (85.7)	5 (83.3)	7 (87.5)

Documented presumed clinical foci of infection were fewer in severe neutropenic episodes compared to non neutropenic episodes evaluated in the study.

4.4 Laboratory evaluation of the febrile episodes

The laboratory evaluation of the febrile episodes was inadequate in comparison to the detailed laboratory work up needed for a febrile episode as described in the Kasili's synopsis. For a febrile neutropenic episode, blood culture, urinalysis and culture, Chest X-rays, Liver Function tests, Urea and /Electrolytes, Blood Sugar, WBC+ESR, Blood film and Malaria parasites are the minimum recommended to be done.

The guideline does not however mention about minimum investigations for non-neutropenic fever episodes which were the majority.

Accepted laboratory evaluations were those done at any time during the period of the fever episode. The availability of these investigations in the facility at the time of the febrile episode could not be ascertained.

Table 19: Laboratory evaluation of the febrile episodes

Laboratory evaluation	Frequency	Percent
FBC (n=136)		
No	31	28.2
Yes	105	77.2
ESR (n=133)		
No	114	85.7
Yes	19	14.3
UEC (n=137)		
No	56	40.9
Yes	81	59.1
LFT (n=136)		
No	99	72.8
Yes	37	27.2
Blood culture (n=139)		
No	123	91.8
Yes	11	8.2
Urinalysis & urine culture (n=133)		
No	116	87.2
Yes	17	12.8
B/S for malaria (n=134)		
No	120	89.6
Yes	14	10.4
CRP (n=137)		
No	115	83.9
Yes	22	16.1
CXR (n=126)		
No	118	93.7
Yes	8	6.3

The most consistently done laboratory evaluation was the full/whole blood count with 105/139(77.2%) episodes with an available result in the patients charts.

For the ESR, only 19(14.3%) had this result in their charts. The least frequently done tests were the cultures (blood and urine alike) in 8.2% of the 139 febrile episodes.

Radiological evaluations were also less frequently performed (6.3%). This can be fully appreciated from the table 19 above.

4.4.1 Patterns of microbes grown and their antibiotic sensitivity

This objective was not adequately answered, as there were very few cultures collected in the study. There were a total of 13 febrile episodes during which cultures were collected from the patients during the febrile episodes; urine cultures were predominant; 10 specimens from 10 fever episodes, blood cultures were 7 in number from 7 febrile episodes, and there was one stool culture. The cultures were collected at the start of the febrile episode before empiric antimicrobial therapy.

There was no growth of microorganisms in a majority of the specimens, but 2 specimens; one urine culture grew *Acinetobacter Baumanii* species (multidrug resistant), while one blood culture grew coagulase negative *Staphylococcus aureus*, for which the sensitivity was not done .Table 20 below summarizes these findings.

Table 20: Frequency and types of cultures taken during the fever episodes

Variables	Frequency	Percent
Microbial culture specimen (n=13)		
Blood culture	3	23.1
Blood culture, Urine culture	3	23.1
Blood culture, Urine culture, Stool culture	1	7.7
Urine culture	6	46.2

The sensitivity results of *Acinetobacter Baumanii,* cultured from urine, showed multidrug resistance. It was the only sensitivity result that was reported in the study.

CHAPTER 5: DISCUSSION

This study was aimed at describing the antibiotic prescription patterns, the clinical and laboratory evaluation received by febrile pediatric cancer patients (for the most recent febrile episode), and the antimicrobial sensitivity patterns of organisms grown on cultures from pediatric cancer patients.

The overall objective of this study was to describe the empiric antibiotics prescribed for fever episodes in pediatric patients with suspected or confirmed cancer at the Kenyatta National Hospital. This was achieved by retrospectively reviewing the medical records of pediatric patients with cancer receiving care at the KNH for a 1 year period.

This study is to the best of our knowledge among the first in Kenyatta National Hospital to describe the antibiotic prescription patterns during fever episodes among pediatric cancer patients admitted in the hospital. Moreover the study describes the antibiotic management of neutropenic and non neutropenic febrile episodes, shifting the focus from only febrile neutropenic episodes and recognizing the need for antibiotic stewardship in this population subset. The study setting was unique, in that multiple guidelines could be used to influence the decisions to prescribe empiric antibiotics for febrile children with cancer. This setting bears similarity to the study by Mohammed et al in Ethiopia(60) in which there was no dedicated clinical practice guideline that had been adopted for use for management of febrile neutropenia in their setting.

This study included the neutropenic (ANC< $0.5*10^9$ /µl) and the non-neutropenic episodes, with the non-neutropenic episodes predominating at 69.4% of the total number of fever episodes that were included in the study, while neutropenic episodes constituted 30.6% of the fever episodes that were studied. This finding was in contrast to a study more than 30 years

ago by Pizzo et al(14) that documented both neutropenic and non neutropenic febrile episodes in a single setting, in which only 20.8% of the fever episodes were non neutropenic and a majority(79.2%) of the fever episodes occurred when there was concomitant neutropenic episodes. Subsequent studies have reported on either exclusively neutropenic or non neutropenic episodes but not both within the same study, thus this discussion will also focus on antibiotic management according to the level of neutropenia.

In this study, 86.2% of febrile episodes occurring in children with cancer received empiric antibiotics, while 13.8% had no antibiotic prescription.31/34(92.8%) of neutropenic fever episodes had empiric antibiotics prescription. This findings are in contrast to study reported by Pizzo et al and Bedewi et al, (14,60), in which all neutropenic patients received empiric antibiotic therapy as the standard of care for neutropenic fever episodes. The current acceptable standard of care for neutropenic fever episodes is to prescribe empiric antibiotics(4,5) while awaiting the laboratory and clinical evaluation results. Withholding antibiotics in these neutropenic febrile episodes may have been inadvertent and this is unlikely to be standard practice in the institution. These findings necessitates the urgent development of (or validation of existing) risk strategies in pediatric oncology patients in our setting(4) which when in cooperated into clinical practice guidelines are projected to guide clinical decisions in future and in time impact antimicrobial stewardship efforts among this population

For neutropenic episodes with antibiotic prescription, combinations of antibiotics were more commonly prescribed and the most common were 3rd generation cephalosporin based regimens in 33.3% of the neutropenic fever episodes. There was a significant association between the type of febrile episode and the antibiotic therapy prescribed when a chi square test of independence was done, suggesting the likelihood of antibiotic monotherapy prescription among children with non neutropenic febrile episodes , whereas the neutropenic

children were likely to be prescribed for combined therapy. The choice of B-lactam agent in the antibiotic combinations is similar to the antibiotics prescribed in the studies by Mohammed et al, Llamas et al (60,61), however the prescription patterns in the present study are more varied, as only 33.3 % had 3rd generation cephalosporin based regimens compared to 77.8% in the Ethiopian study, and 75% in the Mexican study(60,61) . Moreover, in this study the common additional antimicrobials included antifungals, antimalarials, and antiviral agents, effectively suggesting that the third generation cephalosporins were mostly used as "monotherapy" as regards antibacterial cover, while in the studies above combination therapy consisted of B-lactam agent and aminoglycoside.

Non-neutropenic febrile episodes constituted the majority in this study, accounting for approximately 70% of all febrile episodes in the study. This percentage is higher than reported in a systematic review by Allaway et al who reported that the frequency of non-neutropenic fever episodes was between 38-49% among pediatric patients with cancer(62). However the setting of the studies included in the review was in resource rich settings unlike the setting of the current study. 62/77(80.5%) of non neutropenic fever episodes in this study had empiric antibiotic prescribed. This approach to non neutropenic fevers is in contrast to work done by Pizzo et al, whose standard of care for non-neutropenic febrile episodes was to withhold empiric antibiotics until a clinically or microbiologically defined infection was identified (14). In the systematic review by Allaway, 2 of the studies included therein reported on withholding antibiotics for some non neutropenic fever episodes, with only few adverse outcomes(admission for inpatient care for few episodes) reported(62). Withholding of empiric antibiotics has been practiced in non-neutropenic fever episodes in "well" appearing patients elsewhere with no adverse events reported and led to an overall avoidance in antibiotic exposure in > 90% of the fever episodes(63).

For non neutropenic febrile episodes in this study, antibiotic monotherapy was more frequently used than combination therapy. The most common antibiotic used in the non-neutropenic febrile episodes was ceftriaxone, used in 18/42(42.9%) of the febrile non-neutropenic episodes. The systematic review by Allaway et al also identified ceftriaxone as the most commonly used empiric antibiotic prescribed in the studies included therein(62). Collectively 3rd and 4th generation cephalosporins were used in 54.8% of the febrile non-neutropenic episodes in this study. The proportion of non-neutropenic febrile episodes with antibiotic duration exceeding 5 days reported in the study was >76% of the total, implying prolonged antibiotic use even for non-neutropenic fever episodes . This is in contrast to collective findings of the systematic review by Allaway and colleagues that found antibiotic durations not exceeding 48-72 hours among the various studies for febrile non-neutropenic episodes(62). These findings in the study imply antibiotic overuse in non-neutropenic fever episodes in the Kenyan setting, however prospective studies are suggested to further interrogate these findings.

The mean antibiotic duration in the study was 9 days (SD=5 days) for both neutropenic and non-neutropenic fever episodes in the study. This finding is similar to the Ethiopian study in which the mean antibiotic duration was found to be 9 days(SD=5days)(60).The proportion of neutropenic fever episodes with antibiotic duration more than 5 days was slightly higher than in the non-neutropenic fever episodes. In comparison to both the existing local and international guidelines the mean antibiotic duration in the study is longer than the prescribed duration(4,5). However, the duration of antibiotic is may at times be influenced by the clinical status of the patient in question and practice in different settings may not be easily comparable.

In both febrile neutropenic and non neutropenic episodes, recent antibiotic use (14 days prior to febrile episode under study) was documented. Neutropenic fever episodes had a higher

proportion of febrile episodes with prior antibiotic prescription compared to non neutropenic febrile episodes but this difference was not significant based on the Chi-square test of independence conducted. Penicillin based combination therapy was the most frequent of the antibiotic regimens prescribed. This finding may indicate either the prescriptions may have been used either as prophylaxis or as initial treatment regimen for a prior febrile episode. The current institutional guideline recommends the use of co-trimoxazole as prophylaxis in pediatric cancer patients(5). Other centers have documented the use of amoxicillin clavulanic acid or quinolones such as levofloxacin as prophylactic treatment given to neutropenic patients even prior to development of febrile episodes. These findings indicate non-standardized management of neutropenic and non neutropenic episodes in pediatric cancer patients and further strengthen the case for a standardized approach to local antibiotic prescription in febrile episodes in children with cancer.

As mentioned above, 19/138(13.8%) of the febrile episodes in the study had no antibiotics prescribed. There was no significant association of antibiotic prescription with age, duration of febrile episode, underlying cancer diagnosis, begin of chemotherapy or level of neutropenia when statistical tests were applied. However cautious interpretation of this information is needed as the sample size in the study was small. Possible reasons for withholding antibiotics especially for the febrile neutropenic episodes could be an alternative temperature -defining -diagnosis of fever held by the primary health care workers attending to the paediatric patient with cancer. Fever definition in this study was modified to be consistent with the definition indicated in the local guideline for fever and neutropenia (Kasili's), defined as an (axillary) temperature of >37.8°C or two consecutive readings of >38.0°C for 4 hours This was done in consideration that the definition in the local guideline may influence the clinicians' diagnosis of febrile neutropenic / non neutropenic episodes and thus their prescription decisions.

The impact of fever threshold on over diagnosis of febrile neutropenia has been studied by Ammann et al(64) who concluded that a lower threshold of temperature limit defining fever led to earlier diagnosis of febrile episodes among which in 96% there was spontaneous defervescence without any antibiotics. These findings imply that a temperature limit as used in this study (37.8 degrees Celsius) may have led to over diagnosis of fever episodes in neutropenic and non neutropenic episodes. This observation is important as in the study it was noted that in 19/138(13.8%) of the febrile episodes, no antibiotic was prescribed with any obvious increase in adverse events. A large proportion of these episodes were non-neutropenic 11/14 (78.6%).

In the present study, when a temperature threshold of 38 degrees Celsius (temperature defining start of empiric antibiotic in Kasili's) was applied, 83.2% of the febrile episodes with antibiotic prescription still met the diagnostic criteria for a fever episode. Similarly 16/19 (84.2%) of fever episodes with no antibiotic prescribed still met the criteria when this threshold was applied. However, when a more commonly used temperature limit defining fever (38.3 degrees Celsius) was used only 52.9% (63/139) of the episodes without antibiotic prescription met the criteria for fever diagnosis, and 7/19(36.8%) of the fever episodes without antibiotic prescription met the threshold for fever definition. These findings imply that antibiotics may have been deliberately withheld for some of the febrile episodes.

The results of the study suggest that there is a wide variation of antibiotic regimens that are prescribed during fever episodes in paediatric patients with cancer, and that antibiotic combination containing 3rd generation cephalosporins are most commonly prescribed for neutropenic febrile episodes, while antibiotic monotherapy with 3rd generation cephalosporins is the most frequently prescribed for non-neutropenic febrile episodes in children with a cancer diagnosis.

Clinical evaluation of the febrile neutropenic episodes was greatly affected by poor documentation; but neutropenic episodes had fewer documented foci of infection compared to non neutropenic episodes. This was expected for febrile neutropenic episodes and is similar to the findings in the study by Mohammed in Ethiopia in which more than 83% of the neutropenic fever episodes ,studied had no infection focus(60).

Microbiological evaluation of the fever episodes was also inadequate, with only 13 (9.3%) febrile episodes having either blood or urine cultures taken. There was no growth obtained for most of these cultures apart from two specimen that grew coagulase negative *Staph. Aureus* and multidrug resistant *A.baumanii*. Similar culture rates were in the Ethiopian study in which only 13(9.6%) of the participants had their cultures taken(60). In our study growth was comparable to the Ethiopian study in which growth was obtained in five cultures.

All-cause mortality was reported in 3 cases (2.2%) of the participants, all of whom had progressive disease at the time of death. This was less than the deaths reported in the Ethiopian study (5.2%), Llamas et al (17.1%), and Kar.et al (13.2%). The difference in this observation may be due to methodological difference, with the above studies having predominantly febrile neutropenic population in contrast with the current study, with febrile neutropenia being a known risk factor for prolonged and more severe infections

Study Limitations

Being a retrospective study, the medical records had incomplete/ missing data as they were recorded for clinical use and not for study purposes. This was handled during analysis as only the available results for each variable were analyzed.

The sampling method used in this study was a non-random hence it affects the generalizability of results obtained; however it was the most suitable for this type of

population, being a small population, with the probability of occurrence of the phenomenon (febrile episodes) under study being rare.

Availability of the antibiotics and laboratory reagents in the facility at the time of the fever episodes could not be ascertained and this could have affected the results as reported.

Actual timing of antibiotic prescription relative to the laboratory evaluation was not documented in the records and the definition of "empiric antibiotic" was imprecise and this could have affected the study outcomes.

Conclusion

Antibiotic combination therapy containing 3rd generation cephalosporins are the most frequently prescribed in neutropenic febrile episodes in paediatric patients with cancer at the Kenyatta National Hospital.

Antibiotic monotherapy with 3rd generation cephalosporins is most commonly prescribed antibiotic regimen (54.8%) for non neutropenic febrile episodes in pediatric patients with cancer.

There was a varied pattern of antibiotic prescription for both neutropenic and non neutropenic fever episodes

There was inadequate documentation of clinical evaluation findings and subpar microbiological laboratory evaluation in the study.

Recommendations

We recommend developing local clinical practice guidelines for the management of febrile non neutropenic episodes in pediatric oncology patients.

Adherence to current local fever and neutropenia guidelines on empiric antibiotics

Proper documentation of clinical examination findings especially during febrile episodes is emphasized.

Judicious use of antibiotics in this subset of patients should be emphasized

Further research with a prospective design and adequate microbiological evaluation is recommended to further elucidate the microbiological organisms implicated in febrile episodes in this population.

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Study Budget

NAME OF THE ITEM	COST OF EACH ITEM	NUMBER OF ITEMS NEEDED	TOTAL COST
Pens	Ksh 10	5	Ksh 50
Printing and binding	Ksh 10		Kshs 10000
Airtime			Kshs 2,000
Statistician			Kshs 50,000
Ethics Committee KNH			Kshs 2,000
Dissemination costs	Ksh 6000		Kshs 6000
GRAND TOTAL			Kshs 55,050

TIME LINES/ GANTT CHART

(Time in months: Oct 2018- Feb2020)

	1	2	3	4	5	6	7	8	9	10	11	12
Proposal writing												
Ethical approval												
Data Collection												
Data analysis												
Report writing												
Presentation of Results												

APPENDICES

Appendix I: Data Abstraction Tool

STUDY TITLE: ANTIBIOTIC MANAGEMENT OF FEBRILE EPISODES IN PAEDIATRIC PATIENTS 1-18 YEARS WITH CANCER AT THE KENYATTA NATIONAL HOSPITAL

Serial no: …….. Date of abstraction…. /…/…. (dd/mm/yy)

Date of admission……. Date of last admission…./…/…

1. PATIENT CHARACTERISTICS

a) Date of birth: …/…/……..(dd/mm/yyyy)
   i. Date of febrile episode…/…/…. (dd/mm/yyyy)
   ii. Current age…….
   iii. Age during the febrile episode …….(years)…….(months)
   iv. Duration of hospital stay ……days

b) Gender(shade the appropriate bullet)
   - Male
   - Female

c) Actual cancer diagnosis
   - ……

d) Cancer diagnosis Confirmed (shade the appropriate bullet)
   - Yes
   - No

e) Chemotherapy started (shade the appropriate bullet)
   - Yes
   - No

   (If yes indicate the cycle of chemotherapy; ……

f) Status of malignancy

   - **Hematological**
   - in remission
   - relapsed
   - Not in remission
   - Not documented
   - **Solid tumor**
     - Staging**……**
   - Lymphoma
     - Staging…

g) Time since last dose of chemotherapy (before the febrile episode)……

a. List chemotherapy drugs given……

h) Time since last surgery (where applicable)…….

2. CHARACTERISTICS OF FEBRILE EPISODES

a) Actual temperature at diagnosis……

b) Duration of febrile episode……days

c) Clinical examination findings during the febrile episode

System	**Clinical findings** *Normal findings- to be indicated as N* *Abnormal findings –to be indicated as AbN* *For solid tumors, the system affected by cancer is indicated as T* *if not documented indicated (-)*
General examination	
Systemic examination **EYES AND ENT**	
MOUTH	
RESPIRATORY	
CARDIOVASCULAR	
CENTRAL NERVOUS	
GASTROINTESTINAL	
GENITOURINARY	
SKIN	
MUSCULOSKELETAL	
OTHER	

d) If N in all systemic examination above, is it an **unexplained fever**?

- Yes
- No

3. LABORATORY EVALUATIONS

a.) Quality of evaluation –were the following tests done for the evaluation of febrile episode

Laboratory test	Result available?(Yes/ no)
FBC	
ESR	
UEC	
LFT	
Blood culture	
Urinalysis and urine culture	
Blood slide for malarial parasites	
CRP	
Others(as dictated by presentation(CSF cultures, wound swabs, throat and rectal swabs, stool cultures gene-expert) Indicate in writing those available	
CXR	

b) FULL HEMOGRAM

Laboratory test	**Result at admission**	**Result at diagnosis of febrile episode**
(WBC)		
(ANC)		
(AMC)		
Hemoglobin level (Hb)		
Platelet count		

c.) CULTURE RESULTS

Are culture results available?

- Yes
- No

i) Organism grown……

ii) Specimen type……..

iii) Antibiotic sensitivity results

Antibiotic tested	**sensitivity**	**Antibiotic tested**	**sensitivity**

4. ANTIBIOTIC MANAGEMENT

a). empiric antibiotic prescribed *(indicate" YES" on the appropriate row to indicate the prescribed combinations. For other combinations print the antibiotic combination)*

Combinations	Prescribed?	Single antibiotic	prescribed
Crystalline penicillin & gentamicin		Crystalline penicillin	
Crystalline penicillin gentamicin & metronidazole		Gentamicin	
Ceftriaxone		Metronidazole	

Ceftriaxone and amikacin		Ceftriaxone	
Meropenem		Amikacin	
Meropenem and amikacin		Meropenem	
Piperacillin/tazobactam & amikacin		Ceftazidime	
Cefepime and amikacin		Piperacillin/tazobactam	
Ceftazidime and amikacin		Cefepime	
Ceftriaxone and amikacin and metronidazole			
Others			

b). what is the duration of empiric antibiotic received in days……..

Combinations	Duration?	Single antibiotic	duration
Crystalline penicillin & gentamicin		Crystalline penicillin	
Crystalline penicillin gentamicin & metronidazole		Gentamicin	
Ceftriaxone		Metronidazole	
Ceftriaxone and amikacin		Ceftriaxone	
Meropenem		Amikacin	
Meropenem and amikacin		Meropenem	
Piperacillin/tazobactam & amikacin		Ceftazidime	
Cefepime and amikacin		Piperacillin/tazobactam	
Ceftazidime and amikacin		Cefepime	
Ceftriaxone and amikacin and metronidazole			
Others			

c.) Is there prior use of antibiotic in the last 14 days preceding the febrile episode?

- Yes
- No

d.) does the patient have co-morbidity (yes/no)…… *(If Yes Shade as appropriate)*

- Kidney failure …….
- Human immunodeficiency virus……
- Other (indicate) ……..