RATIONAL USE OF ANTIBIOTICS AMONG PATIENTS ADMITTED TO CRITICAL CARE UNITS AT KENYATTA NATIONAL HOSPITAL AND ITS IMPACT ON CLINICAL OUTCOMES

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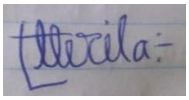
Signature:  Date: 28/11/2020

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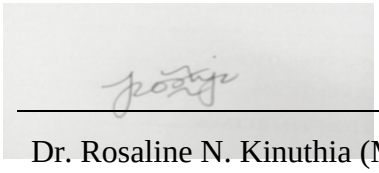

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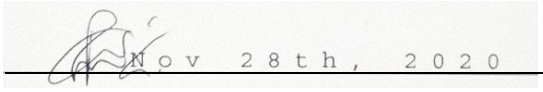

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Dedication

This dissertation is dedicated to every health care professional who is passionate about the judicious use of antibiotics and is making every effort within their power to ensure that we lower the rise of antimicrobial resistance brought about by irrational use of antimicrobials.

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Special thanks to my husband and son who tolerated my absence during the many late nights, my precious parents and siblings for the prayers and encouragement even when I didn't believe in myself may the Lord richly bless you. My dear friend Tabitha who took her time to read my dissertation.

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AKI	Acute Kidney Injury
CAUTI	Catheter Associated Urinary Tract Infection
CCU	Critical Care Unit
CLABSI	Catheter Line Associated Blood Stream Infection
COPD	Chronic Obstructive Pulmonary Disease
CST	Culture and Susceptibility Testing
EML	Essential Medicines List
HCAI	Health Care Associated Infection
ICON	Intensive Care Over Nations
IPC	Infection Prevention Control
KDIGO	Kidney Disease Improving Global Outcomes
KNH	Kenyatta National Hospital
KNH/UON-ERC	Kenyatta National Hospital/University of Nairobi-Ethics and Research Committee
LMIC	Low Middle Income Country
LOS	Length of Stay
PI	Principal Investigator
USA	United States of America
VAP	Ventilator Associated Pneumonia
WHO	World Health Organization
WHO/ESAC	World Health Organization/European Surveillance of Antimicrobial Consumption

OPERATIONAL DEFINITION OF TERMS

Antibiotics:	Medicines that are used to treat or prevent bacterial infections.
Critical care unit:	Also known as Intensive care unit (ICU), is a specialized section of a hospital that provides comprehensive and continuous care for critically ill patients.
Irrational use of antibiotics:	Use of antibiotics where they are not indicated, use of incorrect dose, frequency, duration and route of administration.
Rational use of antibiotics:	Prescribing of correct antibiotic choice when necessary, at correct dose, frequency, duration and route of administration.

ABSTRACT

Background: Studies have postulated that approximately a third of the antibiotic use worldwide is irrational, posing a major global challenge to containment of drug-resistant infections. In the critical care units, irrational antibiotic use is associated with high mortality rates. In Kenya, there is scarce data on rational use of antibiotics within critical care units and its impact on patient clinical outcomes.

Study Objective and Setting: This study sought to evaluate rational use of antibiotics among patients admitted to various Critical Care Units at Kenyatta National Hospital (KNH) and its impact on clinical outcomes.

Methods: A retrospective cross-sectional study was conducted by reviewing 220 eligible patient medical records from various Critical Care Units at the Kenyatta National Hospital. Patients were recruited by stratified proportionate sampling depending on the admission capacity of each unit. The data extracted into predesigned tool included patient demographics, antibiotic choice, dosage and clinical outcome which was either discharge or death. Raw data was coded, entered into Microsoft Excel Version 2013 to create a database and then exported to STATA Version 13 for analysis. Pearson's Chi square and Fischer's exact test were used to determine associations between predictor variables such as patient demographics and outcome variables like rational prescribing. Logistic regression was used to measure the independent correlates of rational antibiotic prescribing and mortality. Statistical significance was set at 95% confidence interval and values with $p \leq 0.05$ were considered statistically significant.

Results: The mean age of participants was 31.2±15.7 years with a male preponderance (n=129, 58.6 %). Cephalosporins (49.6%), 5-nitroimidazoles (18.2%) and penicillins (14.2%) were the most frequently prescribed classes of antibiotics. The prevalence of irrational use of antibiotics was high at 81.5%, with antibiotic choice, dose, duration and frequency being incorrect for 51%, 14.4%, 32.3% and 29.2 of the instances, respectively. Rational use of ceftriaxone was statistically significantly associated with the type of disease being treated (p=0.012). Mortality at critical care units was 11.1%, with the odds of death being at least five times among intubated patients compared to those who were not (AOR 5.5, 95% CI=1.1-28.1, p=0.042).

Conclusion: The prevalence of rational antibiotic use was 18.5%. The high proportion of irrational use was contributed by incorrect choice and incorrect duration of antibiotic use. The outcome of antibiotic therapy in critical care units was correlated with extent of the disease.

Recommendations: The hospital antimicrobial stewardship committee needs to focus on potential targets for improvement such as the choice and duration of treatment with antibiotics. Further research is required on determinants of antibiotic prescribing among clinicians in order to give a better understanding on the factors that guide antibiotic prescribing.

CHAPTER ONE: INTRODUCTION

1.1 Background

1.1.1 Rational and irrational use of antibiotics

Antibiotics play a critical role in management of various disease conditions in modern healthcare. Their use encompasses preventing and treating life threatening infections, prophylaxis for individuals who have compromised immune systems as well as promoting growth and diseases prevention in livestock (1).

An increase of 65% in global consumption of antibiotics was noted in the period between 2000 and 2015 (2). The increase was attributed to an increase in antibiotic consumption by the low-middle income countries. The classes of antibiotics most commonly consumed were the broad-spectrum penicillins, cephalosporins, quinolones and the macrolides. Of concern was the increased consumption rate of the newer and last-resort antibiotics, specifically the carbapenems and polymyxins (2). Studies done in Kenya show that the commonly prescribed class of antibiotics are the broad spectrum penicillins, the third generation cephalosporins, imidazole derivatives like metronidazole and tetracyclines (3–5).

The World Health Organization (WHO) defines rational use of medicines as patients receiving medicines that are appropriate to their clinical needs, in doses that meet their specific individual requirements, for a period that is adequate and at a cost lowest to them and their community (6). Rational use of antibiotics requires that a correct diagnosis is made based on the patient's condition, the location and severity of the infection, and the sensitivity of the microbe to antimicrobial agents. The pharmacokinetics and pharmacodynamics of the antimicrobials, their side effects and cost are some of the factors that must be considered on decisions made on their use (7).

1.1.2 Prevalence of irrational use of antibiotics

Globally, irrational use of medicines is a major concern (6). Estimates by the WHO show that more than half of all the medicines that are prescribed, dispensed or even sold are used inappropriately (6). Among the many examples of irrational use of medicines is

inappropriate use of antimicrobials which quite often is in inadequate dosages and for non-bacterial infections due to failure to prescribe in accordance to the clinical guidelines (6). According to the WHO, about two thirds of antibiotics used in the community are sold without prescriptions and about a third of the antibiotic use is irrational (8). In the United States of America (USA), studies have shown that about a third of antibiotic prescribing and use in the outpatient set up is inappropriate. There is paucity of data in the inpatient set up even though studies estimate that slightly more than half the patients admitted in hospitals are on antibiotics (9).

On the eastern European front, the findings from a survey done in 2012 among the group members of the European Surveillance of Antimicrobial Consumption (WHO/Europe-ESAC) project found that more than half of the antibiotics are sold over the counter in most of these countries (10). In West Africa, a study done in two tertiary facilities in Nigeria found that even after all the necessary laboratory investigations had been done to guide antibiotic prescribing, only 15.66% of the investigations were used and this was a major contributor to irrational use of antibiotics (11).

In Tanzania, 88% of the adults who participated in the study on use of antibiotics were found to be using antibiotics irrationally (12). In Kenya, irrational use of antibiotics is also prevalent. For instance, a study done at a referral hospital in the Rift Valley found that of all the antibiotics that had been prescribed, 65.4% were irrational (3). In addition, a similar study done in western Kenya among the surgical patients found that of the antibiotics that had been prescribed for prophylaxis, 45.4% of them were inappropriate while 33.4% prescribed for treatment were inappropriate. Furthermore, this study also indicated that 40.1% and 52.6% of the antibiotics prescribed were inappropriately prescribed during hospitalization and discharge, respectively (13). Another study done at the Kenyatta National Hospital (KNH) found that the irrational use of medicines generally was at 95.6% at the facility (14).

1.1.3 Factors associated with irrational use of antibiotics

Several factors have been found to underlie irrational use of medicines (15). Studies have categorized the major forces as those emanating from patients, prescribers, the workplace,

the supply system and generally a combination of these factors (15). Studies done on factors that contribute to inappropriate use of antibiotics among healthcare providers found that lack of adequate education on antibiotic prescribing, knowledge, attitudes and perceptions with regards to antibiotic use and resistance, pharmaceutical promotion, lack of rapid and sufficient diagnostic tests and patient-doctor interaction led to irrational use of antibiotics (16).

1.1.4 Guidelines on use of antibiotics

Generally, the principles of antimicrobial therapy require consideration of certain factors for appropriate use of antibiotics (17). These factors include obtaining an accurate diagnosis for the patient's condition as well as making appropriate decisions on the need and timing on initiating antimicrobial therapy. Healthcare practitioners should have knowledge on how dosing can affect the antimicrobial activities of different agents and optimize treatment depending on host characteristics. Other factors include de-escalation from broad spectrum to narrowest spectrum, using the shortest duration of therapy, and switching to oral agents soonest possible (17).

In the critical care unit (CCU) the principles of antimicrobial therapy still apply. However, in order to reduce mortality and morbidity in critically ill patients, healthcare practitioners need to manage and control infections promptly and appropriately (18). Special considerations need to be factored in with regards to dosing of antimicrobials. This is due to the altered drug pharmacokinetics in these patients. Therapeutic drug monitoring is required to ensure that maximal efficacy is achieved and decrease the risk of antimicrobial resistance as well as minimize toxicity (18). In a bid to help combat antimicrobial resistance, KNH unveiled antibiotic use guidelines that would help healthcare practitioners in their day to day management of patients requiring antibiotic use (19). Furthermore, a study done in Kenya on the knowledge of antibiotics found that there are marked variations in the antibiotic classes including the critically important antimicrobials and hence antimicrobial stewardship needed to be strengthened (20). Since KNH has a functional antibiotic use policy guideline, this tool can help promote the rational use of antibiotics within the facility.

1.2 Problem statement

Kenya, just like the rest of the world, is heading towards the post-antibiotic era with few new antimicrobial agents expected in the near future. Irrational use of antibiotics may cause emergence of drug-resistant microbes and decrease in the quality of antimicrobials available in the management of the drug-resistant infectious diseases. This practice may also result in wastage of resources especially finances as more expensive medications have to be relied upon to manage the diseases. In addition, it increases the prevalence of adverse drug reactions (ADR) due to reliance on second and third-line drugs that are usually more toxic and expensive (21).

Irrational use of antibiotics within the CCUs has been associated with high mortality rates and poor clinical outcomes (22). One study done on antimicrobial susceptibility of *Pseudomonas aeruginosa* in the inpatient set up found it resistant to multiple antimicrobial agents among the critical care unit isolates (23). Another study done in the CCUs found that susceptibility of *Klebsiella pneumoniae* to the antimicrobial agents, piperacillin-tazobactam, cefotaxime and meropenem, declining over time (24).

Similar studies have revealed high mortality rate and poor clinical outcomes associated with irrational prescribing of antibiotics (22). Over the years the consumption and total expenditure on antibiotics has been steadily increasing in the hospital (25) and irrational use of antibiotics has been implicated.

1.3 Research questions

1. What is the prevalence of both rational and irrational use of antibiotics in the CCUs at KNH?
2. What are the factors associated with irrational use of antibiotics at the CCUs at KNH?
3. What are the factors associated with clinical outcomes of CCU patients receiving antibiotic therapy?

1.4 Study objectives

1.4.1 General objective

This study aims to determine rational use of antibiotics among patients admitted to CCUs at KNH and its impact on clinical outcomes.

1.4.2 Specific objectives

1. To ascertain the prevalence of rational and irrational use of antibiotics among patients admitted to CCUs of KNH.
2. To characterize the factors associated with rational/irrational use of antibiotics at CCUs of KNH.
3. To identify the factors associated with clinical outcomes of CCU patients at KNH receiving antibiotic therapy.

1.5 Justification of the study

Assessment of rational use of antibiotics will help reduce the mortality rates and improve the clinical outcomes for patients. Furthermore rational use of antibiotics serves to help reduce the unnecessary risk of development of ADRs that occur when patients have to use higher classes of antibiotics due to the development of resistance (21).

With devolved governments, there have been efforts to increase the number of CCUs in the country. This study will provide a basis for rational use of antibiotics in these set ups. The study will give information on the best practices for appropriate antibiotic use in the CCU setting in the region. To the healthcare practitioners, this study will help to inform the use of antibiotics and help promote rational prescribing of antibiotics.

While many studies done at the hospital have focused on rational use of medicines, none have made any attempts to show the impact of rational or even irrational use of antibiotics on clinical outcomes. This study seeks to investigate the impact utilization of antibiotics has had on the patients admitted at the KNH CCU.

1.6 Delimitations

This study only included the medical records of the patients who were admitted to the CCUs at KNH in between February 2018 and February 2020. As such the results may not be generalizable to other CCUs in the country.

1.7 Conceptual framework

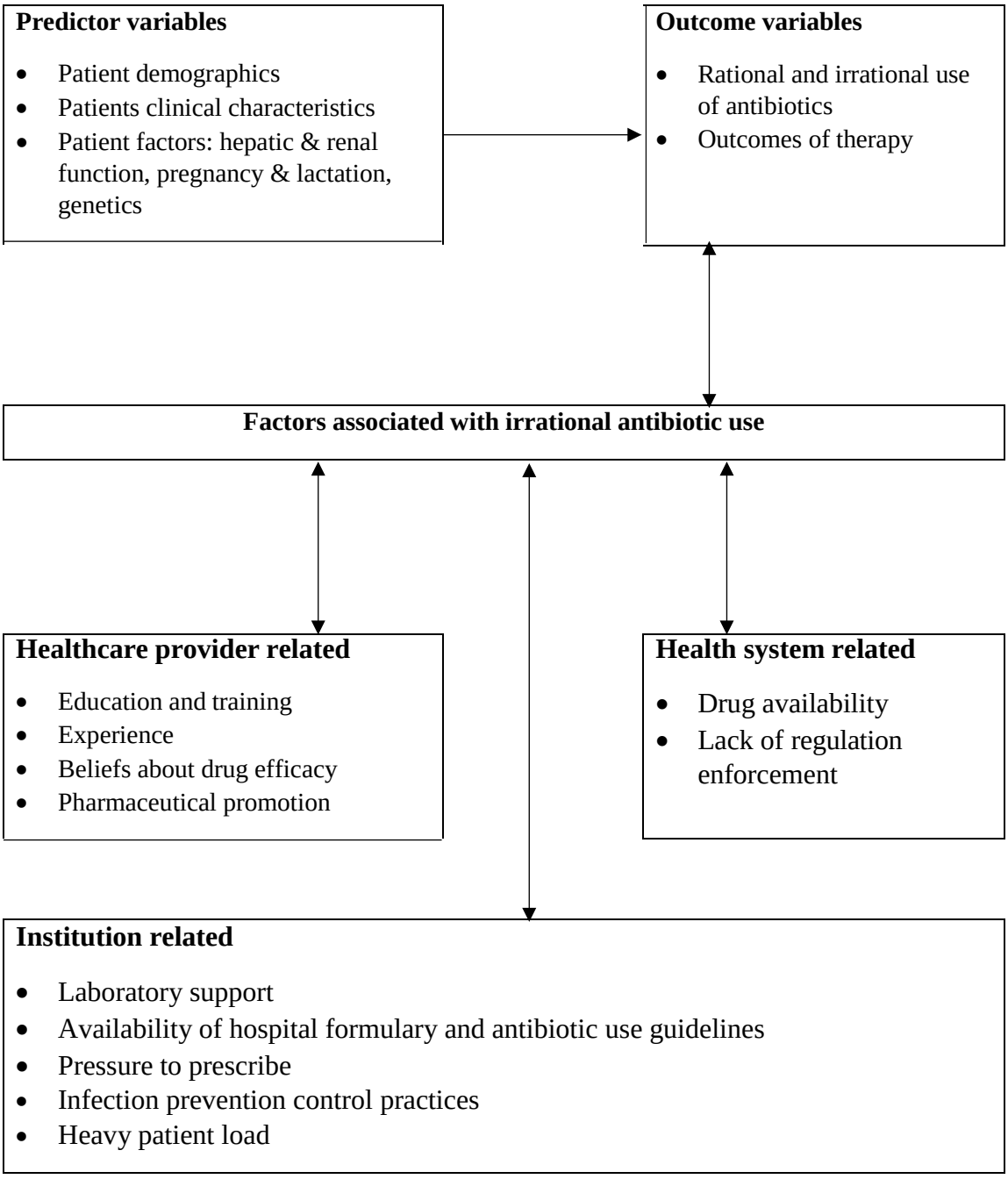

Figure 1. Conceptual framework

The conceptual framework illustrates the interaction between the predictor variables and the outcome variables. The outcomes of interest are rational and irrational use of antibiotics and clinical outcome (which was either discharge or death). Patient characteristics for instance the clinical condition affects the antibiotic to be used in treatment, which when later assessed can be found to either be rational or irrational. Similarly, factors associated with irrational use also will have an effect on the outcome variable. For instance, lack of availability of results of culture and sensitivity from the laboratory. This has a hand in increasing prevalence of irrational use of antibiotics as prescribers will be forced to prescribe antibiotics empirically.

CHAPTER TWO: LITERATURE REVIEW

2.1 Rational and irrational use of antibiotics

World Bank defines rational use of medicines with a focus on two key principles (26). The first is using medicines in accordance to data on efficacy, safety, and compliance while the second is using medicines that are cost effective within the limitations of a particular healthcare system. Although both the WHO and World Bank definitions of rational use of medicines are based on the medical therapeutic view, it should be noted that this definition can also be viewed from the patient's point of view (26).

Rational use of antibiotics implies that the criteria for rational prescribing is met (15). This criterion dictates that an appropriate indication is present for the antibiotic chosen and that the antibiotic is appropriate with regards to efficacy, safety, suitability and cost. The antibiotic should be appropriate for the patient, no contraindications should exist, the antibiotic should have minimal risks ADRs and it should be acceptable to the patient. Patients should be provided with appropriate information. They should have knowledge on their conditions and the antibiotics prescribed to them. Furthermore, appropriate evaluation on the effects of the antibiotics both the expected and unexpected need to be done. Monitoring of the patient’s response to the antibiotics and prompt action in the event of unanticipated reactions is key (15).

Irrational use of antibiotics refers to the utilization of antibiotics where indications are non-existent. For instance, the use of antibiotics in the treatment of viral infections. It also includes suboptimal use of antibiotics in responsive conditions, the over reliance on extended-spectrum antibiotics when narrow-spectrum ones are equally effective, incorrect dosage and lack of adherence to the prescribed antibiotics (27).

Contrary to the presumed notion that the major contributors of inappropriate use of antibiotics is by the developing countries, recent studies have revealed that developed countries also have challenges in antibiotic use (28). In the USA, a study done in the inpatient setting found an increasing trend in the use of broad-spectrum antibiotics like the carbapenems, third and fourth generation cephalosporins and glycopeptides. This was observed to be 52% greater in the CCU setting than the other non-critical care settings (29). A further study in China found that one in every two antibiotic prescriptions were deemed

to be medically unnecessary (30). In Australia, a study found that of all the patients' receiving antibiotic therapy, 47% was inappropriate. The high prevalence was contributed to by the injudicious use of antibiotics, poor choices of antibiotics, poor choices on dosages and route of administration (31).

2.2 Prevalence of irrational use of antibiotics

Naturally, antibiotic resistance is a phenomenon that occurs with time, irrational use of antibiotics which encompasses the overuse, misuse and prolonged use of antibiotics is a major contributor (32). Several studies have shown that in between the years 2000 and 2010 the consumption of antibiotics by the lower-middle income countries (LMICs) increased and that the rise is continuing (1,2). The studies revealed that the 80% of the use was in the communities where most use was inappropriate as the consumers could easily access antibiotics without prescriptions (1).

In Nigeria the use of antibiotics in children was found to be wanting. The study revealed an underuse of about 20.4% and an overuse of 5% in the prescriptions orders containing antibiotics (33). In Uganda a study showed that for all the patients who had been prescribed with an antibiotic, 9 out of 10 had no clinical indication that warranted antibiotic therapy. It further revealed a prevalence of about 42% of inappropriately prescribed antibiotics. In addition of the 10% who had a definite clinical condition that required antibiotic therapy, 11% ended up not being prescribed an antibiotic (34).

Antibiotic use can either be empirical or targeted. The empirical approach is where by a patient receives antibiotic therapy while investigations are being done to identify the likely organism that caused the infection. In contrast, targeted antibiotic therapy is whereby the organism causing an infection has been identified and the antibiotic the organism is susceptible to is used to manage the infection. In Indonesia, studies from a CCU set up revealed that of the empirical regimens used, about three quarters were inappropriate while 78.51% of the regimens used as targeted therapy were inappropriate (35).

As had been mentioned earlier, irrational use of antibiotics can result from poor antibiotic selection and poor choices of dosages. In Kenya a study at KNH in the neurosurgical ward showed that prescriptions raised from the unit had unspecified dose, route, frequency and duration of administration. Thirty five percent of the patients in the unit received antibiotics

for a longer duration and unfortunately all these patients developed surgical site infections. There were also challenges on the dosing of antibiotics, about 25% and 20% of patients that were receiving cefuroxime and ceftriaxone, respectively, had inappropriate doses (36).

2.3 Guidelines on use of antibiotics

To encourage rational use of antibiotics, the judicious use of a number of documents is required to guide decisions on the procurement, prescribing and dispensing of antibiotics. The WHO recommends the use of clinical guidelines as one of the strategies to improve rational use of medicines (6). Other documents that can be used include the essential medicines list (EML), standard treatment guidelines depending on the level of facility and hospital formularies. It is expected that prescribers use these documents in their daily practice. However in Kenya a survey by the Ministry of Health showed that only 40% of health facilities within the public sector prescribed in accordance to the national treatment guidelines at the minimum 90% of the time (37).

Principles of antimicrobial therapy in the promotion of their rational use requires that an accurate diagnosis is made, precise decisions are made with regards to the timing and need for antimicrobial therapy. Prescribers should have adequate knowledge on how dosing can affect the activity of an antibiotic, their decisions on treatment options should factor in host characteristics. To help combat the emergence of resistance, the antibiotics chosen should be of the narrowest spectrum and shortest duration. There is also value in switching to oral agents as soon as it is convenient (17).

On the selection and initiation of an antibiotic regimen, an appropriate diagnosis should be made. This can be achieved by carefully examining how the patient presents clinically, patients characteristics like age and immune status and the establishment of a microbiological diagnosis are some key factors that should be considered before a final decision is made (17). Resolutions made with regards to the timing of when to start antimicrobial therapy should be guided by how urgent the patient situation is. For instance, critically ill patients will require empiric therapy while the more stable patients can receive targeted therapy. Studies have shown that delaying the initiation of antimicrobial therapy has a high association with mortality (38,39). Generally, it takes about 24-72 hours for microbiological results to be available, as such empiric antibiotic therapy is therefore

initiated. However once the results are available, every effort should be made to switch to the narrow-spectrum antibiotics (40). Studies have shown the use of extended-spectrum antibiotics seem to offer no benefit over the narrower spectrum antibiotics (41,42).

2.4 Factors associated with irrational use of antibiotics

2.4.1 Patient factors

Factors related to patients that contribute to irrational use of antibiotics include, lack of knowledge and awareness of the use of antibiotics, ease of acquiring antibiotics without prescriptions and use of antibiotics remaining from earlier prescriptions (16). In Kenya, a study conducted in an urban population showed that more than half of the respondents admitted they lacked sufficient knowledge about the correct use of antibiotics (43). The study further revealed that in this population, the respondents would rely on previous prescriptions during prior visits to health facilities to seek treatment at community pharmacies whenever they experienced similar symptoms. This showed that they clearly did not understand that once an antibiotic prescription had been dispensed it could not be used and that there is need for a fresh visit to a health facility whenever they experienced similar or newer symptoms. They lacked the basic understanding that self-medication in itself is very dangerous and worse that it adds on to the menace of antibiotic resistance (43).

The ease of access to antibiotics without a valid prescription is increasing. In Nigeria, a study showed about 82.2% of patients attending a clinic reported to have accessed antibiotics without a prescription (44). When asked on whether the practice of self-medication with antibiotics was acceptable or not, about half (48.2%) of the respondents thought that the practice was acceptable while the rest were unsure about the practice. Among the dangers of self-medication with antibiotics is development of ADRs, some of which are fatal such as the anaphylactic reaction associated with penicillin-based antibiotics. The same study revealed that very few (3.9%) were aware that self-medication with antibiotics could lead to ADRs.

2.4.2 Healthcare provider factors

Physicians have the responsibility to make a resolve on whether a patient deserves antibiotic therapy and eventually the choice of antibiotic to use is solely on them. Their decisions ultimately contribute to either rational or irrational use of antibiotics. It has been

suggested that their knowledge, attitudes and practices towards antibiotics, the level of training and experience on antibiotics, the effect of pharmaceutical promotion and their level of interaction with patients are some of the factors on how they contribute towards irrational use of antibiotics (16).

Regarding the knowledge on antibiotic use, a survey done on physicians at KNH in Kenya found that most respondents had sufficient knowledge on when an antibiotic needed to be initiated (45). Whenever an antibiotic is being prescribed, among the factors that are usually considered is the organ functionality. For instance, in hepatic failure certain medications may require dose reductions while others require dose increments; in renal failure, patients on antibiotics require dose adjustments. Results of this survey showed that only about half (47.7%) of the respondents recognized that the doses of the two antibiotics (ceftriaxone and gentamicin) in the survey required dose adjustments in the event of renal failure (45).

Antimicrobial resistance is an ongoing threat to the survival of the human race in the event of resistant infections. Knowledge on the issue is required among the healthcare providers as a strategy to combat it. A study in Kenya found that 92.2% of physicians understood that antimicrobial resistance is an issue of global concern They all agreed that it is a challenge they all faced in their daily practice and that the decisions they make with regard to antibiotics were in one way or another contributing to it (45).

Rational use of antibiotics dictates that an appropriate antibiotic is selected whenever a correct diagnosis has been made. Challenges in selection and the injudicious use of antibiotics usually contribute to the prevalence of irrational use. Findings of a survey revealed that about one third of physicians (33.6%) studied agreed that they had challenges in the selection of antibiotic (45). A further 82.2% of them reported that when faced with this situation, they would sometimes seek review and guidance from their senior colleagues. In Australia, a study found that almost one third (29%) of the antibiotics that had been selected for treatment were incorrect choices (31).

Training and continuous medical information are important sources of information about antibiotics. Healthcare providers are usually encouraged to attend these fora as they usually impact their practice. Some professional organizations have even taken a step further and

made it mandatory that members attain a minimum number of points as proof of continuous professional development to renew their practicing licenses. Approximately 85.9% physicians who participated in a survey admitted to having attended only less than four teaching sessions on antibiotics within the last year in their departments (45). Information about the use of antibiotics needs to keep being reinforced if any meaningful effort is to be made towards combating antimicrobial resistance and promoting rational use of antibiotics.

The influence of pharmaceutical promotion as a contributory factor towards irrational use of antibiotics should not be taken lightly (46). Anecdotal evidence from pharmaceutical staff processing prescriptions following visits to physicians by the medical representatives reveals the huge influence of pharmaceutical promotion. These pharmacy staff pointed out that once a specific medication had been promoted by medical representatives, the turnover of prescriptions with the so promoted medicine would greatly increase. Results from a systematic review revealed that whenever physicians had had direct interactions and received information from pharmaceutical companies, their prescribing frequencies increased, incidences of higher cost implications increased and the quality of prescriptions generated was increasingly lower (46).

2.4.3 Institution related factors

Several key players are involved in the promotion of rational use of antibiotics. Among them are managers who are involved in one way or another in the running of institutions. They have a duty to ensure that the systems that are put in place to promote these activities are functional and that they provide the necessary support in terms of infrastructure to promote rational use of antibiotics. They work together with medicine therapeutic committees to ensure that essential documents like hospital formularies, treatment guidelines, and antibiotic use guidelines are available to the prescribers for use in their practice.

Adequate laboratory support is an indispensable strategy in the promotion of rational use of antibiotics (47). Laboratory data gives information that is key in guiding the selection of antibiotics once an accurate diagnosis has been obtained. A diagnosis can only be relied upon once the results of culture and sensitivity are available to the physicians. Laboratories should make efforts to occasionally do tests on the patterns of infections encountered in

hospitals and determine susceptibility of the infectious agents. The information obtained should then be disseminated to all the departments within the hospital for the necessary action (47).

The spread of infections within the hospital should be kept at bay with the introduction of infection prevention control (IPC) practices. This should be spear headed by IPC teams that are mandated to provide information on ways to control, contain and prevent the spread of infections. These teams can also hold departmental meetings and seminars where they can educate healthcare providers on infection prevention practices. Simple procedures like use of alcohol hand rubs or proper hand washing after handling patients go a long way in preventing spread of infections.

2.5 Factors associated with clinical outcomes and mortality of CCU patients

Critical illness continues to be an increasing burden in all populations. Therefore to comprehend the magnitude of this burden, patient clinical outcomes need to be evaluated (48). Results of an international audit of patients admitted to the CCU worldwide revealed a mortality rate of 16.2% across the whole population. The major contributors to this mortality rate were general infections at 24.6%, sepsis at 18% and comorbidities at 12.3%. The commonest comorbidities were chronic obstructive pulmonary diseases (COPD), non-metastatic cancers, diabetes mellitus, heart failure and chronic renal failure (48). A study done at a CCU set up at a referral hospital in western Kenya found a mortality rate of 53.6% (49).

Nosocomial infections also known as health care-associated infection (HCAI), are infections which develop in patients while they are receiving medical care (50). HCAIs have been associated with increased mortality, morbidity, prolonged length of stay within the CCU, disability and a heavy economic burden (51,52). The common types of nosocomial infections include ventilator associated pneumonia (VAP), catheter associated urinary tract infection (CAUTI), central line associated blood stream infection (CLABSI) and surgical site infections. According to the WHO, 10 in every 100 hospitalized patients in developing countries are likely to develop at least one HCAI. The burden of nosocomial infections is particularly higher in neonates and patients in CCUs. About a third of patients in the CCUs are affected by at least one episode of HCAI. Inappropriate use of antibiotics

has been implicated among the factors putting patients at risk of developing nosocomial infections (50). A previous study done at the KNH CCU in 2006 found a 42% mortality rate owing to nosocomial infections (53).

Patient hospital length of stay (LOS) can be defined as the total number of days spent in a healthcare facility within a single admission (54). Prolonged LOS within the CCU set up increases the risk of patients developing infections (50). This in turn has a spill-over effect of increasing the mortality rates when patients succumb to these infections. Prolonged LOS following critical illness has been found to be associated with increased mortality and morbidity (55).

The Society of Critical Care Medicine defines sepsis as a life-threatening organ dysfunction as a result of dysregulation of host response to infection (56). They further define septic shock as a subset of sepsis where there's ongoing circulatory, cellular and metabolic abnormalities. Sepsis still remains to be a major challenge in all CCU patients globally and is associated with high mortality rates (57). Up to 39% of patients admitted in CCUs have been found to develop sepsis. An audit by Intensive Care Over Nations (ICON) found sepsis related mortality rates of 26% worldwide which was revealed to be twice higher than that in non-septic patients (48,57). A study done in a CCU set up at a referral hospital in western Kenya found a mortality rate of 80% for patients who presented with sepsis (49).

Several organ related complications occur in critically ill patients. Acute kidney injury (AKI) is one such complication and it is correlated to increased risk of mortality (58). According to Kidney Disease Improving Global Outcomes (KDIGO) guideline, AKI is defined as "an increase in serum creatinine (SCr) by $\geq$ 0.3 mg/dl ($\geq$26.5µmol/l) within 48hours; or increase in SCr to $\geq$1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 mL/kg/h for 6 hours" (59). Use of nephrotoxic drugs has been implicated in the development of AKI (60). Among the drugs implicated are antibiotics such as vancomycin, piperacillin/tazobactam, polymixins and aminoglycosides (58).

2.6 Gaps in the literature

Publications on rational use of antibiotics in the CCU set up in Kenya are scarce. Inappropriate use of antibiotics has been associated with poor clinical outcomes and mortality rates within the CCU (22). While literature review has revealed that studies have been done on the utilization of antibiotics in the Kenyan population, these studies focused mainly in the outpatient and inpatient set ups but none in the CCU settings. Furthermore, none of these studies have made any attempts to show the impact of rational use of antibiotics on patient clinical outcomes. This study sought to fill in the gaps in the literature of rational use of antibiotics in the CCU and its impact on clinical outcomes and mortality rates within the Kenyan population.

CHAPTER THREE: METHODOLOGY

3.1 Introduction

This chapter elaborates on how the objectives set for the study were achieved. It contains the chosen design for the research, where the study was conducted, and the target population for the study with details on inclusion and exclusion criteria. It also incorporated how the sample size estimation was done, the research instruments used in collection of data and how data was analyzed.

3.2 Research design

This was a retrospective cross-sectional study. It involved review of records of admissions to the KNH CCUs in the period February 2018 to February 2020. The study aimed at assessing the rational use of antibiotics specifically after the dissemination of the KNH antibiotics policy guidelines in February 2018 (19). The design enabled documentation of commonly prescribed antibiotics, assessment of compliance with the antibiotics policy guidelines and highlighted the deviations. The design was appropriate as one of the objectives of this study was determination of the prevalence of both rational and irrational use of antibiotics. The design also helped in the identification of some associations between the variables.

3.3 Study area and site

The study was conducted at the CCUs in KNH. Kenyatta National Hospital is the largest teaching and referral hospital in Kenya serving East and Central Africa region with a bed capacity of 2000. It is situated in Nairobi County in the capital city of Kenya along Hospital Road in Upper Hill. KNH has one main critical care unit with a bed capacity of 21. Additionally, it has five subsidiary intensive care units (ICUs), namely the neonatal ICU, paediatric ICU, medical ICU, neurological ICU and cardiology ICU, giving an additional bed capacity of 20. The study site was chosen since the KNH offers the largest CCUs bed capacity in the country that serve as a referral centre for the whole country with extensions to East and Central Africa. The site was ideal as it enabled achievement of the required sample size. In addition, the hospital has developed its own antibiotics policy guidelines which will be used a reference for assessing rational use of antibiotics.

3.4 Target population

The target population for this study comprised of all the patients admitted to KNH CCUs the period following dissemination of antibiotic policy guidelines and were receiving systemic antibiotics. The inclusion and exclusion criteria were used to generate a study population from which the sample size was drawn.

3.4.1 Inclusion criteria

The inclusion criteria for this study were:

1. Medical records of patients admitted to KNH CCUs in the period February 2018 to February 2020 and were receiving systemic antibiotic therapy.
2. Patients between the age of 2 and 60 years. This was because the study intended to use Cockroft and Gault equation in the determination of renal function that is applicable only in those aged between 2 and 60 years.
3. Patients hospitalized for at least 48 hours in the CCU. This was because the study hoped to identify development of HCAIs after antibiotic therapy.

3.4.2 Exclusion criteria

The following medical records were excluded:

1. Medical records of patients not receiving any systemic antibiotic therapy.
2. Medical records of patients below 2 years and those above 60 years.
3. Medical records of those admitted in the CCU less than 48 hours.
4. Medical records from the paediatric and neurological ICUs were excluded from the study since the two had not been fully operational since the launch of antibiotic guidelines.

3.5 Sampling

3.5.1 Sample size estimation

The sample size was calculated using the Fischer formula (61) given in Equation 1.

$$n = \frac{z^2 p(1-p)}{d^2} \qquad \text{Equation 1}$$

Where n was the sample size, Z the standard normal deviation at 95% confidence interval set at 1.96, P was the prevalence

of rational antibiotic use and d the precision of the study, which was set at 5%.

The primary outcome of the study was the prevalence of rational antibiotic use. A study done at a referral hospital in Rift valley in Kenya found a prevalence of 27.9% of rational antibiotic use (3). Another study done at the KNH found a prevalence of 4.4% on rational prescribing practices (14). For the purpose of this study, p was 16% obtained by getting an average of the two rates of prevalence from the studies mentioned as shown in Equation 2.

$$P = \frac{27.9+4.4}{2} = 16.15\% \approx 16\% \qquad \text{Equation 2}$$

For this study, the actual sample size was calculated as shown in Equation 3.

$$n = \frac{1.96^2\ 0.16(1-0.16)}{0.05^2} = 206.52 \approx 207 \text{ medical records} \qquad \text{Equation 3}$$

To cater for unforeseen data losses such as missing data in the files, a 10% over estimation of the sample size was done to give the final sample of approximately 230 patients' files.

The study was able to attain a 95.7% sample size (n=220). This was due to challenges in getting files that had qualified the inclusion criteria but had been retained in the security records as a result of non-clearance of hospital bills.

3.5.2 Sampling technique

The sampling technique used was stratified proportionate random sampling. A proportionate sample was obtained from each CCU as shown in Table 1. Medical records from each CCU were first assessed to check whether they had the relevant information, then the patient file numbers were entered into the Microsoft Excel version 2013 and the computer then generated a random sample of files to be studied. The process was repeated until the required sample size was attained.

3.6 Research instruments and data collection techniques

A data collection tool (Appendix 1) was used to capture relevant data for the specific objectives of the study. The tool captured details of patient demographics, antibiotic prescribed, the dosage, the diagnosis, comorbidities, culture and sensitivity tests (CST) done, renal function, dose adjustments in form of escalations and de-escalations, white blood cell counts, fever, length of hospital stay and the ultimate clinical outcome which

was either discharge or death. The tool also captured details on generic prescribing, whether there was compliance with the guideline and whether treatment was empiric or targeted.

Table 1: Proportionate sampling of the KNH CCUs according to bed capacity

Specific CCU	Bed capacity	Proportion	No of medical records sampled
Main	21	21/31 × 230	156
Cardiology	5	5/31 × 230	37
Medical	5	5/31 × 230	37
Total	31	31/31 × 230	230

CCU = Critical care unit.

3.7 Pilot study

A sample size of 20 was used to conduct a pilot study by the PI using the data collection tool (Appendix 1) on randomly selected CCU medical records. This was done after ethical approval by the Kenyatta National Hospital /University of Nairobi Ethics and Research Committee (KNH/UON- ERC). The pilot sample size was a 10% estimate approximation of the actual sample size for the retrospective cross-sectional study. The data generated was then assessed for its ability to accurately capture the objectives of the study.

3.8 Validity

Validity refers to the extent to which a test or research instrument measures the variable it is supposed to (62). Validity for this study was achieved by piloting the Data Collection Tool within the same conditions and procedures as was done in the main study. The obtained data was analyzed using descriptive and inferential statistics to evaluate whether the Data Collection Tool captured relevant data capable of fulfilling the objectives of the study. Additionally, the obtained descriptive and inferential statistics gave an indication of whether the generated data was generalizable to study population and by extrapolation to the general public. Presence of any internal inconsistencies that would bring in bias were identified by pretesting.

3.9 Reliability

Reliability is a measure of how consistent the results obtained from a test or research instrument are (62). During piloting, the data collection tool was pretested to check and ensure that it met all the objectives the study set out to achieve. The study site and area was a good representation of the Kenyan population, given that KNH is a tertiary referral hospital that attends to patients who come from all over the country.

3.10 Data management

The data collected daily from the medical records were coded and entered into Microsoft Excel version 2013. This data was then validated for completeness and correctness. Electronic data was protected by passwords whose access codes were only privy to the PI. This data was stored and backed up regularly in a separate location from the primary data. The hard copies of the primary data base collection tool were kept in a private cabinet under lock and key and kept for period of three years after which they will be shredded and incinerated.

3.10.1 Study variables

Predictor variables

Predictor variables included the patient demographics like the age, sex, diagnosis and the specific CCU the patient was admitted in.

Outcome variables

Outcome variables comprised of the type of antibiotic chosen, indication, dose, route of administration, frequency and duration of treatment. It also included the patients' clinical outcome which was either a discharge from the CCU or death.

3.10.2 Data analysis

STATA version 13 was used for analysis. Frequency tables were used to show the commonly prescribed antibiotics. Several indicators were used to show rational and irrational use of antibiotics. These included appropriate choice of antibiotic, correct dose, correct frequency, correct duration and appropriate route of administration. Other indicators of quality antibiotic prescribing such as generic prescribing and targeted versus empiric prescribing were also assessed. The prevalence of rational and irrational antibiotics was computed as proportions or frequencies of the total number of antibiotics that were

dispensed. The Pearson's Chi square and Fischer's exact test were used in determining the associations between predictor variables such as socio-demographic factors and outcome variables like the antibiotic prescribed. Logistic regression was used to measure the independent correlates of rational antibiotic prescribing and mortality. Statistical significance was set at 95% confidence interval.

3.11 Logistical and ethical considerations

Ethical approval was obtained from the Kenyatta National Hospital /University of Nairobi Ethics and Research Committee (KNH/UON-ERC) reference number P79/02/2020. Further approval was obtained from the KNH Research and Program department before embarking on the study. Confidentiality of the patient data was highly regarded: to this effect there were unique identifications for each patient record. Hard copy records were stored in a locked cabinet while the electronic record was protected by passwords whose access was solely with the PI.

CHAPTER FOUR: RESULTS

4.1 Sociodemographic and clinical characteristics of the study population

The sociodemographic and clinical characteristics of the study population are presented in Table 2**.**

Table 2: Sociodemographic and clinical characteristics of study population

Variable	Characteristic	Frequency, n (%)
Age in years	≤10	24 (10.9)
	11-20	34 (15.5)
	21-30	56 (25.5)
	31-40	39 (17.7)
	41-50	38 (17.3)
	51-60	29 (13.2)
Sex	**Male**	**129 (58.6**)
	Female	91 (41.4)
CCU type	Cardiology	32 (14.5)
	Main	**156 (70.9)**
	Medical	32 (14.5)
	Mean (SD)	**Median (IQR)**
Length of stay (days), Mean (±SD); Median (IQR)	11.5 (13.8)	7.0 (4.0 – 13.0)
Co-morbidities	**Hypertension**	**27 (42.9)**
	Cancer	2 (3.2)
	Diabetes	**13 (20.6)**
	Kidney disease	5 (7.9)
	Trauma	**21 (33.3)**
	Liver disease	1 (1.6)
	HIV	4 (6.3)
Risk Category for use of empiric antibiotics	1	99 (45.0)
	2	112 (50.9)
	3	9 (4.1)
Patient's Diagnosis type	**Surgical**	**156 (70.9)**
	Medical	64 (29.1)
Catheterization	Yes	196 (89.1)
	No	24 (10.9)
Intubation	Yes	138 (62.7)
	No	82 (37.3)
Kidney function	Normal/High	95 (50.8)
	Mildly decreased	56 (29.9)
	Mildly- moderately	17 (9.1)
	Moderately- severely decreased	8 (4.3)
	Severely decreased	6 (3.2)
	Kidney failure	5 (2.7)
Outcome of therapy	Death	22 (10.0)
	Discharge	198 (90.0)

Key: IQR= Interquartile range; SD= Standard deviation

The age of the study population was in the range 2-60 years and a mean age of 31.2 ± 15.7 years. There were more males (129, 58.6%) than females. The main CCU had the largest proportion (156, 70.9%) of the medical files in the study population. The length of hospital stay ranged from 2-113 days with a mean of 11.5 ± 13.8 days.

The most prevalent comorbidity was hypertension (27, 42.9%), followed by trauma (21, 33.3%) and diabetes (13, 20.6%). Most of study population fell in risk category 2 (112, 50.9%) followed by those in risk category 1 (99, 45.0%). Most of the study population that were admitted to the CCU had a surgical type diagnosis (156, 70.9%).

A larger proportion of the study population (196, 89.1%) had been catheterized while 24 (10.9%) patients did have any form of catheter. A total of 138 (62.7%) patients were intubated. From the study population, 22 (10%) had died while 198 (90%) were discharged from the CCU.

4.2 Culture and sensitivity tests

Table 3 shows summary characteristics of culture and sensitivity testing performed at the study site over the review period.

Table 3: Characteristics of the Culture and Sensitivity Tests Performed at CCU

First CST done/days post admission	Frequency (n=88)	Percentage (%)
1	22	25.0
2	26	29.5
3	10	11.4
>3	30	34.1
Days report received in CCU		
1	50	56.8
2	21	23.9
3	5	5.7
>3	12	13.6
Any micro-organism isolated		
Yes	29	33.0
No	59	67.0
CST Requested		
Empirical	31	35.2
Surgical prophylaxis	53	60.2
Not specified	4	1.6

Among those that had CST requests made, 30 (34.1%) took more than 3 days from the day of admission before the CST was done, while 26 (29.5%) had the tests done on the second

day of admission. Only 22 (25.0%) had the CST done on the first day of admission. Fifty (56.8%) CST reports were received back in the CCU after one day while 12 (13.6%) reports were received after more than 3 days. Among the CST done, 29 (33.0%) tests had various micro-organisms isolated. Among the study population that were receiving antibiotics for surgical prophylaxis (n=154), 53 (34.0%) had CST requests made. Of those that received antibiotics for empirical treatment (n=61) only 31 (50.8%) had a CST request made.

4.3 Antibiotic use management

4.3.1 Reasons for the Use of antibiotics in CCU

Most antibiotic prescribing was for surgical prophylaxis (154, 70.0%) as compared to empirical use (61, 27.7%). Non-specified use accounted for 1.8% while targeted antibiotic use was 0.5% (Figure 2).

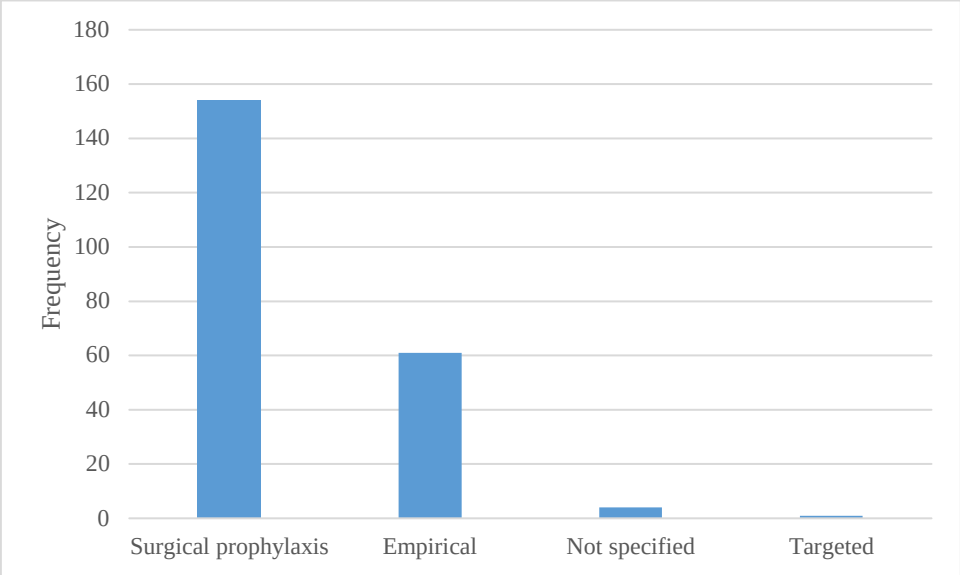

Figure 2: Reasons for use of antibiotics in the CCU.

4.3.2 Types and reasons of antibiotic switch in CCU

The commonest antibiotic change among the study population was prescribing of new antibiotics (55, 83.3%). About 98 (12.1%) had both a stop to their antibiotics and a new antibiotic was then prescribed (Figure 3). Among the 88 patients that had a CST request made, 66 (75.0 %) had their antibiotics changed after the reports were received in the CCU. Analysis showed that for most (53, 80.3%) patients that had their antibiotic therapy

changed, no reason was indicated in their clinical notes. The CST report was used as a reason for change in antibiotic therapy in (11, 16.7%) of the study population (Figure 4).

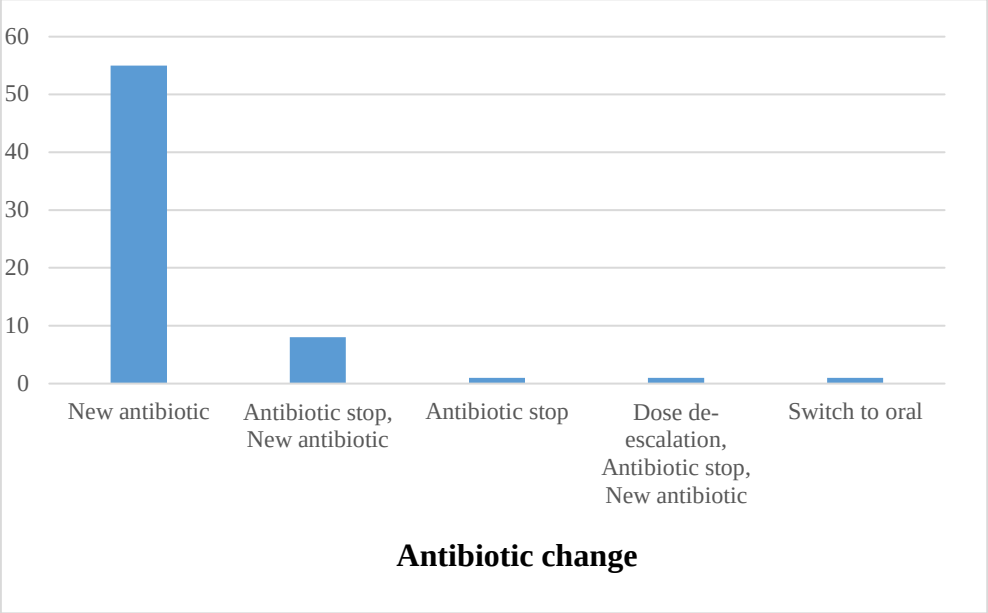

Figure 3: Types of antibiotic changes among study population.

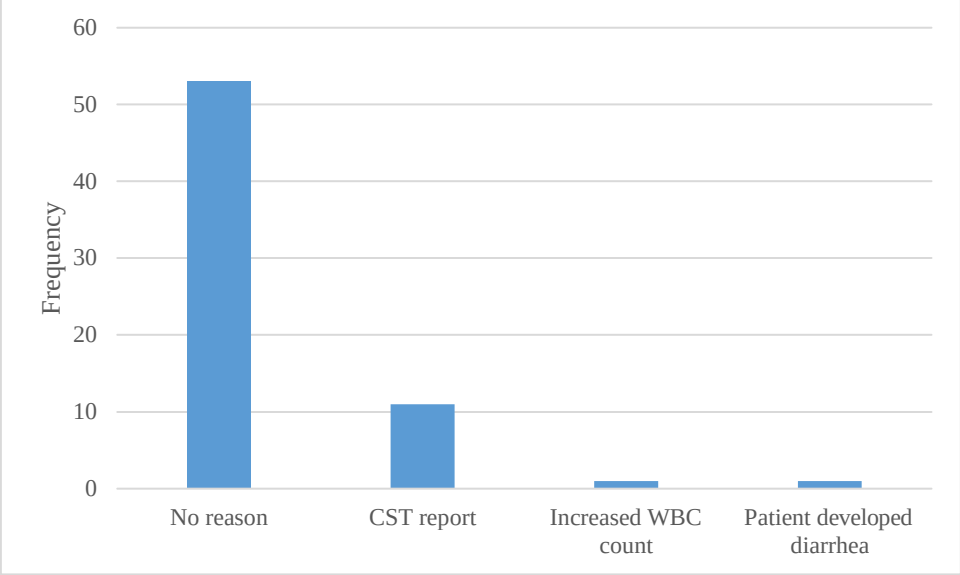

Figure 4: Reasons for antibiotic changes among study population.

4.3.3 Prevalence of antibiotic classes

As depicted in Figure 5, cephalosporins had the highest proportion of use (185, 49.6%) followed by the 5-nitroimidazoles (68, 18.2%) and penicillins (53, 14.2%).

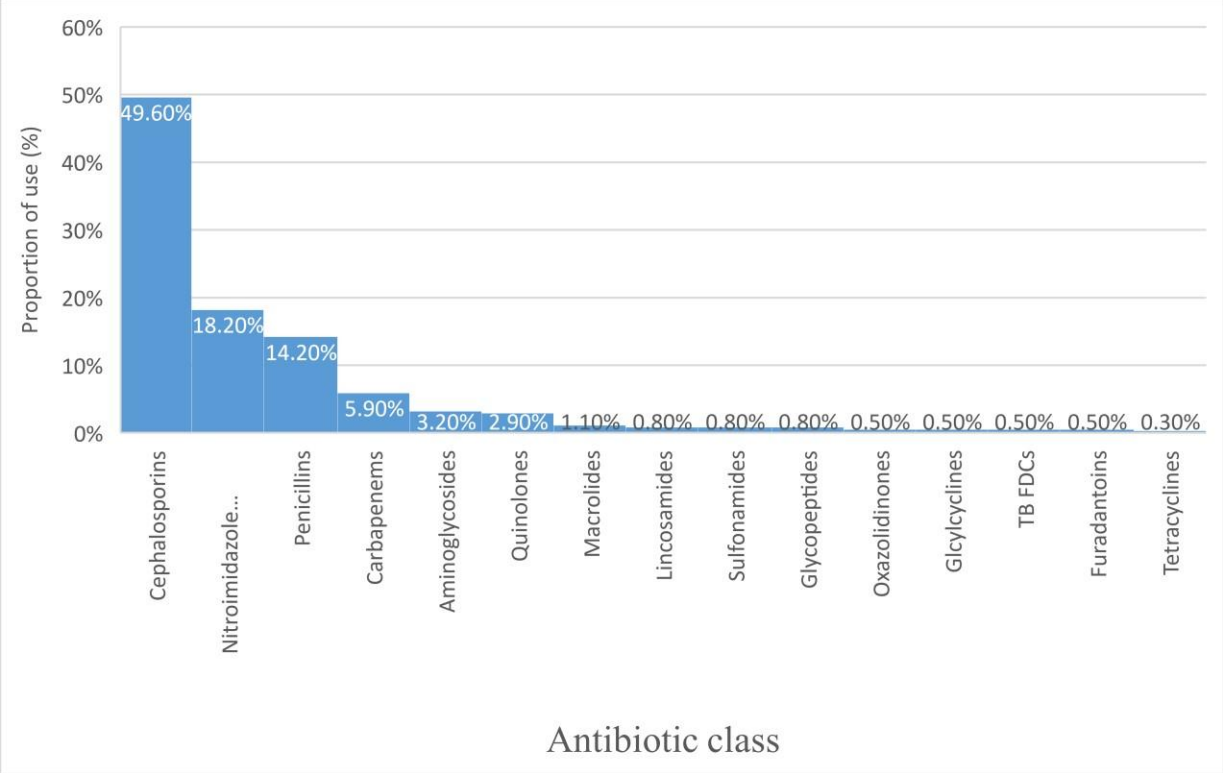

Figure 5: Prevalence of use of various antibiotics in CCUs.

4.3.4 Prevalence of specific antibiotics prescribed

Ceftriaxone had the highest proportion of use (112, 28.7%) followed by metronidazole (67, 17.2%) then cefuroxime (60, 15.4%) (Figure 6).

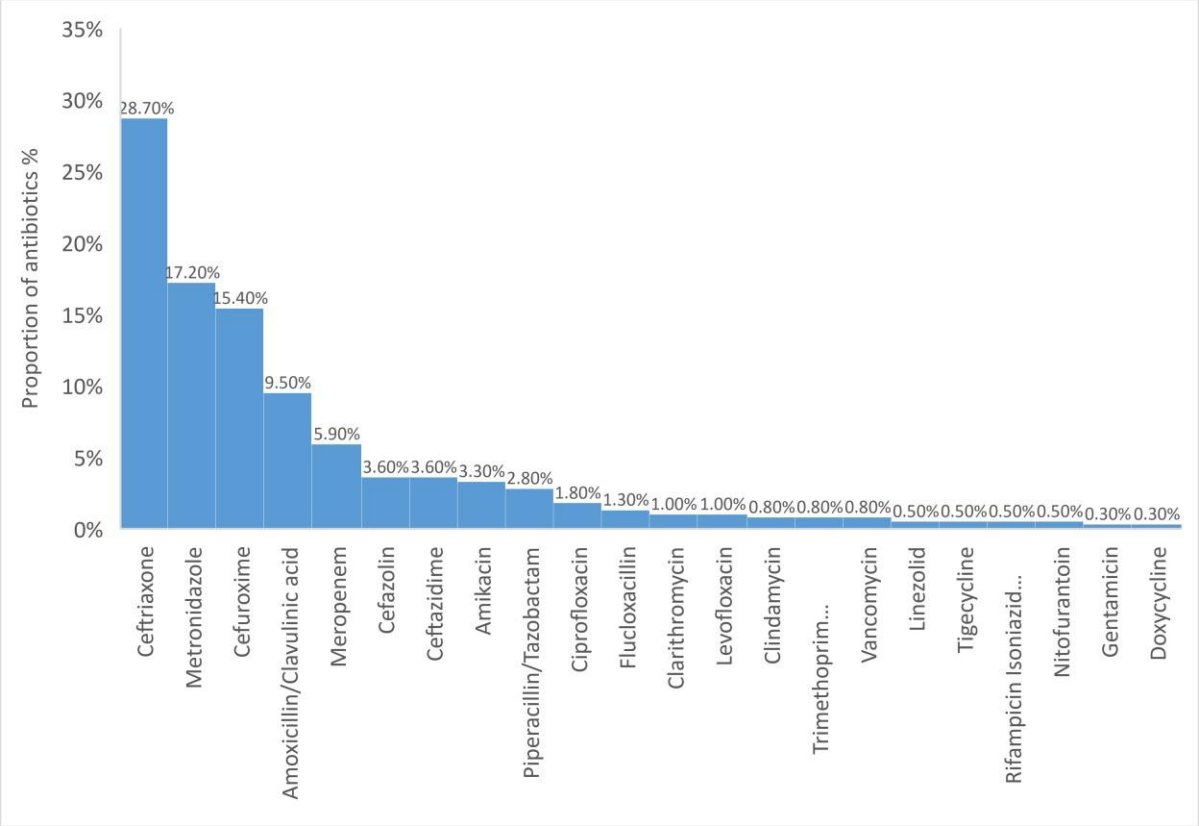

Figure 6: Prevalence of specific antibiotics prescribed.

4.4 Rational use of antibiotics

4.4.1 Evaluation of rational antibiotic prescribing

There were 390 antibiotic encounters and their rational or irrational use is detailed in Table 4. Out of the 390 antibiotic encounters, 37.9% (n=148) were appropriate choices for the specific diagnoses while 51% (n=199) were inappropriate choices for the various diagnoses. Correct doses were prescribed in 76.7% (n=299) according to their indication and diagnosis while 14.4% (n=56) had incorrect doses. Correct duration of antibiotics was prescribed in 55.1% (n=215) according to their indication and diagnosis while 32.3% (n=126) had incorrect duration. Correct frequencies were prescribed in 69.5% (n=271) according to their indication and diagnosis while 29.2% (n=114) had incorrect frequencies. Almost all prescriptions 99.4% (n=388) had the correct route of administration prescribed according to their indication and diagnosis while 0.3% (n=1) had incorrect routes of administration.

Table 4: Evaluation of rational antibiotic prescribing

Specific antibiotic	Right Choice			Right Dose			Right Duration			Right Frequency			Correct route		
	Y	N	U	Y	N	U	Y	N	U	Y	N	U	Y	N	U
Amikacin	7	1	5	10	2	1	10	2	1	11	2	0	13	0	0
Amoxicillin/Clavulanic acid	15	19	3	33	0	4	33	0	4	31	6	0	37	0	0
Cefazolin	14	0	0	14	0	0	14	0	0	2	12	0	14	0	0
Ceftazidime	2	10	2	12	0	2	12	0	2	14	0	0	14	0	0
Ceftriaxone	65	45	2	72	38	2	72	38	2	45	66	1	112	0	0
Cefuroxime	2	55	3	50	7	3	50	7	3	41	18	1	60	0	0
Ciprofloxacin	5	2	0	7	0	0	7	0	0	7	0	0	7	0	0
Clarithromycin	1	1	2	2	0	2	2	0	2	4	0	0	4	0	0
Clindamycin	2	0	1	1	1	1	1	1	1	2	1	0	3	0	0
Flucloxacillin	0	5	0	4	0	1	4	0	1	5	0	0	5	0	0
Gentamicin	0	1	0	1	0	0	1	0	0	1	0	0	1	0	0
Levofloxacin	2	0	2	3	0	1	3	0	1	3	1	0	4	0	0
Linezolid	1	1	0	2	0	0	2	0	0	2	0	0	2	0	0
Meropenem	4	9	10	13	1	9	13	1	9	20	1	2	22	0	1
Metronidazole	12	48	7	57	4	6	57	4	6	62	4	1	66	1	0
Piperacillin/Tazobactam	6	2	3	10	0	1	10	0	1	9	2	0	11	0	0
Trimethoprim Sulfamethoxazole	3	0	0	3	0	0	3	0	0	3	0	0	3	0	0
Vancomycin	2	0	1	0	2	1	0	2	1	2	1	0	3	0	0
Tigecycline	0	0	2	0	1	1	0	1	1	2	0	0	2	0	0
Rifampicin Isoniazid Pyrazinamide Ethambutol	2	0	0	2	0	0	2	0	0	2	0	0	2	0	0
Nitrofurantoin	2	0	0	2	0	0	2	0	0	2	0	0	2	0	0
Doxycycline	1	0	0	1	0	0	1	0	0	1	0	0	1	0	0
Total (%)	**148 (37.9)**	**199 (51)**	**43 (11.1)**	**299 (76.7)**	**56 (14.4)**	**35 (8.9)**	**215 (55.1)**	**126 (32.3)**	**49 (12.6)**	**271 (69.5)**	**114 (29.2)**	**5 (1.3)**	**388 (99.4)**	**1 (0.3)**	**1 (0.3)**

Key: Y=Yes, N=No, U= Unknown.

4.4.2 Rational prescribing of specific antibiotics

As shown in Table 5, only 72 (18.5%) instances of antibiotics prescriptions were rational, while 276 (70.8%) instances were prescribed irrationally. For all the five instances where flucloxacillin was prescribed, its use was found irrational (100%), while cefuroxime was used irrationally in 56 (93.3%) of the 57 prescriptions. Equally striking, cefazolin, a first-generation cephalosporin, was irrationally prescribed in 12 (85.7%) of the 14 instances it was encountered while ceftriaxone was irrationally prescribed for 93 (83%) of the 109 encounters. Other specific antibiotics with notable irrational use were metronidazole (74.6%), ceftazidime (71.4%), vancomycin (66.7%), and co-amoxiclav (62.2%). The rationality for 42 (10.7%) instances of antibiotics prescriptions remained indeterminate.

Table 5: Rational prescribing of specific antibiotics

Antibiotic	**Rational n (%)**	**Irrational n (%)**	**Unknown n (%)**	**Total n**
Amikacin	5 (38.5)	4 (30.8)	4 (30.8)	13
Amoxicillin/Clavulanic acid	11 (29.7)	23 (62.2)	3 (8.1)	37
Cefazolin	2 (14.3)	12 (85.7)	0 (0)	14
Ceftazidime	2 (14.3)	10 (71.4)	2 (14.3)	14
Ceftriaxone	16 (14.3)	93 (83)	3 (2.7)	112
Cefuroxime	1 (1.7)	56 (93.3)	3 (5)	60
Ciprofloxacin	5 (71.4)	2 (28.6)	0 (0)	7
Clarithromycin	1 (25)	1 (25)	2 (50)	4
Clindamycin	1 (33.3)	1 (33.3)	1 (33.3)	3
Flucloxacillin	0 (0)	5 (100)	0 (0)	5
Gentamicin	0 (0)	1 (100)	0 (0)	1
Levofloxacin	1 (25)	1 (25)	2 (50)	4
Linezolid	1 (50)	1 (50)	0 (0)	2
Meropenem	4 (17.4)	9 (39.1)	10 (43.5)	23
Metronidazole	10 (14.9)	50 (74.6)	7 (10.4)	67
Piperacillin/Tazobactam	4 (36.4)	4 (36.4)	3 (27.3)	11
Trimethoprim Sulfamethoxazole	3 (100)	0 (0)	0 (0)	3
Vancomycin	0 (0)	2 (66.7)	1 (33.3)	3
Tigecycline	0 (0)	1 (50)	1 (50)	2
Rifampicin Isoniazid Pyrazinamide Ethambutol	2 (100)	0 (0)	0 (0)	2
Nitrofurantoin	2 (100)	0 (0)	0 (0)	2
Doxycycline	1 (100)	0 (0)	0 (0)	1
Total (%)	**72 (18.5)**	**276 (70.8)**	**42 (10.7)**	**390**

4.5 Bivariate analysis

Penicillins were statistically significantly prescribed class of antibiotics with age (p=0.046) (Table 6).

Table 6: Association between age category and antibiotic class

Antibiotic class	Age category in years, n (%)						p-value
	≤ 10	11-20	21-30	31-40	41-50	51-60	
Aminoglycosides	4 (33.3)	2 (16.7)	2 (16.7)	1 (8.3)	1 (8.3)	2 (16.7)	0.239
Penicillins	5 (9.4)	6 (11.3)	20 (37.7)	13 (24.5)	6 (11.3)	3 (5.7)	**0.046**
Cephalosporins	21 (11.4)	30 (16.2)	44 (23.8)	30 (16.2)	36 (19.5)	24 (13)	0.227
Quinolones	0 (0)	2 (18.2)	4 (36.4)	1 (9.1)	2 (18.2)	2 (18.2)	0.816
Macrolides	0 (0)	1 (25)	1 (25)	2 (50)	0 (0)	0 (0)	0.629
Lincosamides	0 (0)	1 (33.3)	1 (33.3)	0 (0)	0 (0)	1 (33.3)	0.730
Oxazolidinones	0 (0)	0 (0)	0 (0)	0 (0)	1 (50)	1 (50)	0.338
Carbapenems	2 (9.1)	2 (9.1)	9 (40.9)	3 (13.6)	2 (9.1)	4 (18.2)	0.524
5-Nitroimidazoles	7 (10.3)	11 (16.2)	19 (27.9)	13 (19.1)	11 (16.2)	7 (10.3)	0.954
Sulfonamides	0 (0)	0 (0)	0 (0)	2 (66.7)	1 (33.3)	0 (0)	0.297
Glycopeptides	0 (0)	1 (33.3)	1 (33.3)	1 (33.3)	0 (0)	0 (0)	0.953
Glycylcyclines	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)	1 (50)	0.292
TB FDCs	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)	0 (0)	0.675
Furadantoins	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)	1 (50)	0.742
Tetracyclines	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0.395

TBFDCs = Tuberculosis Fixed Drug Combinations.

As bivariate analyses in Table 7 illustrate, there was no statistically significant association between the choice of specific antibiotic and the participant's age category. Statistical significance was found in the prescribing of macrolides (p=0.023) in the main CCU (1, 25%) and the medical CCU (3, 75%). Carbapenems were statistically significantly prescribed in cardiology (3, 13.6%), main (11, 50%) and the medical CCU (8, 36.4%). Sulfonamides were significantly used in the medical CCU (3, 100%) (p=0.006) (Table 8).

Table 7: Association between age and specific antibiotics

Antibiotic	Age category in years, n (%)						p-value
	≤ 10	11-20	21-30	31-40	41-50	51-60	
Amikacin	3 (23.1)	3 (23.1)	2 (15.4)	2 (15.4)	1 (7.7)	2 (15.4)	0.573
Co-Amoxiclav	3 (8.1)	6 (16.2)	14 (37.8)	9 (24.3)	4 (10.8)	1 (2.7)	0.096
Cefazolin	3 (21.4)	0 (0)	2 (14.3)	2 (14.3)	6 (42.9)	1 (7.1)	0.058
Ceftazidime	0 (0)	3 (21.4)	6 (42.9)	3 (21.4)	1 (7.1)	1 (7.1)	0.467
Ceftriaxone	13 (11.6)	19 (17)	28 (25)	18 (16.1)	21 (18.8)	13 (11.6)	0.931
Cefuroxime	6 (10)	11 (18.3)	11 (18.3)	8 (13.3)	11 (18.3)	13 (21.7)	0.144
Ciprofloxacin	0 (0)	0 (0)	3 (42.9)	1 (14.3)	2 (28.6)	1 (14.3)	0.761
Clarithromycin	0 (0)	1 (25)	1 (25)	2 (50)	0 (0)	0 (0)	0.614
Clindamycin	0 (0)	1 (33.3)	1 (33.3)	0 (0)	0 (0)	1 (33.3)	0.730
Flucloxacillin	0 (0)	0 (0)	4 (80)	1 (20)	0 (0)	0 (0)	0.217
Gentamicin	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.110
Levofloxacin	0 (0)	2 (50)	1 (25)	0 (0)	0 (0)	1 (25)	0.396
Linezolid	0 (0)	0 (0)	0 (0)	0 (0)	1 (50)	1 (50)	0.384
Meropenem	2 (8.7)	2 (8.7)	10 (43.5)	3 (13)	2 (8.7)	4 (17.4)	0.531
Metronidazole	7 (10.4)	10 (14.9)	19 (28.4)	13 (19.4)	11 (16.4)	7 (10.4)	0.954
Piperacillin/Tazobactam	2 (18.2)	0 (0)	2 (18.2)	3 (27.3)	2 (18.2)	2 (18.2)	0.539
Trimethoprim-Sulfamethoxazole FDC	0 (0)	0 (0)	0 (0)	2 (66.7)	1 (33.3)	0 (0)	0.280
Vancomycin	0 (0)	1 (33.3)	1 (33.3)	1 (33.3)	0 (0)	0 (0)	0.953
Tigecycline	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)	1 (50)	0.292
Rifampicin-Isoniazid-Pyrazinamide-Ethambutol FDC	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)	0 (0)	0.674
Nitrofurantoin	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)	1 (50)	0.742
Doxycycline	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0.397

Key: FDC = Fixed-dose combination

Table 8: Association between CCU type and antibiotic class

Antibiotic class	Critical care unit, n (%)			p-value
	Cardiology	Main	Medical	
Aminoglycosides	1 (8.3)	9 (75)	2 (16.7)	0.998
Penicillins	6 (11.3)	36 (67.9)	11 (20.8)	0.297
Cephalosporins	28 (15.1)	133(71.9)	24 (13)	0.362
Quinolones	1 (9.1)	8 (72.7)	2 (18.2)	0.893
Macrolides	0 (0)	1 (25)	3 (75)	**0.023**
Lincosamides	1 (33.3)	1 (33.3)	1 (33.3)	0.205
Oxazolidinones	0 (0)	1 (50)	1 (50)	0.500
Carbapenems	3 (13.6)	11 (50)	8 (36.4)	**0.015**
5-Nitroimidazoles	9 (13.2)	47 (69.1)	12 (17.6)	0.703
Sulfonamides	0 (0)	0 (0)	3 (100)	**0.006**
Glycopeptides	0 (0)	2 (66.7)	1 (33.3)	0.647
Glycylcyclines	0 (0)	2 (100)	0 (0)	0.998
TB FDCs	0 (0)	1 (50)	1 (50)	0.500
Furadantoins	0 (0)	1 (50)	1 (50)	0.500
Tetracyclines	1 (100)	0 (0)	0 (0)	0.292

TB FDCs = Tuberculosis Fixed Drug Combinations.

Table 9 shows that prescriptions of cephalosporins were statistically significantly associated with surgical procedures (p=0.001) at (141, 76.2%) and the medical uses (44, 23.8%). Carbapenems were also significantly utilized (p= 0.005) in the medical diagnosis (12, 54.5%) and surgical cases (10, 45.5%). Penicillins were significantly prescribed (p=0.007) for the surgical diagnosis (30, 56.6%) and the medical diagnosis (23, 43.4%).

Table 9: Antibiotic prescribing according to the type of patient diagnosis

Antibiotic class	Surgical	Medical	p-value
Aminoglycosides	7 (58.3)	5 (41.7)	0.333
Penicillins	30 (56.6)	23 (43.4)	**0.007**
Cephalosporins	141 (76.2)	44 (23.8)	**0.001**
Quinolones	8 (72.7)	3 (27.3)	0.997
Macrolides	1 (25)	3 (75)	0.073
Lincosamides	2 (66.7)	1 (33.3)	0.998
Oxazolidinones	1 (50)	1 (50)	0.494
Carbapenems	10 (45.5)	12 (54.5)	**0.005**
5-Nitroimidazoles	43 (63.2)	25 (36.8)	0.079
Sulfonamides	0 (0)	3 (100)	**0.023**
Glycopeptides	2 (66.7)	1 (33.3)	0.998
Glycylcyclines	1 (50)	1 (50)	0.494
TB FDCs	1 (50)	1 (50)	0.494
Furadantoins	0 (0)	2 (100)	0.082
Tetracyclines	1 (100)	0 (0)	0.998

TB FDCs = Tuberculosis Fixed Drug Combinations.

The prescribing of cefuroxime (p=0.001), meropenem (p=0.005) and amoxicillin/clavulanic acid (p=0.033) were significantly associated with the patient's diagnosis type. Cefuroxime (53, 88.3%) was commonly prescribed for surgical diagnosis and meropenem (12, 52.2%) for the medical diagnosis type (Table 10).

Table 10: Association between specific antibiotics and patient diagnosis

	Surgical	Medical	p-value
Amikacin	9 (69.2)	4 (30.8)	0.997
Amoxicillin/Clavulanic acid	21 (56.8)	16 (43.2)	**0.033**
Cefazolin	14 (100)	0 (0)	**0.012**
Ceftazidime	7 (50)	7 (50)	0.204
Ceftriaxone	81 (72.3)	31 (27.7)	0.716
Cefuroxime	53 (88.3)	7 (11.7)	**0.001**
Ciprofloxacin	4 (57.1)	3 (42.9)	0.413
Clarithromycin	1 (25)	3 (75)	0.073
Clindamycin	2 (66.7)	1 (33.3)	0.998
Flucloxacillin	3 (60)	2 (40)	0.627
Gentamicin	0 (0)	1 (100)	0.288
Levofloxacin	4 (100)	0 (0)	0.581
Linezolid	1 (50)	1 (50)	0.494
Meropenem	11 (47.8)	12 (52.2)	**0.005**
Metronidazole	42 (62.7)	25 (37.3)	0.064
Piperacillin/Tazobactam	6 (54.5)	5 (45.5)	0.302
Trimethoprim Sulfamethoxazole	0 (0)	3 (100)	**0.023**
Vancomycin	2 (66.7)	1 (33.3)	0.999
Tigecycline	1 (50)	1 (50)	0.494
Rifampicin Isoniazid Pyrazinamide Ethambutol	1 (50)	1 (50)	0.494
Nitrofurantoin	0 (0)	2 (100)	0.082
Doxycycline	1 (100)	0 (0)	0.998

4.5.1 Relationship between rational use of selected antibiotics versus the sociodemographic and clinical characteristics of the study population

There was statistically significant relationship (p=0.012) between rational use of ceftriaxone and the patient diagnosis; and between Amoxicillin/Clavulanic acid prescription with the patient's risk category (p=0.039). There was no statistically significant relationship between metronidazole, cefuroxime, meropenem and sociodemographic characteristics and clinical characteristics.

Table 11: Rational use of selected antibiotics versus the sociodemographic and clinical characteristics of the study population

	Ceftriaxone			Metronidazole			Cefuroxime			Amoxicillin/Clavulanic acid			Meropenem		
	Rational	**Irrational**	**p-value**	**Rational**	**Irrational**	**p-value**	**Rational**	**Irrational**	**p-value**	**Rational**	**Irrational**	**p-value**	**Rational**	**Irrational**	**p-value**
Age (Years)															
	(n=16)	**(n=93)**		**(n=10)**	**(n=50)**		**(n=1)**	**(n=56)**		**(n=11)**	**(n=22)**		**(n=4)**	**(n=9)**	
≤10	1 (7.7)	12 (92.3)	0.96	1 (20)	4 (80)	0.384	0 (0)	5 (100)	0.228	0 (0)	2 (100)	0.153	-	-	
20-Nov	2 (11.1)	16 (88.9)		0 (0)	9 (100)		0 (0)	10 (100)		1 (20)	4 (80)		0 (0)	1 (100)	0.681
21-30	4 (14.3)	24 (85.7)		2 (11.1)	16 (88.9)		0 (0)	11 (100)		7 (53.8)	6 (46.2)		3 (50)	3 (50)	
31-40	3 (16.7)	15 (83.3)		2 (16.7)	10 (83.3)		1 (12.5)	7 (87.5)		1 (11.1)	8 (88.9)		0 (0)	2 (100)	
41-50	4 (21.1)	15 (78.9)		3 (33.3)	6 (66.7)		0 (0)	11 (100)		1 (33.3)	2 (66.7)		0 (0)	2 (100)	
51-60	2 (15.4)	11 (84.6)		2 (28.6)	5 (71.4)		0 (0)	12 (100)		1 (100)	0 (0)		1 (50)	1 (50)	
Sex															
Male	10 (14.9)	57 (85.1)	1	8 (24.2)	25 (75.8)	0.162	0 (0)	37 (100)	0.351	3 (21.4)	11 (78.6)	0.278	3 (37.5)	5 (62.5)	1
Female	6 (14.3)	36 (85.7)		2 (7.4)	25 (92.6)		1 (5)	19 (95)		8 (42.1)	11 (57.9)		1 (20)	4 (80)	
CCU type															
Cardiology	0 (0)	9 (100)	0.093	0 (0)	5 (100)	0.86	0 (0)	10 (100)	1	0 (0)	2 (100)	0.699	0 (0)	1 (100)	1
Main	11 (13.1)	73 (86.9)		8 (18.2)	36 (81.8)		1 (2.2)	45 (97.8)		8 (33.3)	16 (66.7)		3 (37.5)	5 (62.5)	
Medical	5 (31.3)	11 (68.8)		2 (18.2)	9 (81.8)		0 (0)	1 (100)		3 (42.9)	4 (57.1)		1 (25)	3 (75)	
Comorbidity															
Yes	8 (25)	24 (75)	0.073	5 (21.7)	18 (78.3)	0.485	0 (0)	12 (100)	1	4 (57.1)	3 (42.9)	0.186	2 (33.3)	4 (66.7)	1
No	8 (10.4)	69 (89.6)		5 (13.5)	32 (86.5)		1 (2.2)	44 (97.8)		7 (26.9)	19 (73.1)		2 (28.6)	5 (71.4)	
Risk Category															
1	12 (22.6)	41 (77.4)	0.067	4 (13.3)	26 (86.7)	0.588	0 (0)	27 (100)	0.526	9 (52.9)	8 (47.1)	**0.039**	1 (100)	0 (0)	0.308
2	4 (7.4)	50 (92.6)		6 (20.7)	23 (79.3)		1 (3.8)	25 (96.2)		2 (13.3)	13 (86.7)		3 (25)	9 (75)	
3	0 (0)	2 (100)		0 (0)	1 (100)		0 (0)	4 (100)		0 (0)	1 (100)				

Patient's Diagnosis type															
Surgical	7 (8.9)	72 (91.1)	**0.012**	4 (11.1)	32 (88.9)	0.178	0 (0)	50 (100)	0.123	4 (23.5)	13 (76.5)	0.282	1 (16.7)	5 (83.3)	0.559
Medical	9 (30)	21 (70)		6 (25)	18 (75)		1 (14.3)	6 (85.7)		7 (43.8)	9 (56.3)		3 (42.9)	4 (57.1)	
Catheterization															
Yes	16 (16.7)	80 (83.3)	0.209	10 (19.6)	41 (80.4)	0.333	1 (1.9)	52 (98.1)	1	10 (35.7)	18 (64.3)	0.643	4 (33.3)	8 (66.7)	1
No	0 (0)	13 (100)		0 (0)	9 (100)		0 (0)	4 (100)		1 (20)	4 (80)		0 (0)	1 (100)	
Intubation															
Yes	13 (17.8)	60 (82.2)	0.189	10 (22.2)	35 (77.8)	0.054	1 (3)	32 (97)	1	5 (31.3)	11 (68.8)	1	4 (36.4)	7 (63.6)	1
No	3 (8.3)	33 (91.7)		0 (0)	15 (100)		0 (0)	24 (100)		6 (35.3)	11 (64.7)		0 (0)	2 (100)	
Kidney function															
Normal/High	6 (12.2)	43 (87.8)	0.051	3 (16.7)	15 (83.3)	0.802	0 (0)	28 (100)	0.061	3 (30)	7 (70)	0.686	1 (50)	1 (50)	1
Mildly decreased	6 (21.4)	22 (78.6)		4 (19)	17 (81)		0 (0)	14 (100)		4 (33.3)	8 (66.7)		1 (33.3)	2 (66.7)	
Mildly to moderately	0 (0)	8 (100)		2 (25)	6 (75)		0 (0)	4 (100)		3 (50)	3 (50)		2 (66.7)	1 (33.3)	
Moderately to severely decreased	2 (50)	2 (50)		0 (0)	2 (100)		0 (0)	1 (100)		0 (0)	1 (100)		0 (0)	1 (100)	
Severely decreased	0 (0)	2 (100)		0 (0)	3 (100)		0 (0)	1 (100)		1 (100)	0 (0)		0 (0)	1 (100)	
Kidney failure	2 (66.7)	1 (33.3)		1 (50)	1 (50)		1 (100)	0 (0)					0 (0)	1 (100)	
CST requested															
Yes	8 (15.7)	43 (84.3)	0.793	4 (12.9)	27 (87.1)	0.5	1 (6.3)	15 (93.8)	0.281	5 (31.3)	11 (68.8)	1	2 (28.6)	5 (71.4)	1
No	8 (13.8)	50 (86.2)		6 (20.7)	23 (79.3)		0 (0)	41 (100)		6 (35.3)	11 (64.7)		2 (33.3)	4 (66.7)	

4.5.2 Relationship between outcomes of therapy and the sociodemographic and clinical characteristics of the study population

There was a statistically significant association (p=0.019) between co-morbidity and mortality (11, 17.5%) and discharge (52, 82.5%). There was also a statistically significant association (p=0.004) between intubation and death (20, 14.5%) and discharge (118, 85.5%) (Table 12).

Table 12: Relationship between outcomes of therapy versus the sociodemographic and clinical characteristics of the study population

Characteristic		Death (n=22)	Discharge (n=198)	p-value
Age	≤10	2 (8.3)	22 (91.7)	0.992
	11-20	3 (8.8)	31 (91.2)	
	21-30	7 (12.5)	49 (87.5)	
	31-40	4 (10.3)	35 (89.7)	
	41-50	3 (7.9)	35 (92.1)	
	51-60	3 (10.3)	26 (89.7)	
Sex	Male	15 (11.6)	114 (88.4)	0.338
	Female	7 (7.7)	84 (92.3)	
CCU type	Cardiology	0 (0)	32 (100)	0.064
	Main	17 (10.9)	139 (89.1)	
	Medical	5 (15.6)	27 (84.4)	
Comorbidity	Yes	11 (17.5)	52 (82.5)	**0.019**
	No	11 (7.0)	146 (93.0)	
Risk Category	1	13 (13.1)	86 (86.9)	0.269
	2	8 (7.1)	104 (92.9)	
	3	1 (11.1)	8 (88.9)	
Patient's Diagnosis type	Surgical	13 (8.3)	143 (91.7)	0.198
	Medical	9 (14.1)	55 (85.9)	
Catheterization	Yes	22 (11.2)	174 (88.8)	0.142
	No	0 (0)	24 (100)	
Intubation	Yes	20 (14.5)	118 (85.5)	**0.004**
	No	2 (2.4)	80 (97.6)	
		Median (IQR)	**Median (IQR)**	
Length of stay (days)*		8.0 (3.0 – 15.0)	7.0 (4.0 – 13.0)	0.559

*p-Value was calculated using the median test IQR; IQR = interquartile range.

4.5.3 Bivariate and multivariate logistic regression analysis

To understand the influence of the predictor variables on the outcome (mortality), binary logistic regression was done. The odds ratio from univariate analysis and adjusted odds ratio from multivariate analysis are shown in Table 13.

Table 13: Bivariate and multivariate logistic regression analysis for correlates of outcomes of therapy

Variable		COR (95% CI)	p-value	AOR	p-value
Age	≤10	Reference		Reference	
	11-20	1.1 (0.2 – 6.9)	0.948	1.1 (0.1 – 8.7)	0.903
	21-30	1.6 (0.3 – 8.2)	0.591	1.0 (0.2 – 6.5)	0.966
	31-40	1.3 (0.2 – 7.4)	0.801	0.7 (0.1 – 5.2)	0.716
	41-50	0.9 (0.1 – 6.1)	0.951	0.8 (0.1 – 6.8)	0.813
	51-60	1.3 (0.2 – 8.3)	0.803	1.4 (0.2 – 12.5)	0.755
Sex	Male	1.6 (0.6 – 4.0)	0.341	1.5 (0.5 – 5.0)	0.481
	Female	Reference			
ICU type	Cardiology	-		-	
	Main	0.7 (0.2 – 1.9)	0.451	1.5 (0.3 – 8.0)	0.636
	Medical	Reference		Reference	
Comorbidity	Yes	2.8 (1.1 – 6.9)	**0.024**	2.1 (0.7 – 6.3)	0.204
	No	Reference		Reference	
Risk Category	1	Reference		Reference	
	2	0.5 (0.2 – 1.3)	0.153	0.5 (0.2 – 1.9)	0.345
	3	0.8 (0.1 – 7.2)	0.863	2.0 (0.1 – 40.5)	0.654
Patient's Diagnosis type	Surgical	0.6 (0.2 – 1.4)	0.203	0.6 (0.1 – 2.5)	0.442
	Medical	Reference		Reference	
Catheterization*	Yes	-		-	
	No	Reference		Reference	
Intubation	Yes	6.8 (1.5 – 19.8)	**0.011**	5.5 (1.1 – 28.1)	**0.042**
	No	Reference			
Length of stay (days)*		1.0 (0.9 – 1.1)	0.566	1.0 (0.9 – 1.2)	0.913
Antibiotic		0.9 (0.4 – 2.3)	0.928	0.4 (0.1 – 1.1)	0.071
Ceftriaxone		1.7 (0.7 – 4.1)	0.265	1.2 (0.4 – 3.4)	0.785
Metronidazole		0.2 (0.1 – 1.1)	0.061	0.2 (0.1 – 1.2)	0.051
Cefuroxime		0.5 (0.1 – 2.2)	0.341	0.5 (0.1 – 2.5)	0.366
Co-Amoxiclav		2.1 (0.6 – 6.8)	0.221	1.1 (0.2 – 4.8)	0.920
Meropenem					

Key: *Calculations for length of stay are relative to the median interquartile range; COR = crude odds ratio; AOR = adjusted odds ratio.

The odds of dying among those that had comorbidities was 2.8 times the odds of those that did not have a comorbidity, and this was statistically significant (p=0.024). The relationship between comorbidity and mortality was positive (AOR: 2.1 (CI: 0.7-6.3)) but not statistically significant (p=0.204).

The odds of dying for patients with intubation was 6.8 times the odds of those that were not intubated (p=0.011). There was a strong positive relationship between intubation and mortality (AOR: 5.5 (CI: 1.1-28.1)) and this was significant (p=0.042).

CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Discussion

A total of 220 medical records of patients admitted to the KNH ICUs from February 2018 to February 2020 formed the study population whose mean age was 31.2±15.7 years with a male preponderance. These findings tally with those of a study done in Malawi where there was a relatively younger population being admitted to the ICU (63). This was however contrasted among the studies done in the USA, Europe, Turkey, Iran and India where the patients admitted to the ICU were much older than in the current study (64–66). This could probably be attributed to the fact that most of the population in African countries is comprised mostly of a young population who may engage in dangerous activities that may likely need critical care services.

The mean length of hospital stay was 11.5±13.8 days that tallied with a study on antimicrobial utilization in an ICU of a tertiary hospital in India where the average length of stay for almost half the patients was 11-15 days (64). This was a sharp contrast to many studies done in the ICU where the mean length of stay ranged from 2-7 days (65,66). This is because in these ICUs, the major reason for patient admission was medical conditions like cardiovascular diseases, respiratory infections and febrile illnesses while in our study most patients were admitted pending surgeries or post-surgical procedures.

The commonest comorbidity was hypertension (27, 42.9%), followed by trauma (21, 33.3%) and diabetes (13, 20.6%). This finding was similar to a study done in India where the commonest comorbidity in patients on antimicrobial agents was hypertension followed by diabetes (65).

Culture and sensitivity tests were requested and done in only less than half of the study population. Among those that received antibiotics empirically, only half of them had CST done. About a third had CSTs done more than three days post admission, most likely after antibiotics had already been initiated. These findings are similar to those of a study done in an ICU set up in South Africa where not all the patients on antibiotic therapy had CST done and that more than half (56.3%) of the tests were done after patients had already started receiving antibiotics (68). Most clinicians prescribe empirical therapy based on their clinical judgement and professional experience, while some put into consideration the

epidemiology of the infection rather than the approved guidelines based on antibiograms (67). Other considerations include drug availability and cost. This is contrary to the antibiotic stewardship principles that require careful interpretation of antibiograms to give a guide in decisions on proper selection of an antimicrobial agent and de-escalation of therapy from broad-spectrum antibiotics to those of a narrow spectrum. The low number of CSTs done in the current study could be attributed to challenges with regards to cost and availability of reagents required to conduct the tests.

The largest proportion of antibiotic use was for surgical prophylaxis as compared to empirical use. Most of the patients who had been admitted to the ICU were being monitored post major surgeries as a result of trauma and major accidents and therefore probably required prophylaxis against infections.

Cephalosporins were the most commonly used antibiotic class (49.6%), followed by 5-nitroimidazoles (18.2%) and penicillins (14.2%). These findings concurred with those of the global antibiotic consumption in 2010, where about 60% of the total antibiotic consumption was accounted for by the cephalosporins and penicillins (1). In contrast, a previous study of antimicrobial use in Kenya over a five-year period (1997-2001) indicated that penicillins were among the most widely used class of antibiotics (4). The frequent use of cephalosporins in the present study can most probably be attributed to their broader spectrum of activity and wider availability in most Kenyan hospitals.

Overall, ceftriaxone was the most frequently prescribed antibiotic followed by metronidazole and cefuroxime. This also concurred with the findings of antimicrobial utilization in an ICU in South India where the most commonly prescribed antibiotics were ceftriaxone (22.7%) and metronidazole (12%) (65). This was similar to a study done in an ICU set up of a tertiary hospital in Malawi where the most frequently prescribed antibiotics were ceftriaxone (73.4%) and metronidazole (55.3%) although they had much higher proportions. This is because ceftriaxone is recommended as the first initial course of treatment in Malawi standard treatment guidelines before blood culture is done (63). However, these findings were contrary to those of a study done in ICU set ups in Southern Europe, Turkey and Iran where the most frequently prescribed antibiotics were carbapenems (30.2%), followed by anti-gram-positive agents (vancomycin, teicoplanin,

linezolid, daptomycin, and tigecycline (25.9%), and the fourth generation cephalosporins (23.9%) (68). The variations could be explained by the differences in geographical location, disease patterns, existing national antibiotic-use guidelines and probably an increased incidence of drug resistant organisms that require higher classes of antibiotics. The high use of metronidazole in the current study could be attributed to its availability and cheap cost in covering for the anaerobic organisms in comparison to agents like clindamycin, meropenem or even piperacillin/tazobactam.

It was noted that clinicians use broad-spectrum antibiotics like meropenem (5.9%), ceftazidime (3.6%), vancomycin and linezolid (1.3 %). This observation was also similar for USA where a study found that there was an increasing trend in the use of broad-spectrum antibiotics like meropenem, ceftazidime and vancomycin and this was greatly so in the CCU setting (29). This finding could be a reflection of an increasing concern about infections caused by antibiotic-resistant gram-negative bacteria and the emergence of methicillin-resistant *Staphylococcus aureus*, a common cause of community acquired skin and soft tissue infections.

Quality indicators of antibiotic prescribing include documentation of the reason an antibiotic was prescribed in the patient's clinical notes, compliance to recommended guidelines and switching from parenteral route as soon as the patient improves (69). Although more than three quarters of the patients had antibiotic therapy changes made, no reasons were indicated in their clinical notes. Less than a quarter had reasons indicated where some of the reasons noted were CST results, increased WBC count, and patient developing diarrhea. This differed quite measurably where reasons for antibiotic prescriptions were documented in three quarters of the patient medical records in a point prevalence survey carried out in 25 European countries; interestingly the documentation was more in the critical care settings (69). In this study, lack of reason documentation could be because most of the antibiotics were given for surgical prophylaxis.

In this study, five main indicators were used to evaluate rational prescribing of antibiotics. These were correct choice of antibiotic depending on the diagnosis, appropriate dose, right frequency, correct duration and correct route of administration. The five indicators were assessed in accordance to the KNH antibiotic use guidelines for empiric therapy and

surgical prophylaxis. An antibiotic was termed as rational if it met all the five main indicators and irrational if it missed even one out of the five indicators.

For all the antibiotic encounters, 51% were found to be incorrect choices, 14.4% had incorrect doses prescribed, 32.3% had incorrect frequencies while 0.3% had an incorrect route of administration. Incorrect duration of antibiotic therapy was majorly attributed to prolonged duration of use of antibiotics for surgical prophylaxis, this is because most were prescribed for durations longer than what was recommended. This finding was similar to that of a study done in an ICU in USA, where about 35% of cefazolin prescribed for the peri-operative prophylaxis was used longer than the recommended maximum duration by the institutional guidelines (66). Furthermore, WHO estimates that more than half of all the medicines that are prescribed, dispensed or even sold are used inappropriately(6). In addition, it has been estimated that about a third of antibiotic use in Africa is irrational (8). The findings of irrational use of antibiotics in the current study was in contrast to the findings of a study of appropriate antimicrobial use in a Dutch hospital where incorrect antibiotic choice was at 8.1%, incorrect dose at 2.6%, incorrect duration at 3.3% and incorrect route of administration at 2.0% (70). The contrast could be explained by the fact that Netherlands being a high-income country, there are effective interventions in the cited Dutch hospital that have been put in place by antimicrobial stewardship aimed at improving antimicrobial use.

Cephalosporins were significantly associated with patients who had a surgical type of diagnosis while carbapenems were significantly used for patients who had a medical type of diagnosis. This is because ceftriaxone, cefazolin and cefuroxime were prescribed for surgical prophylaxis while carbapenems were used for empiric therapy in the medical ICU.

The overall prevalence of irrational use of antibiotics was 81.5%s comparable to a study by Ali et al. that found 86% irrational prescribing of antibiotics in an ICU in Pakistan (22). The high proportion of irrational prescribing could be due to poor compliance to the recommended duration of surgical prophylaxis and poor choice of antibiotic since most of the antibiotic use in the ICUs was for surgical prophylaxis.

Rational use of ceftriaxone was significantly associated with the type of diagnosis ($p=0.012$). There was a high proportion of irrational use for surgical diagnosis. This could

be because ceftriaxone was prescribed for duration longer than what is recommended for surgical prophylaxis. There was 100% rational use of tetracyclines and tuberculosis fixed drug combinations, this was attributed to established guidelines in the use of these antibiotics.

The KNH antibiotic use guidelines recommend risk stratification of patients into different categories for the use of empirical antibiotics. The parameters used in the stratification include hospitalization in the last 90 days, use of antibiotics in the past 90 days, and co-morbidities. Rational use of amoxicillin-clavulanic acid was significantly associated with patient's risk category. Patients in risk category 2 had a higher proportion of irrational use of amoxicillin-clavulanic acid. This could be because patients from category 2 have had a recent antibiotic exposure, or recent hospital admission that may pose a challenge when it comes to proper selection of antibiotics to use if guidelines are not available.

The present study did not find any significant relationship between rational use of antibiotics and mortality unlike a similar study done in Pakistan (22).

Significant proportions of patients with comorbidity (p=0.019) and intubation (p=0.004) died. Multivariate analysis showed that the most important correlate for death was intubation, with patients who were intubated being almost six times more likely to die than those who were not (AOR 5.5, 95% CI=1.1-28.1, p=0.042). This could be because the patient's infections worsened necessitating intubation and while in the process they succumbed. Intubation is also associated with increased risk of development of stress ulcers and bleeding. Mortality has been found to be higher in patients with cardiovascular comorbid conditions like hypertension, heart failure and coronary artery disease (71).

5.2 Study limitations

There were challenges in getting all the medical records for all the participants that had met the eligibility criteria (n=230). As a result, we only managed to attain a 95.7% (n=220) response rate. Patients that had multiple diagnoses as is common in the ICU posed a challenge during the assessment of rational use of antibiotics and how the antibiotics complied with the KNH antibiotic guidelines. For a patient who had two diagnoses that would use the same antibiotic in treatment, the PI made assumptions as to which diagnosis was being treated.

5.3 Summary

5.3.1 Key findings

Judicious use of antibiotics in the ICU still poses a big challenge and this has led a high prevalence of irrational use at 81.5%. This was contributed to majorly by incorrect choice and incorrect duration of antibiotics when assessed in accordance to the KNH antibiotic use guidelines. Most of the antibiotics given for surgical prophylaxis were incorrect choices and were given for longer than the recommended durations.

Antibiotics prescriptions were done without any documented reasons in the patient's clinical notes. An antibiotic would be stopped and another one prescribed without clear reasons. Cephalosporins, 5-nitroimidazoles and penicillins were the most commonly prescribed antibiotics. Widespread use of broader spectrum antibiotics like carbapenems, the third and fourth generation cephalosporins and glycopeptides was also noted.

Intubation was found to be an important correlate for outcome of therapy among patients on antibiotics and this was statistically significant.

5.3.2 Implications of the findings

Irrational use of antibiotics has been implicated in the rise of antimicrobial resistance. Therefore, there will be increased reliance on higher classes of antibiotics with higher cost implications as can already be noted in our study.

5.4 Conclusions

The prevalence of rational antibiotic use in the ICU is 18.5% while that of irrational use is 81.5%. The high proportion of irrational use was contributed by incorrect choice and incorrect duration of surgical prophylaxis.

Cephalosporins, 5-nitroimidazoles and penicillins were the most frequently prescribed classes of antibiotics. Ceftriaxone was the most prescribed antibiotic and surgical prophylaxis was the most common use of antibiotics in the ICU.

Intubation was an important correlate for outcome of therapy. This is a common cause of hospital-acquired infection when the procedures of insertion are not done aseptically.

5.5 Recommendations

5.5.1 Recommendations on Policy and Practice

There is a need to improve the rationality in the use of antibiotics at KNH ICUs. This could be done by increasing and strengthening antimicrobial stewardship on potential targets like surgical prophylaxis, choice of antibiotics and duration of treatment with antibiotics.

Prescribers should be encouraged to document the reasons for which they make changes in antibiotic therapy. This has been shown to improve rational use of antibiotics.

Although this was not a prime focus of our study, compliance to the KNH antibiotic use guidelines was low. The hospital antimicrobial stewardship committee could probably conduct a training among the prescribers on the available guidelines or do a study to find out the reasons for the low compliance to the guidelines.

5.5.2 Recommendations on Future Areas of Research

A study on antibiotic use with regards to the choice, duration and dosage in the surgical departments at the KNH hospital as they were found to be the major contributors of irrational use of antibiotics. Most of the antibiotics that were prescribed for surgical prophylaxis were incorrect choices and were given for durations longer than what was recommended.

A study on determinants of antibiotic prescribing among clinicians in the ICU to give a better understanding on the factors that guide antibiotic prescribing.

Additional studies on antibiotic use focusing on rational use, factors that are associated with rational use across the different ICUs in the country to better understand what the situation really is.

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Appendices

Appendix I: Data collection tool for antibiotic use at the critical care units of Kenyatta National Hospital

SECTION I: Patient Demographic Data

1. Patient unique identifier ID:_____ 2. CCU: _____

3. Gender: Male ☐ Female ☐ 4. Age in years _____

5. Weight in kilograms _____

6. Admission date: dd/mm/yy_____ 7. Discharge/death date: dd/mm/yy_____

SECTION II: Risk Factor Information

8. Has the patient been hospitalized in the last 90 days? Yes ☐ No ☐

9. Has the patient been on antibiotics in the past 90 days? Yes ☐ No ☐

10. Was the patient admitted directly to the CCU? Yes ☐ No ☐

11. If No to question 10, where was the patient admitted from?

Other wards in KNH ☐ Transfer in from another health facility ☐

12. What is the patient's diagnosis?

Bloodstream infection ☐ Intra-abdominal infection ☐ Urinary tract infection ☐

Skin and soft tissue infection ☐ Pneumonia ☐ Others specify_____

13. Does the patient have any comorbidity? Yes ☐ No ☐

14. If yes to question 13, which comorbidity? (Tick appropriately)

Hypertension ☐ Cancer ☐ Diabetes ☐ Kidney disease ☐ Liver disease
Myocardial infarction/Angina/stroke ☐ HIV ☐ Trauma ☐

Others specify _____

15. Is the patient on any form of catheterization? Yes ☐ No ☐

16. If Yes to question 15, which of the following catheterization?

Urinary ☐ Central line ☐ Haemodialysis ☐ Peripheral ☐ Peritoneal ☐

17. Does the patient have any intubation? Yes ☐ No ☐

18. If Yes to question 17, which one?

Endotracheal ☐ Tracheostomy ☐ Nasogastric/Feeding ☐ Gastroduodenal ☐

19. What is the patients risk category as per the details below? 1 ☐ 2 ☐ 3 ☐ 4 ☐

Category 1	No contact with healthcare system in the last 90 days, no prior antibiotic treatment in the last 90 days, patient young with no co-morbidities and no organ failure.
Category 2	Patient with recent hospital admission, invasive procedure and/or recent exposure to antibiotic

Category 3	Patient who has had long hospitalization with invasive procedure, recent and multiple antibiotic therapies or severe neutropenia
Category 4	Patient unresponsive to antibacterial agents

SECTION III: Monitoring parameters

Date (dd/mm/yy)	Serum Creatinine(umol/L)	WBC count before antibiotic	WBC count after antibiotic	Fever before antibiotic	Fever after antibiotic

SECTION IV: Information on Patient Management

20. Was the patient initiated on antibiotic agent on admission? Yes ☐ No ☐

21. If Yes to question 20, which agent?

Date of Antibiotic initiation (dd/mm/yy)	Name of Antibiotic	Dose strength (mg)	Duration	Frequency OD,BD,TDS,QID	Route P,R,O, IV

22. Is the treatment empirical or targeted? _____

23. If empirical, does it comply with the KNH Antibiotic policy guideline? Yes ☐ No ☐

SECTION IV: Antibiotic use management

24. Has Culture and Susceptibility test been requested? Yes ☐ No ☐

25. On which day of admission was the 1st CST requested? _____

26. After how many days was the report for CST received in the CCU? _____

27. Was any micro-organism isolated? Yes ☐ No ☐

28. If Yes to 27, which micro-organism? _____

29. If Yes to 28, what was the susceptibility pattern of the micro-organism isolated?

Collected Specimen type	Antibiotic Resistant	Antibiotic Susceptible

29. If CST was available did it inform antibiotic choice? Yes ☐ No ☐

30. Is there a stop/review for antibiotic therapy? Yes ☐ No ☐

31. Is there any change in antibiotic therapy? Yes ☐ No ☐

32. What is the reason for change of antibiotic therapy?

CST report ☐ Fever ☐ Increased WBC count ☐ Worsening patient condition ☐

Poor renal function ☐ Initial inappropriate antibiotic agent ☐ No reason ☐

Others specify _____

33. What type of antibiotic therapy change was made?

Dose escalation ☐ Dose de-escalation ☐ Antibiotic stop ☐ Change of frequency ☐

New antibiotic prescribed ☐ Others (Specify) _____

34. What is the new antibiotic prescribed?

Antibiotic	Dose strength (mg)	Duration	Frequency OD,BD,TDS,QID	Route P,R,O, IV

35.Apart from the antibiotics given at admission, are there any other antibiotics used by the patients during their hospital stay? YES ☐ NO ☐

36. If yes to question 35, please list them below.

Date of Antibiotic initiation (dd/mm/yy)	Name of Antibiotic	Dose strength (mg)	Duration	Frequency OD,BD,TDS,QID	Route P,R,O, IV

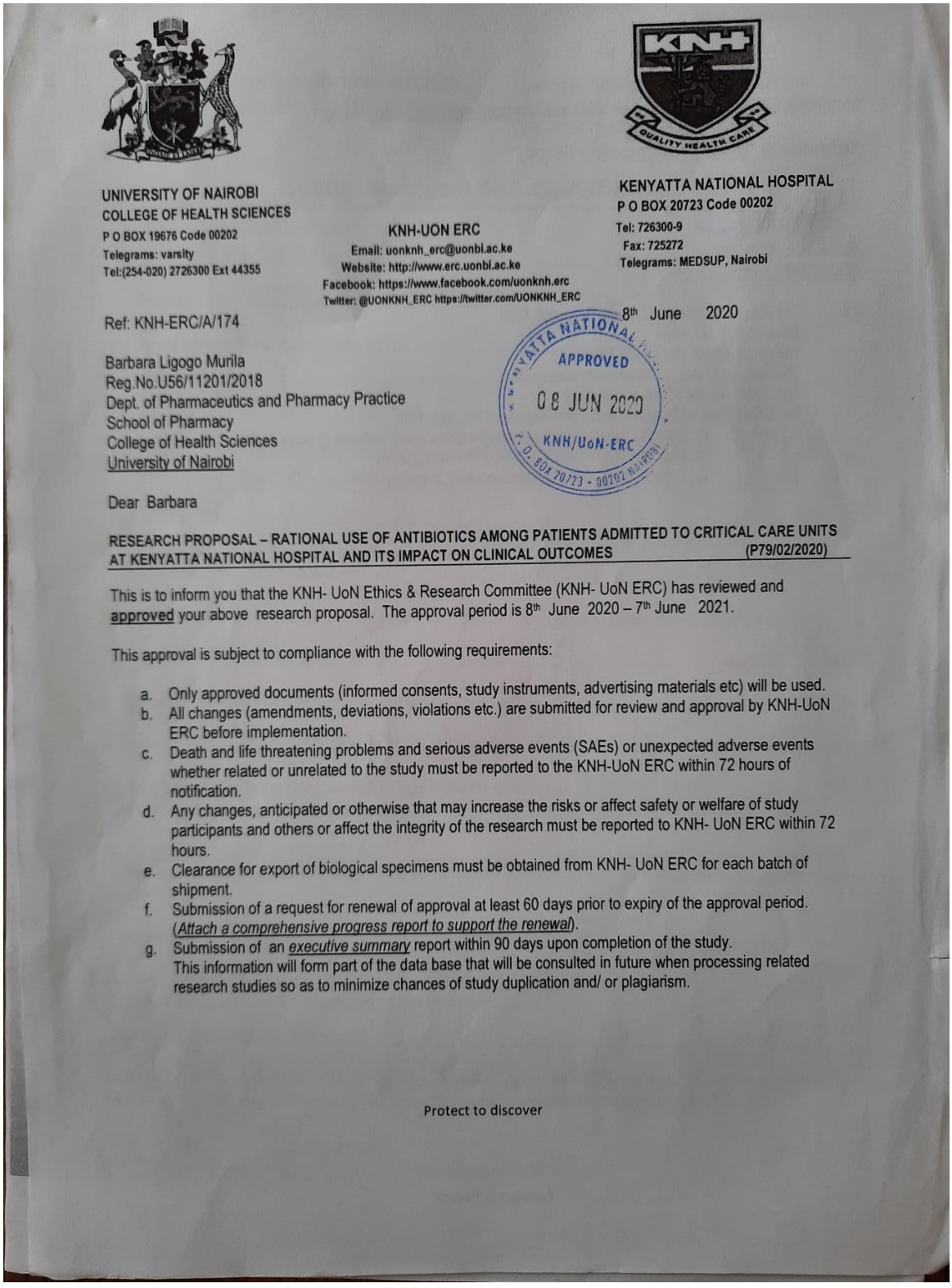
37. For the antibiotics used above kindly fill as appropriate

Antibiotic	Indication	Correct drug choice as per guideline	Correct duration of therapy	Appropriate dose prescribed	Dosage interval correct	Route and mode of administration correct

Key

- Indication 1. Prophylactic 2. Empiric 3. Definitive 4. Don't know
- Correct drug choice 1. Yes 2. No 3. Unknown
- Correct duration of therapy 1. Yes 2. No 3. Unknown
- Appropriate dose prescribed 1. Yes 2. Under-dose 3. Over-dose
- Dosage interval correct 1. Yes 2. No
- Route and mode of administration correct 1. Yes 2. No

Appendix II: Ethical Approval



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Facebook: https://www.facebook.com/uonknh.erc
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KENYATTA NATIONAL HOSPITAL
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Tel: 726300-9
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Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/174

8th June 2020

KENYATTA NATIONAL HOSPITAL
APPROVED
08 JUN 2020
KNH/UoN-ERC
P. O. BOX 20723 - 00202 NAIROBI

Barbara Ligogo Murila
Reg.No.U56/11201/2018
Dept. of Pharmaceutics and Pharmacy Practice
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Barbara

RESEARCH PROPOSAL – RATIONAL USE OF ANTIBIOTICS AMONG PATIENTS ADMITTED TO CRITICAL CARE UNITS AT KENYATTA NATIONAL HOSPITAL AND ITS IMPACT ON CLINICAL OUTCOMES (P79/02/2020)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and approved your above research proposal. The approval period is 8th June 2020 – 7th June 2021.

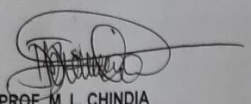
This approval is subject to compliance with the following requirements:

a. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
g. Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

Protect to discover

For more details consult the KNH- UoN ERC website**http://www.erc.uonbi.ac.ke**

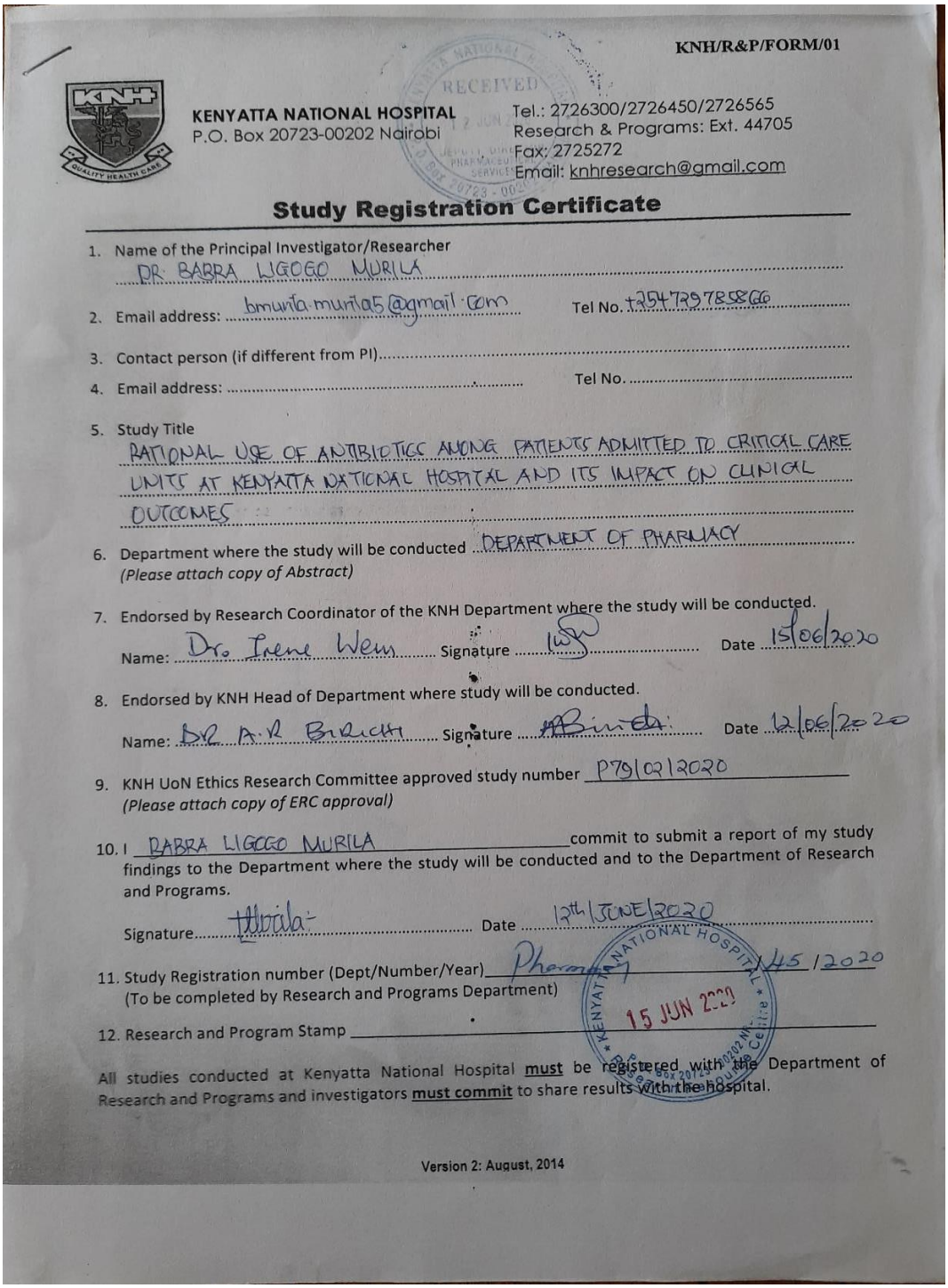
Yours sincerely,



PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
The Dean, School of Pharmacy, UoN
The Chair, Dept. of Pharmaceutics and Pharmacy Practice, UoN
Supervisors: Dr. David G. Nyamu, Dept.of Pharmaceutics and Pharmacy Practice,UoN
Dr. Rosaline N. Kinuthia, Division of Pharmacy, KNH
Dr. Peter Njogu, Dept.of Pharmaceutical Chemistry, UON

Appendix III: Institutional Approval



KNH/R&P/FORM/01

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Research & Programs: Ext. 44705
Fax; 2725272
Email: knhresearch@gmail.com

RECEIVED
12 JUN 2020

Study Registration Certificate

1. Name of the Principal Investigator/Researcher
   DR. BARRA LIGOGO MURILA
2. Email address: bmurila.murila5@gmail.com Tel No. +254729785866
3. Contact person (if different from PI)
4. Email address: Tel No.
5. Study Title
   RATIONAL USE OF ANTIBIOTICS AMONG PATIENTS ADMITTED TO CRITICAL CARE UNITS AT KENYATTA NATIONAL HOSPITAL AND ITS IMPACT ON CLINICAL OUTCOMES
6. Department where the study will be conducted DEPARTMENT OF PHARMACY
   (Please attach copy of Abstract)
7. Endorsed by Research Coordinator of the KNH Department where the study will be conducted.
   Name: Dr. Irene Wem Signature Date 15/06/2020
8. Endorsed by KNH Head of Department where study will be conducted.
   Name: DR A.R BIRICH Signature Date 12/06/2020
9. KNH UoN Ethics Research Committee approved study number P79/02/2020
   (Please attach copy of ERC approval)
10. I BARRA LIGOGO MURILA commit to submit a report of my study findings to the Department where the study will be conducted and to the Department of Research and Programs.
    Signature Date 12th JUNE 2020
11. Study Registration number (Dept/Number/Year) Pharmacy /45 /2020
    (To be completed by Research and Programs Department)
12. Research and Program Stamp

KENYATTA NATIONAL HOSPITAL
15 JUN 2020
P.O. Box 20723-00202 Nairobi

All studies conducted at Kenyatta National Hospital **must** be registered with the Department of Research and Programs and investigators **must commit** to share results with the hospital.

Version 2: August, 2014

Appendix IV: Plagiarism Report

RATIONAL USE OF ANTIBIOTICS AMONG PATIENTS ADMITTED TO CRITICAL CARE UNITS AT KENYATTA NATIONAL HOSPITAL AND ITS IMPACT ON CLINICAL OUTCOMES

ORIGINALITY REPORT

11%	9%	5%	2%
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3	qims.amegroups.com Internet Source	<1%
4	bmcgeriatr.biomedcentral.com Internet Source	<1%