Antimicrobial prescribing patterns in critical care and compliance to guideline at the Kenyatta National Hospital.

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A thesis submitted in partial fulfillment for the degree of Master of Pharmacy in Pharmacoepidemiology and Pharmacovigilance in the department of Pharmacology and Pharmacognosy in the University of Nairobi

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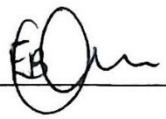
Signature 

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DEDICATION

To my son Shawn and daughter Megan, thank you for your love, patience and unwavering support during this journey of faith.

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LIST OF ABBREVIATIONS

AM	Antimicrobial
AMR	Antimicrobial Resistance
AMS	Antimicrobial Stewardship
BSI	Blood Steam Infection
CCU	Critical Care Unit
CR	Carbapenem-Resistant
CST	Culture and Susceptibility Test
EPIC	European Prevalence of Infection in Intensive Care
ESAC	European Surveillance of Antimicrobial Consumption
HAI	Hospital Acquired Infection
ICU	Intensive Care Unit
INN	International Nonproprietary Name
KNH	Kenyatta National Hospital
PPS	Point Prevalence Survey
RVPH	Rift Valley Provincial Hospital
VAP	Ventilator-Associated Pneumonia

DEFINITIONS OF OPERATIONAL TERMS

Empiric therapy: Initial antimicrobial therapy/treatment guided by clinical presentation before the specific micro-organism causing the infection is known.

Antimicrobial agent: a chemical substance that kills or stops the growth of micro-organisms such as bacteria, fungi, viruses, and parasites. This term is frequently used interchangeably with antibiotic agent

Antimicrobial resistance: A property of some micro-organisms which make a number of antimicrobial agents not effective when used to treat infections. Resistance may either be intrinsic or may be acquired by exposure to the antimicrobials.

Targeted treatment: Once microbiology has identified the pathogen causing the infection and the antimicrobial susceptibility profile, treatment is narrowed down to the antimicrobial spectrum.

Guideline compliance: Adherence to the Critical Care Unit guideline for antimicrobial therapy on the choice of antimicrobial agent, dose, frequency, duration and route of administration.

Nosocomial infection: An infection acquired in the hospital.

ABSTRACT

Background: Antimicrobial resistance (AMR) is a serious and growing threat to global health today. Critically ill patients have a high risk of developing life-threatening infections. Hence, antimicrobial agents are the most commonly prescribed medicines for these patients. The extensive and indiscriminate use of antimicrobial agents in the Critical Care Unit (CCU) is a major contributor to the development of resistant pathogens.

Study Objective:

To determine the patterns of antimicrobial prescribing among the patients admitted to the CCU and the level of compliance to the Kenyatta National Hospital Guide to Antimicrobial Therapy in the Critical Care Unit.

Methods:

A retrospective longitudinal study was conducted at the selected CCUs of Kenyatta National Hospital (KNH). The study involved the extraction of data from medical records of patients aged 13 years and above admitted to the CCUs from January to December 2017. Data were abstracted from patient medical records, treatment sheets and laboratory culture and sensitivity reports using a pre-designed standardized data collection tool. The two primary outcomes of interest were the degree of compliance to KNH-CCU guidelines in terms of the choice of antimicrobial agent prescribed and the level of antimicrobial switch informed by culture and susceptibility results. All data were subjected to descriptive statistical analysis and reported as proportions and percentages (%). The association between predictor variables and outcome variables was determined using the Chi-square test. Logistic regression was undertaken to measure the relationship between the outcome variable compliance to the KNH guideline and several predictor variables such as patients' age, sex, and diagnosis. The level of significance was set at 0.05.

Results:

The total number of patients included in this study was 309. The median age was 37 years [IQR 13, 83]. There were more males (n=158, 51.1%) than females (n=151, 48.9%). The mean length of CCU stay was 7.3 days [IQR=1-37]. At least one co-morbidity was reported in 74.1% of the patients with hypertension (35.3%), diabetes (20.7%) and kidney disease (20.1%) being the top three. Most patients (70.2%, n=217) were admitted to the CCU from other wards in KNH, while 29.8% (n=92) of the patients entered the CCU directly from the community or through referral from another health care facility.

The prevalence of antimicrobial prescribing at admission to KNH was 98.4%. The compliance of empiric treatment to the guideline was observed in 25% of the patients. The antimicrobial agents commonly prescribed were Ceftriaxone (36.8%), Metronidazole (16.9%) and Meropenem (12.4%). About 108 (35%) participants were on a single antimicrobial agent while 111 (36%), 60(19.4%), and 25(8.1%) were on two, three and four antimicrobials respectively during the hospital stay. Less than 2% (n=5) of the patients had more than five antimicrobial agents. The proportion of patients who had a review or stoppage of antimicrobial therapy documented in their medical records was 11.7% (n=36). The indication for an antimicrobial prescription was documented on in 16.5% of patients. The International Non-Proprietary Name (INN) was used in 66.7% of the 651 prescription encounters in this study. Metronidazole (85%) and amoxicillin clavulanic acid (98%) were the antimicrobial agents that were most prescribed using brand names.

A total of 158 (51.1%) patients admitted to the CCU had a request for Culture and Sensitivity Testing (CST) made and the positivity rate was 42.7%. The most commonly isolated microorganisms were *Klebsiella pneumonia* (23.9 %), *Acinetobacter baumanii* (16.4%) and

Escherichia coli (10.5%). 11(67%) *K. pneumonia* isolates were sensitive to meropenem. In 106 (67%) patients, the choice of the antimicrobial agent prescribed was informed by the CST result.

Compliance of targeted treatment to the guideline was observed in 41.6% of the patients. None of the organisms isolated were sensitive to ceftriaxone, the antimicrobial agent prescribed the most. The isolated organisms were noted to have the highest sensitivity to Amikacin followed by Meropenem and Ciprofloxacin.

Conclusion and recommendations:

The prevalence of antimicrobial prescribing in the KNH CCU was high which is consistent with findings across many CCUs. Ceftriaxone was the most common antimicrobial agent prescribed despite most micro-organisms isolated showing resistance. Compliance with the antimicrobial guideline was suboptimal. Therefore, there is a need to strengthen the stewardship programs to improve antimicrobial prescribing in KNH.

CHAPTER ONE: INTRODUCTION

1.1 Background

An antimicrobial agent is a type of medicine that stops the growth or kills microbes such as bacteria, fungi, viruses, and parasites. Antibiotics are the most commonly used antimicrobial agents. Inappropriate use of these medicines is a growing concern in the healthcare setting (1,2).

Thirty to fifty percent of antimicrobial agents prescribed in hospitals are either unnecessary or inappropriate (3). These may include the use of an antimicrobial agent when there is no indication; consumption of a broad-spectrum antimicrobial agent when a narrow-spectrum agent would have been equally effective, and for a prolonged duration of use and at inappropriate doses (4).

The irrational and unnecessary use of antimicrobial agents is a major driver for the development of resistant pathogens (3). The consequence of antimicrobial resistance (AMR) include poor clinical outcomes and increased health care costs to the patient (5). In addition, patients that are exposed to antimicrobial agents unnecessarily are at higher risk of adverse effects, toxicity, and AMR (6). The potential for spread of resistant organisms means that the misuse of antimicrobial agents can adversely affect the health of patients who are not even exposed to them (7) a risk that is absent in other medicines.

For proper clinical management, diagnosis must precede appropriate treatment. Availability and adherence to guideline has been shown to improve clinical outcomes in patients such as mortality, treatment duration and length of hospital stay (8). Compliance to guideline was reported as 67.9% for Africa, 73% for Asia and 80% for Europe in a study conducted in 53 countries worldwide (8).

Poor compliance has been reported to contribute to factors responsible for AMR (9). A meta-analysis reported a 35% relative risk reduction for mortality when guidelines are adhered to during

empiric antimicrobial prescribing. Advocating and promoting the appropriate use of antimicrobial agents through Antimicrobial Stewardship (AMS) is pivotal in curbing antimicrobial resistance (1).

AMS employs quality improvement and patient safety programs to contain the irrational use of antimicrobial agents with the overall objective of maximizing patient outcomes while minimizing adverse events (10). AMS focuses on improved prescribing patterns which can lead to high quality of patient care. It may also reduce treatment failure translating to an improvement in patient outcomes (4).

Critically ill patients have a high risk of developing life-threatening infections (11) because of a number of factors that make them vulnerable to hospital-acquired infections. These include the need for mechanical ventilation because of the severity of illness at the time of admission into Critical Care Unit (CCU), immuno-suppression and major surgery such as kidney transplant (12,13). Hence, a majority of CCU patients will receive an antimicrobial agent. The adequate and timely initiation of antimicrobial therapy in the CCU is instrumental to the survival of the patients and curbing AMR (3). To date, there are no published data on the patterns of antimicrobial use in the CCU of Kenyatta National Hospital (KNH). Therefore, this study seeks to obtain information that will enhance the rational use of antimicrobial agents at KNH.

1.2 Statement of the problem.

The critical care unit admits severely ill patients who are often exposed to invasive procedures used in diagnosis and management which increases the risk of developing healthcare-associated infections. To manage such infections, studies have documented the extensive and indiscriminate

use of antimicrobial agents. These patients are often prescribed broad-spectrum antimicrobials agents (2,6).

A majority of these prescriptions are empiric, mainly based on the doctor's experience and preference (6). This leads to overuse or misuse of these medicines, which in turn leads to selective pressure for resistant microbes in this unit.

The extensive and frequent use of antimicrobial agents exposes these patients to adverse effects, toxicity and the increasing burden of antimicrobial resistance.

There is increasing drug resistance against commonly used antimicrobial agents globally especially among patients in CCU (2). Due to the specific risk profile of the patients in this unit, the CCU is considered an epicenter of resistance development. In addition, hospital-acquired infections and AMR have a crippling clinical and economic burden (2,3,6).

Several studies conducted at KNH have revealed the common pathogens that cause infections in the CCU and the resistance patterns to the antimicrobial agents used (14–16). But there are no published data on the patterns of use of antimicrobial agents in the CCU at KNH. The KNH Antimicrobial Stewardship Committee implemented a guideline for antimicrobial therapy in the Critical Care Unit in 2014 and so far, compliance with this guideline has not been objectively measured. Neither has the extent of its use in the CCU been determined. Therefore, this study sought to describe the antimicrobial prescribing patterns in the CCU in terms of the antimicrobial class/agents frequently used and the dosages. The study will also measure the level of compliance to the KNH guide to Antimicrobial Therapy in the Critical Care Unit (17).

1.3 Research questions.

1. What is the prevalence of antimicrobial use in the critical care units at KNH?
2. What are the prescribing patterns of antimicrobial agents used in the Critical Care Unit at KNH?
3. To what extent does the prescribing of antimicrobial agents in CCU comply with the KNH Guideline on Antimicrobial Therapy in Critical Care Unit?
4. What proportions of antimicrobial susceptibility testing result inform the choice of antimicrobial agents?

1.4 Main objective

The main objective of this study is to determine the patterns of antimicrobial use and level of compliance to the Kenyatta National Hospital Guide to Antimicrobial Therapy in the Critical Care Unit.

1.4.1 Specific objectives

The specific objectives of the study are:

1. To describe the prescribing patterns of antimicrobial agents used in the critical care units at KNH.
2. To assess the compliance of antimicrobial prescribing patterns to the KNH Guide to Antimicrobial Therapy in the CCU using selected indicators.
3. To describe the extent to which culture and sensitivity tests are used to guide the choice of antimicrobial agent.

CHAPTER TWO: LITERATURE REVIEW

2.1 Nosocomial infections

A nosocomial infection which is also called a "hospital-acquired infection" is defined as an infection acquired in the hospital within 48 hours of admission for a reason other than that infection. It also means that this infection was not present or incubating at the time of admission. Infections that are acquired in the hospital but appear after the patient is discharged are also referred to as healthcare-associated infections (18). Hospital-acquired infections (HAI) occur in an estimated 5-10% of all patients admitted in CCU (19) and are a common problem in critically ill patients because they are the leading cause of mortality (20).

Infections that occur in CCU are associated with high costs due to the expensive medicines, prolonged hospital stay and the increased risk of developing infections caused by resistant organisms (21). Nosocomial infections are among the most frequently reported adverse events in healthcare in the United States (20) where the prevalence in critical care is estimated to be 5%; with more than 30% of the patients succumbing to the infection. In a large point prevalence survey of ICU in Europe, 40%-50% of patients in critical care units acquired an infection during the course of admission (11).

These infections can be either in the lower respiratory tract (11%), on the surgical site (20%), in the bloodstream (11%) or in the urinary tract (36%) (11). Several micro-organisms are responsible for hospital-acquired infections. These include *Acinetobacter*, *Klebsiella*, *Pseudomonas*, *Staphylococcus* and *Escherichia coli* (22).

A study conducted among CCU patients at KNH in 2009 isolated *Klebsiella* (23.1%), *Citrobacter* (12.8%), *Staphylococcus aureus* (12.8%), *Pseudomonas aeruginosa* (10.3%) and *Acinetobacter spp* (10.3%) as the common causes of VAP (16).

2.2 Infections in the critical care unit

Critical Care Units (CCUs) are also referred to as intensive Care Units (ICU) or Intensive Therapy Units (ITUs). They are a specialized hospital unit that provides advanced treatment, close monitoring, and diagnostic technology to patients facing an immediate life-threatening health conditions such as failure of vital organs (23). The aim is to maintain the functioning of the vital organs and to improve the patients' condition so as to allow the specialist medical team in the CCUs to treat or manage the underlying illness. Admission into CCUs can be due to conditions such as a serious accident leading to severe head injury, severe burns, a heart attack, a stroke or severe infections such as sepsis and severe pneumonia. In some cases, the admission can be planned as part of recovery from a major surgery or it could be an emergency in case of complications following surgery (23).

A prevalence survey in 55 hospitals representing four WHO regions (Europe, Eastern Mediterranean, South-East Asia, and Western Pacific) revealed that the intensive care unit has the highest prevalence of nosocomial infections (18). In that survey, mortality among patients with severe sepsis was 30-50% and it was dependent on the underlying disease and the severity of the acute illness (20).

2.2.1 Prevalence of nosocomial infections in critical care units

Hospital-acquired infections occur in an estimated 10% of all patients that are admitted into CCU. They are the most prevalent complication among hospitalized patients and they are very frequent in the CCU(24).

There is an increased risk for severe infections among critical care patients because of the weakened physiological condition of the patient and the variety of invasive procedures used for diagnosis and treatment. Critical care patients will have severe illnesses, require mechanical ventilation, be in need of a catheter, stay in hospital for a prolonged period and hence are at an increased risk of acquiring a healthcare-associated infection. An estimated 7% of these patients will develop a bloodstream infection within one month of admission in the critical care unit (13).

2.2.2 Types of infections in Critical Care Unit

In a point-prevalence survey of healthcare-associated infections in Canada, it was found that *Clostridia difficile* caused 12.1% of healthcare-associated infections making it the most common cause, followed by *Staphylococcus aureus* 10.7%, *Klebsiella pneumoniae* 9.9% and *Escherichia coli* 9.3% (25). In Uganda, at the CCUs in Mulago and International Hospitals, a study noted that 60% of all nosocomial infections comprised of ventilator-associated pneumonia (VAP), catheter-associated urinary tract infections and bloodstream infection (BSI) due to the use of intravascular devices (19).

2.2.2.1 Bloodstream infections

Bloodstream infections (BSI) are life-threatening and cause death in 35 to 50% of the cases (26). The high rates of mortality in patients with BSI can be attributed to antimicrobial-resistant gram-negative microorganisms (27).

A study in Hungary showed that 30-55% of all BSIs in children are caused by gram-negative organisms. The hospital-acquired gram-negative infections are a major concern among immune-compromised patients such as those undergoing chemotherapy because they worsen the patient outcome (27).

It is estimated that 10-15% of these infections are from healthcare-associated urinary tract infections. Catheter-related BSIs are the other common type of BSI in the intensive care unit accounting for 30% of all cases of BSI among ICU patients. The extensive use of intravascular catheters is an important contributor to the occurrence of bloodstream infections(13).

2.2.2.2 Ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) is the second most common nosocomial infection in the critical care unit (28). It is defined as pneumonia occurring in a patient within 48-72 hours of mechanical ventilation. About 50% of hospital-acquired pneumonia is attributed to VAP. It occurs in 9-27% of all patients who are on mechanical ventilation for more than 48 hours (28,29). Mechanical ventilation is a major risk factor for pneumonia because it allows aspiration of gastro-intestinal content and bacteria that colonize the upper respiratory tract leading to pneumonia. (24) VAP causes the patient to stay in the hospital for a long period leading to increased health care costs (30). The use of an appropriate antimicrobial regimen leads to a good prognosis while some studies have shown that early initiation of antibiotics could prevent the use of mechanical ventilation for a prolonged period and also reduce mortality in the patients (29).

A study in KNH intensive care unit in 2009 found the incidence of VAP was 28% in mechanically ventilated patients.

This finding is similar to others in a meta-analysis which revealed a VAP prevalence of 35.2% among patients that were on mechanical ventilation for more than 48 hours (29). In the meta-analysis, the pathogens isolated were *Pseudomonas aeruginosa* (23.2%), *Staphylococcus aureus* (20.2%), *Haemophilus influenza* (19.5%), *Acinetobacter baumanii* (10.7%), *Escherichia coli* (10.2%) and *Klebsiella pneumonia* (9.5%). A similar pattern was noted in the bacterial pathogens isolated in tracheal aspirates at KNH (16).

2.2.3 Microbial causes of infections in critical care unit

Several studies have identified the following microorganisms as the major causes of infections in the critical care unit. They include are *Pseudomonas aeruginosa, Klebsiella pneumonia, Staphylococcus aureus, Enterococcus faecium,* and *Acinetobacter baumanii,* (20). These microorganisms are so common such that an acronym ESKAPE has been used since 2008 to describe these microorganisms which pose the greatest risk to patients in CCU. In a point prevalence survey conducted in Italy, *Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa* and *Acinetobacter baumanii* mainly from the abdomen or urinary tract(13) were found to be the most common gram-negative causes of bloodstream infections. In the US, *Escherichia coli(49.5%), Klebsiella pneumonia(17.1%), and Pseudomonas aeruginosa(8.2%)* were the pathogens that were most implicated in the cause of healthcare-associated urinary tract infections (31).

In a Brazil teaching hospital, *Pseudomonas aeruginosa, Staphylococcus aureus Acinetobacter baumannii* and the *Enterobacteriacea*e family were found to be the top four most common cause of VAP in ICU (30).

Another study in KNH showed that the commonest causes of urinary tract infections in CCU included *Escherichia coli* (23%), *Klebsiella* (20%), *Enterococcus*(19%), *Pseudomonas*(10%), *Acinetobacter*(10%), *Citrobacter*(8%), *Enterobacter*(6%), *Staphylococcus*(3%) and *Proteus*(2%)(15). In Uganda, the microorganisms isolated were similar to what was seen in KNH (32).

These organisms have reduced susceptibility to a wide range of antimicrobials that are used for the treatment of VAP hence leaving prescribers with very limited options in the management of these infections. This situation is made worse by the increasing rate of antimicrobial resistance, inappropriate antimicrobial use and lack of new antimicrobials in the market (29).

Risk factors for acquiring infections in a hospital are dependent on the microorganism, patient and environmental factors. For example, the patients in the critical care unit already have decreased immunity. For them to receive the highest quality of care, they will be subjected to a variety of invasive procedures which open up routes of infection and the transmission of drug-resistant microorganisms.

2.2.4 Impact of nosocomial infections in critical care units

The incidence of infections in critically ill patients and the mortality rates have not improved in the last 30 years. About 70% of patients in CCU will be prescribed an AM making this unit have a very high usage of AM which is associated with the development of AMR. (33) In some instances, medical-legal cases have come up when patients and their families perceive the hospital to be responsible for causing the infection hence want to seek compensation (19).

Mortality among patients with severe sepsis is estimated to be between 30-50% and it is dependent on the underlying disease and the severity of the acute illness.

Variation in mortality among critically ill patients who develop nosocomial infections can be explained by the different causative microbes and type of infection, the patient age, the antimicrobial susceptibility patterns and adequacy of antimicrobial therapy (11).

2.3 Antimicrobial use in the critical care unit

2.3.1 Prevalence of Antimicrobial use in Critical Care

In Canada, a PPS conducted in 2013, of antimicrobial utilization among cardiac and pediatric patients admitted in CCU at a teaching hospital reported a prevalence of 79% (34). While in China, a point prevalence survey done every third year over a ten year period in 2016 reported an average antimicrobial use prevalence of 81.8% (35). Similar results were observed in an adult CCU ward in Vietnam with a prevalence of 84.8% in 2013 (36). In a private hospital in South Africa, 28.8% of patients were prescribed for an antimicrobial agent during their CCU stay (37) which is much lower than 65.5% reported in the Global PPS for CCU's in Africa(8).In Nigeria, adult CCU's observed a prevalence of 88.9% -100%(38) while in the PPS done here in Kenya at Jaramogi Oginga Odinga Teaching and Referral hospital (JOOTRH) (39) and Rift Valley Provincial Hospital (Now Nakuru Level V) (40) in 2017 reported a prevalence of 67.7% and 100% respectively.

2.3.2 Importance of Antimicrobial use in Critical Care

In critically ill patients, who develop infections, early initiation of an effective antimicrobial agent is of utmost importance. Any delay occasioned by susceptibility testing or other factors leads to an increase in mortality (13). Hence empiric prescription of broad-spectrum antimicrobials

followed by escalation or de-escalation of therapy depending on availability of susceptibility tests and the patient condition is a common practice in the critical care setting.

2.3.3 Factors influencing Antimicrobial selection in Critical Care

The use of antimicrobial agents in patients that are critically ill is affected by multi-organ disturbances that lead to pathophysiological changes which influence the pharmacokinetic and pharmacodynamic properties of the medicine (11).

The critical illness affects the absorption, distribution, metabolism and elimination processes in the patient and therefore influences the pharmacokinetics of the medicines.

Because of the altered volume of distribution of antimicrobials, critically ill patients require larger loading doses or a higher frequency of administration to overcome the increased elimination of the drug in order to achieve therapeutic levels (33). Admission to a health facility and a recent history of use of an antimicrobial agent are independent risk factors for antimicrobial-resistant infections (31).

The prior use of an antimicrobial agent is a risk factor for multidrug resistance. A study to investigate the effect of prior use of antimicrobials on micro-organism distribution and antimicrobial resistance among patients with hospital-acquired urinary tract infections in the US, showed that use of one or more antimicrobial agents is associated with an increased risk of multidrug resistance and a higher incidence of fluoroquinolone non-susceptibility (31).

2.3.4 Antimicrobial resistance in Critical Care Unit

Antimicrobial resistance in hospital-acquired infections especially those caused by gram-negative pathogens are associated with poor patient outcomes and a limited list of suitable antimicrobial

agents for treatment (31). Overuse of antimicrobial is a key contributing factor to the high prevalence of antimicrobial resistance in the CCU. Other factors include prolonged stay in CCU, use of invasive devices, the presence of co-morbidities and lack of isolation practices when a multi-drug resistant pathogen has been identified (20).

Acinetobacter isolated from a cardiac surgical ICU in New Delhi, India was found to be resistant to most of the antimicrobial classes. In this hospital in India, the resistance patterns were as follows: 86% to imipenem, 62% to piperacillin-tazobactam and 18% to colistin. This meant that there is no class of antimicrobials preserved for future use a situation that is extremely dangerous (41).

The *E.coli* isolates were found to be resistant to amoxicillin-clavulanate (96%), amikacin (60%), ciprofloxacin (92%) and cefotaxime (100%) implying that simple infections may take longer to treat. The *staphylococcus* from the same critical care unit was found to be resistant to amoxicillin-clavulanate (43%) and linezolid (77%) but had a sensitivity of 77% to vancomycin (41).

In KNH CCU, the resistance of isolated microbes from urine samples to the commonly used AM agents was as follows: 48.8% to amoxicillin-clavulanate, 61.9% to ampicillin, 37.1% to gentamycin and 33.8% to cefotaxime (15).

2.4 Antimicrobial stewardship.

Antimicrobial stewardship (AMS) is a rational and systematic approach to the use of antimicrobials in the hospital setting in order to optimize desirable outcomes to the patient while minimizing harm and preserving future therapies (4). AMS brings together strategies focused on achieving rational use of antimicrobial agents all through the medicine use process (42). It aims at limiting the inappropriate use of antimicrobial agents and consequences such as the development

of resistance (5,10). AMS programs target CCUs because of the high antimicrobial consumption (10) and the benefits of an appropriate choice of antimicrobial agent for use on the patient in this setting.

2.4.1 Approaches to Antimicrobial stewardship

The complex nature of critical care setting contributes to the inappropriate use of broad-spectrum antimicrobial agents. This in turn leads to the selection of resistant pathogen necessitating AMS.

AMS employs approaches such as audit and feedback, formulary restrictions and pre-authorization and guidelines to ensure appropriate use of antimicrobials (10).

Several countries have employed multiple AMS approaches to promote the rational use of antimicrobial agents. For example, in France, multiple activities such as preauthorization, formulary restriction, education of prescribers and use of special treatment cadies which identify the indication have been used (42).

The Antimicrobial Stewardship Programs (ASP) mainly focus on achieving the most favorable clinical outcomes for the patient while keeping at minimal, the unintended adverse effects of antimicrobial therapy such development of resistance and toxicity (43). To do that, these two common approaches; prospective audits with intervention and feedback and formulary restriction with prior authorization for select antimicrobial agents are employed by ASP.

2.4.1.1 Prospective audit and feedback in Antimicrobial Stewardship programs

Prospective audit and feedback is the gold standard AMS intervention. In a study at a tertiary hospital in Ontario, Canada, implementing audit and feedback intervention on day 3 and 10 of therapy, reported a 23% reduction in broad-spectrum antimicrobial expenditure and an improved gram-negative susceptibility to meropenem over time in CCU (10).

2.4.1.2 Formulary restriction and pre-authorization guidelines

The use of formulary restriction is only possible when a health institution or department has a defined formulary. The formulary will then provide a list of antimicrobial agents available for prescribers to choose from given the patients' illness. This method has been thought to be less controversial because it does not threaten the authority of the prescriber and results in cost savings for the hospital (43).

Another method based on the formulary restriction approach is the requirement for pre-approval before the administration of restricted antimicrobial agents or the use of a special prescribing form. A tremendous reduction in the overall use of antimicrobial agents is noted when this method is implemented in the presence of a restriction formulary and availability of an infectious disease specialist to approve the prescriptions (43). However, it is time-consuming, labor-intensive and will require the prescriber's cooperation (5). It is also considered an infringement of the prescriber's independence.

Another drawback is that it can be bypassed by waiting until after hours when the infectious disease specialist is not available to place the order for the restricted antimicrobial agents.

The use of formulary restriction as the only approach for antimicrobial stewardship is ineffective if other approaches such as the use of a defined prescription or order forms or health facility utilization criteria are not incorporated. In having a defined utilization criterion, the prescriber is

required to include an appropriate indication or rationale for the selection of the antimicrobial agent before it is dispensed (43).

2.4.2 Antimicrobial Stewardship Activities

Information gathering is a key activity of an AMS program. It is one of the three main activities as shown in Figure 2.1 that the AMS program engages to optimize antimicrobial use. The information needed includes the quantity of antimicrobial use that is obtained through surveillance and the quality of antimicrobial prescribing.

Feedback on the results to the prescribers will highlight areas that need improvement and guide discussion on making the change.

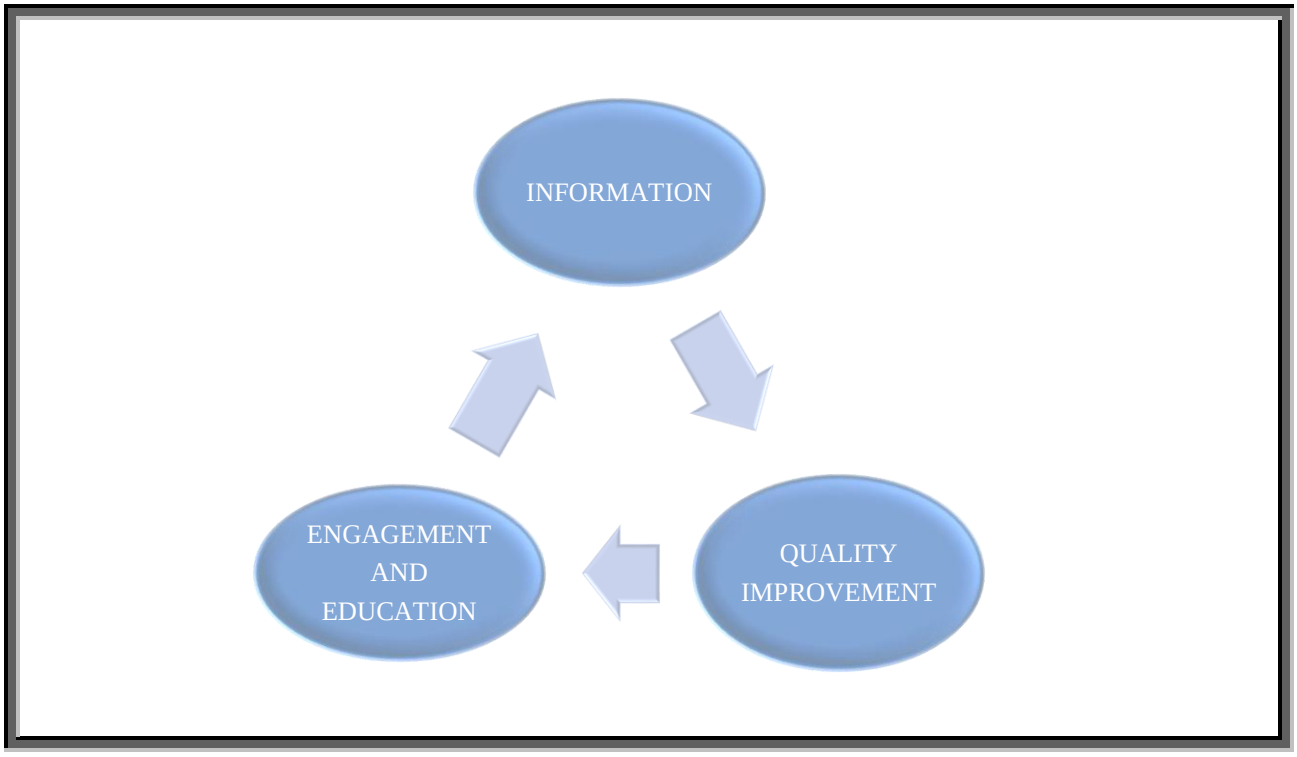

Figure 2. 1: Antimicrobial stewardship activities

Quality Improvement is an AMS activity geared toward changing processes or behavior around antimicrobial use. By use of the Plan, Do, Study and Act cycle, quality improvement allows for testing of changes that may improve practice. Clinical teams are at the center of the AMS activities (44). Engagement and education are ongoing activities of the AMS program focused on local policy and guidelines on antimicrobial use while emphasizing on specific high risk and reserved antimicrobial.

2.5 The Kenyatta National Hospital guide to Antimicrobial Therapy in Critical Care

This guideline developed in 2014 is an important strategy to ensure the appropriate use of antimicrobial agents, managing the growing threat of AMR while providing the highest quality of care to the patients in the CCU. This is the first guide on AM use that is specific to the critical care units in the hospital. It was as a result of the efforts of a multidisciplinary team comprising of medical specialists, microbiologists, clinical pharmacists, infection prevention and control specialists and the Medicine and Therapeutic Committee (MTC). The guideline is structured to assist the team managing the patient to make choices that will enhance appropriate antimicrobial use.

This guideline has identified six key types of infections that are found in CCU. They include bloodstream, intra-abdominal, pneumonia, urinary tract, skin and soft tissue infections. It goes further to stratify patients into four categories according to risk (17). Figure 2.2 shows an extract of the bloodstream infections antibiotic protocol form the KNH guide to antimicrobial therapy in CCUs.

Table 2: Bloodstream infections antibiotic protocol

Patient risk stratification			
	Category 1	Category 2	Category 3
Description	No contact with health care system No prior antibiotic treatment Patient young with no co-morbidities No organ failure	Recent hospital admission, dialysis etc. without invasive procedure Recent antibiotic therapy Patient old with co-morbidities Single organ failure	Long hospitalization With Invasive procedures Recent and multiple antibiotic therapies Advanced immunodeficiency Neutropenia. Multiple organ failure
Common Pathogens	*Staphylococcus aureus*, Coagulase-negative staphylococcus, *Escherichia coli*	*Escherichia coli, Klebsiella, Enterobacter, Citrobacter*	*Acinetobacter*, Pseudomonas, Escherichia coli, Klebsiella, Enterobacter, Citrobacter*
Empiric Therapy	• Coamoxiclav +/- • Aminoglycoside	• Ertapenem or • Ciprofloxacin	Full spectrum Carbepenem (Imipenem or Meropenem) + Amikacin or Piperacillin/Tazobactam + Amikacin ** * For MDR Acinetobacter add Colistin ** In renal dysfunction Ciprofloxacin substitutes Amikacin

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After culture and susceptibility testing			
Pathogen	Recommended	Alternative	Remarks
Staph. aureus MSSA	• Flucoxacillin	• Coamoxiclav	
Staph. aureus MRSA	• Vancomycin or Teicoplanin	• Linezolid	
Coagulase negative Staphylococci	• Flucloxacillin	• Coamoxiclav	Mostly a skin contaminant
Enterococcus	• Vancomycin or Teicoplanin	• Linezolid	
Escherichia coli, Klebsiella, Citrobacter and other Enterobacteriaceae	• Ciprofloxacin	• Ertapenem	For ESBLs use Ertapenem
Pseudomonas	• Ceftazidime + • Aminoglycoside	• Piperacillin/Tazobactam + Aminoglycoside or • Cefepime + Aminoglycoside	Ciprofloxacin may be used in place of Aminoglycosides in patients with renal dysfunction .
Acinetobacter	• Piperacillin/Tazobactam or • Cefepime or • Imipenem or Meropenem + • Amikacin		For MDR Acinetobacter use Colistin or Tigecycline

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Figure 2. 2: Extract from the KNH guideline to antimicrobial therapy in CCU.

2.6 Conceptual framework

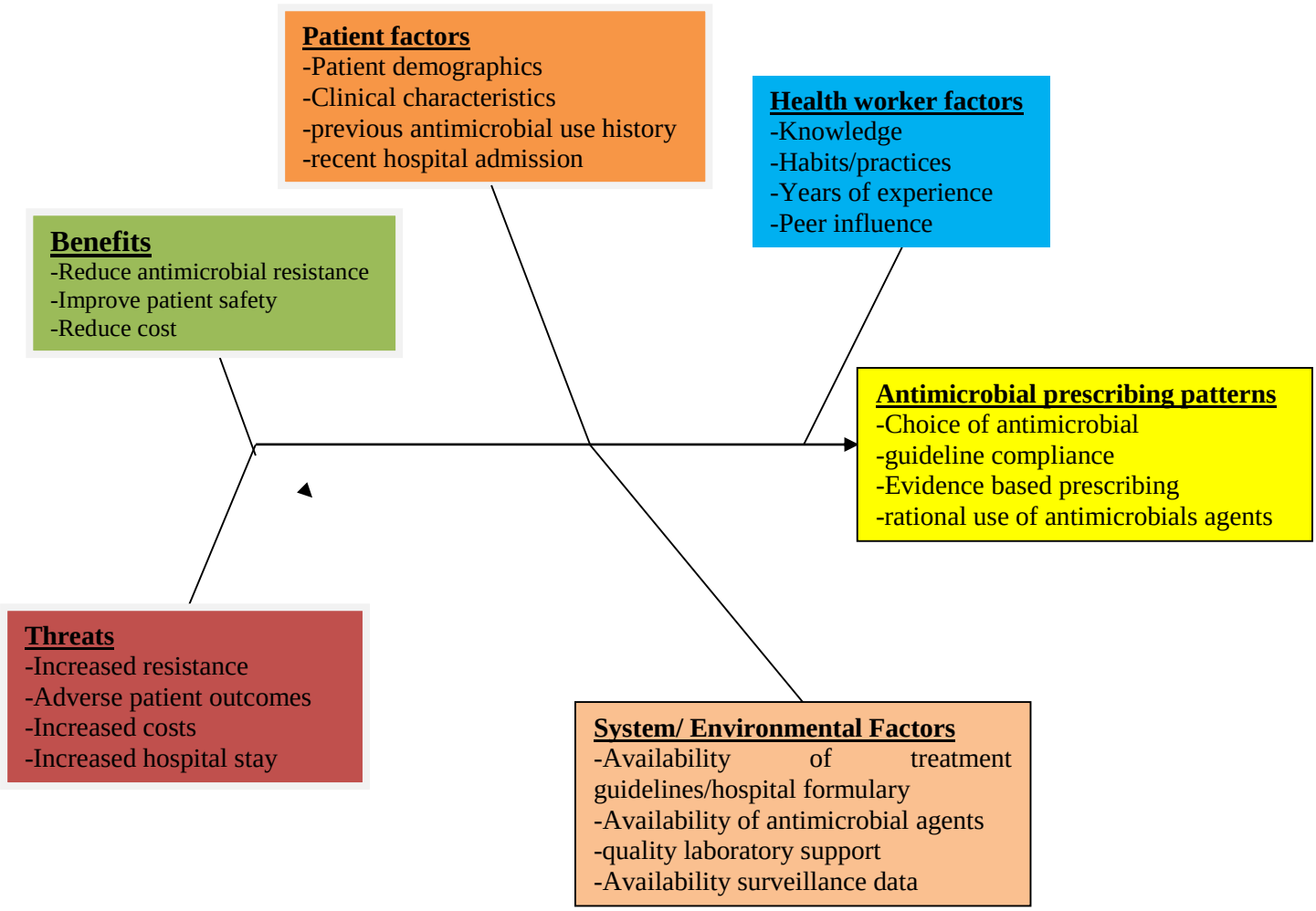


Figure 2. 3: Conceptual framework on influencers of antimicrobial prescribing.

The fight to slow down the development of AMR is multifaceted. Antimicrobial prescribing practices before and during CCU stay are crucial. The interaction of the various factors in figure 2.3, in the health system influence the outcomes of patients admitted to the CCU. Health worker factors such as inappropriate antimicrobial prescribing adversely affect patient care. Figure 2.3 also shows some of the areas that can be acted upon for antimicrobial stewardship. This study will describe a few of these factors that characterize antimicrobial use in KNH CCU.

CHAPTER THREE: METHODOLOGY

3.1 Study design

A descriptive retrospective longitudinal study was conducted to determine the patterns of antimicrobial prescribing in the CCU at KNH. The files of all the patients admitted to the selected CCUs' from January to December 2017 who met the eligibility criteria were reviewed. The data were extracted using a pre-designed data collection tool (Appendix C).

3.2 Study site

The study was conducted at the Kenyatta National Hospital (KNH) which is a 2000 bed National teaching and referral hospital. KNH is the largest referral hospital in Kenya and attends to approximately 60,000 inpatients and 450,000 outpatients annually. The hospital serves as the teaching hospital of the College of Health Sciences, University of Nairobi and Kenya Medical Training College. The hospital services are provided across its 50 wards, 22 outpatient clinics, accident & emergency department and 24 theatres of which 16 are specialized. The hospital offers many specialty services including open heart surgery, neurosurgery, oncology, renal services, and critical care services. KNH has the highest number of CCU beds in the country at 56. There is a main CCU located on the 1st floor of the KNH tower block with a bed capacity of 21. In addition, there is a satellite CCU in the department of medicine with 10 beds (5 beds in ward 7A and 8A) located on the 7th and 8th floor of the KNH tower block. The other CCUs are in the department of pediatrics with 10 beds and Accident & Emergency department with 5 beds. This study was conducted in three CCUs because they were in operation during the study period unlike the cardiothoracic and neuro-surgical CCUs that were not operational while inclusion criteria also meant that the patients in the pediatric CCU were not included in the study.

3.3 Study population

The study population included patients who were admitted to the selected CCUs from January 2017 to December 2017.

3.4 Eligibility criteria

Any patient 13 years of age and above who was admitted to the selected CCUs as from 1st January to 31st December 2017 and had been prescribed an antimicrobial agent during their hospital stay was included in the study. Patients who were admitted to other CCUs in the hospital were not included in this study.

3.5 Sample size consideration

A global point prevalence survey conducted in 53 countries established the rate of compliance with guidelines to be 77.4% (8). To determine the level of compliance to the KNH guideline to antimicrobial therapy in the CCU, a minimum sample size was determined by the fisher's formula at a permissible error of 5%.

$$\mathbf{N=Z^2 \{P (1-P)\} / S^2}$$

Where

N=Estimated sample size

P=Estimated proportion of outcome of interest (Assumed level of compliance of 77%)

S=Standard error (desired level of precision, permissible error, set at 5%)

Z=Z-score value corresponding to 95% confidence interval, which is 1.96.

$N= 1.96^2 \{0.77(1-0.78)\}/ 0.05^2$

=**263.70**

Using the formula, the calculated sample size was 264. This number was inflated by 10% to cater for any missing file or files with missing information and the calculated sample size was 290. This study was able to attain a 106.6% sample size (n=309).

3.6 Sampling method

The KNH CCUs that were selected for this study have a capacity of 31 beds. Simple random sampling was used. The study population consisted of all records of patients who were admitted to the CCUs from January to December 2017. The list of the patients above the age of 13 years that were admitted was obtained from the admission books of the selected wards. The list was presented to the KNH health information department for retrieval of the files. Each file was examined to ensure that only those that met the inclusion criteria were sampled. The sampling frame was made from a list of all patient files that met the inclusion criteria. This list was entered into Microsoft Excel version 2007 and on command; the computer-generated a random sample of files that were reviewed for this study. The random sample obtained from each of the 3 CCUs is as shown below in table 3.1. Data was extracted from these files using a pre-designed and standardized tool (Appendix C)

Table 3. 1: Sampling of the patients from the CCUs of Kenyatta National Hospital

CCUs at KNH	Bed Capacity	Number of patients sampled
Main CCU	21	182
Medical CCU 8A	5	90
Medical CCU 7A	5	37
TOTAL		**309**

3.7 Data Collection

3.7.1 Data collection instrument

A pre-designed and validated data collection instrument (Appendix C) was used to collect data from the sampled patients' medical records. Data was extracted by a thorough review of the patient file. The documents reviewed included: admission notes, nursing summary, treatment sheets, doctor's notes, referral notes and laboratory culture and sensitivity reports.

3.7.2 Data collection procedure

Each patient record was assessed first in terms of whether or not an antimicrobial agent had been prescribed during the study period and thereafter the KNH guide to antimicrobial therapy in the CCU was applied. The antimicrobial therapy was assessed in the context of choice, dosage, and frequency and captured as whether compliant or non-compliant to the KNH guideline to antimicrobial therapy. If microbiological evaluation was conducted, the antimicrobial prescription was further analyzed to include whether or not the choice of antimicrobial agent was consistent with the culture and sensitivity result.

3.7.3 Types of data collected

Patient demographic data such as age and sex were collected. Clinical data such as the reason for admission at KNH, main diagnosis, and date of admission, date of discharge, co-morbidities and patient category according to the KNH guide to antimicrobial therapy in CCU were extracted. Length of stay was recorded for all patients admitted to critical care unit during the study period. Data on organ dysfunction, mechanical ventilation, peripheral or central venous access, intra-arterial line, urinary catheter, surgical line, and parenteral nutrition were also collected.

The antimicrobial therapy data that was collected included antimicrobial name, dose, and frequency of administration, and duration of use. Other data collected included the micro-organisms isolated from culture and the antimicrobial susceptibility profile. The initial antimicrobial therapy before the collection of samples for Culture and Sensitivity Testing (CST) and the change in antimicrobial therapy once the results of the CST had been received was also captured. The prescriptions were assessed for antimicrobial alignment with the guideline recommendation for empirical treatment and organism isolated.

3.8. Variables and definitions

The two primary outcomes of interest were the degree of compliance to KNH-CCU guidelines in terms of the choice of antimicrobial agent prescribed and the level of antimicrobial switch informed by culture and susceptibility results. Other outcomes included the prevalence of various types and classes of antimicrobial agents and documentation of antimicrobial therapy indication in the patients' medical records. The predictor variables include the age and sex of the patient, comorbidities, current diagnosis, patient category according to the KNH antimicrobial use guide and the type of infection. The other variables captured include the length of stay in CCU, catheterization (urinary, central, hemodialysis, peripheral and peritoneal catheters), mechanical ventilation, intubation (endotracheal, Suction, tracheostomy, nasogastric/feeding and gastro duodenal intubation) previous exposure to antimicrobials and a recent history of admission to a health facility.

3.9. Risk categorization of the participants

None of the patients that were sampled for this study were categorized. In the KNH guide to Antimicrobial Therapy in Critical Care Units, the choice of an antimicrobial agent is affected by the patients' risk categorization.

The risk classification is too complex and provides for empirical and targeted treatment in the same context giving room for inappropriate antimicrobial use. But for the sake of conducting the analysis, it was necessary that the patients are categorized based on the criteria that are given in the KNH guideline. The guide below (Table 3.2) was developed based on the existing guideline and was used to come up with the patient risk categories. They reflect admission patterns and disease groups.

Table 3. 2: Risk categorization for critical care patients at Kenyatta National Hospital.

Key trait	Risk category	Implication
No clear risk factors for infections.	one	Consider antimicrobial therapy initiation if an infection is microbiologically identified
Co-morbidities present, no trauma or invasive procedure, No evidence of established infection	two	Consider antimicrobial therapy initiation if an infection is microbiologically identified
HIV, Invasive procedure, Trauma	Three	Consider prophylactic antimicrobial therapy
HIV, Invasive procedure, confirmed infection at admission	Four	Initiate empiric antimicrobial therapy immediately

3.10. Quality assurance and data management

The data collection instrument was pre-tested using medical files from the KNH health information department. Twenty (20) records of patients who had been admitted to the selected CCUs were

randomly selected and data extracted into the data collection instrument to test for suitability in data collection. The instrument was improved appropriately by the researcher.

One research assistant with a bachelor's degree in nursing was recruited and trained on how to extract data from the patient files. The completed data collection instruments were reviewed by the researcher for completeness and accuracy every two days. If any data was not complete, the patient file was reviewed and the missing data filled. All the raw data collected was entered into Epi-Info version 7(2007-2010) software and a database created.

The data was backed up on a weekly basis by the researcher. Data cleaning and validation was done before the data was exported into STATA (version 13) for analysis.

3.11. Data Analysis

All data were subjected to descriptive statistical analysis and reported as proportions (%) for categorical variables and mean (standard deviation) and median (Interquartile range) for the continuous variables. The data on the patients' sex, age, and number of antimicrobial agents per prescription were reported as percentages. In the calculation of the overall prevalence of antimicrobial agent prescription at admission, denominator data was composed of the total number of patients sampled and the numerator was the total number of sampled patients who had a prescription for an antimicrobial agent at admission. The prevalence of antimicrobial agent prescribing in the individual CCUs was also calculated. The most frequent type of antimicrobial agent prescribed in the CCUs was determined and the prevalence calculated. This information was presented in tables and graphs.

To identify inappropriate antimicrobial agent prescribing, the following indicators were identified: documentation of the indication for antimicrobial agent prescription, recording of a formal review

of the medicine prescribed and adherence to the antimicrobial therapy guideline. The KNH guide to antimicrobial therapy in CCU was used. When assessing for compliance, only the choice of antimicrobial agent for empiric, targeted or choice according to organism isolated was considered. The prescriptions were assessed for alignment with the KNH antimicrobial guide in the CCU. Once the patients were categorized into risk classes, the first antimicrobial change after CCU admission was used to assess targeted compliance. While the first prescription at admission was used to assess empirical prescribing compliance and the first positive culture result was use to assess prescribing compliance for organism isolated.

The association between predictor variables and outcome variables was determined using the Chi-square test. Logistic regression was undertaken to measure the relationship between the outcome variable compliance to the KNH guideline and several predictor variables such as patients' age, sex, and diagnosis. Data analysis was conducted using STATA (version 13) software. The level of significance was set at 0.05.

3.12. Ethical consideration

Approval to carry out this study was granted by the Kenyatta National Hospital-University of Nairobi Ethics and Research Committee (KNH-UoN ERC) P692/11/2017 (Appendix A). The study was registered with the Research and Development Department of the Kenyatta National Hospital and recorded in the registry as per the hospital research guidelines.

Approval to access the patient files was also granted by the head of the health information department at Kenyatta National Hospital.

The researcher took utmost care to ensure maximum privacy and confidentiality of the information obtained during the study. The patient files were only used within the health information

department from 8 am to 5 pm. A unique patient code was used during the study instead of patient identifier information. The data instruments were stored in a password-protected database only accessible to the researcher. The data collection instrument and any other materials that were used during the study were kept under lock and key. At the end of the study, these materials were handed over to the Department of Pharmacology and Pharmacognosy, the University of Nairobi for storage for a period of 5 years.

A password-protected electronic version of the primary data has also been deposited to the department e-repository. At the end of the 5 years, the researcher will apply to the KNH/UoN-ERC for the authority to destroy the data.

CHAPTER FOUR: RESULTS

4.1 participants in the study

Of the 745 patient files that were retrieved, 50 were excluded because they did not meet the inclusion criteria for patients of 13 years and above. Eighteen (18) files were excluded for missing information, eight (8) due to absence of antimicrobial use during the admission and eleven (11) because the patients were not admitted to the CCUs included in the study. This is summarized in figure 4.1 below.

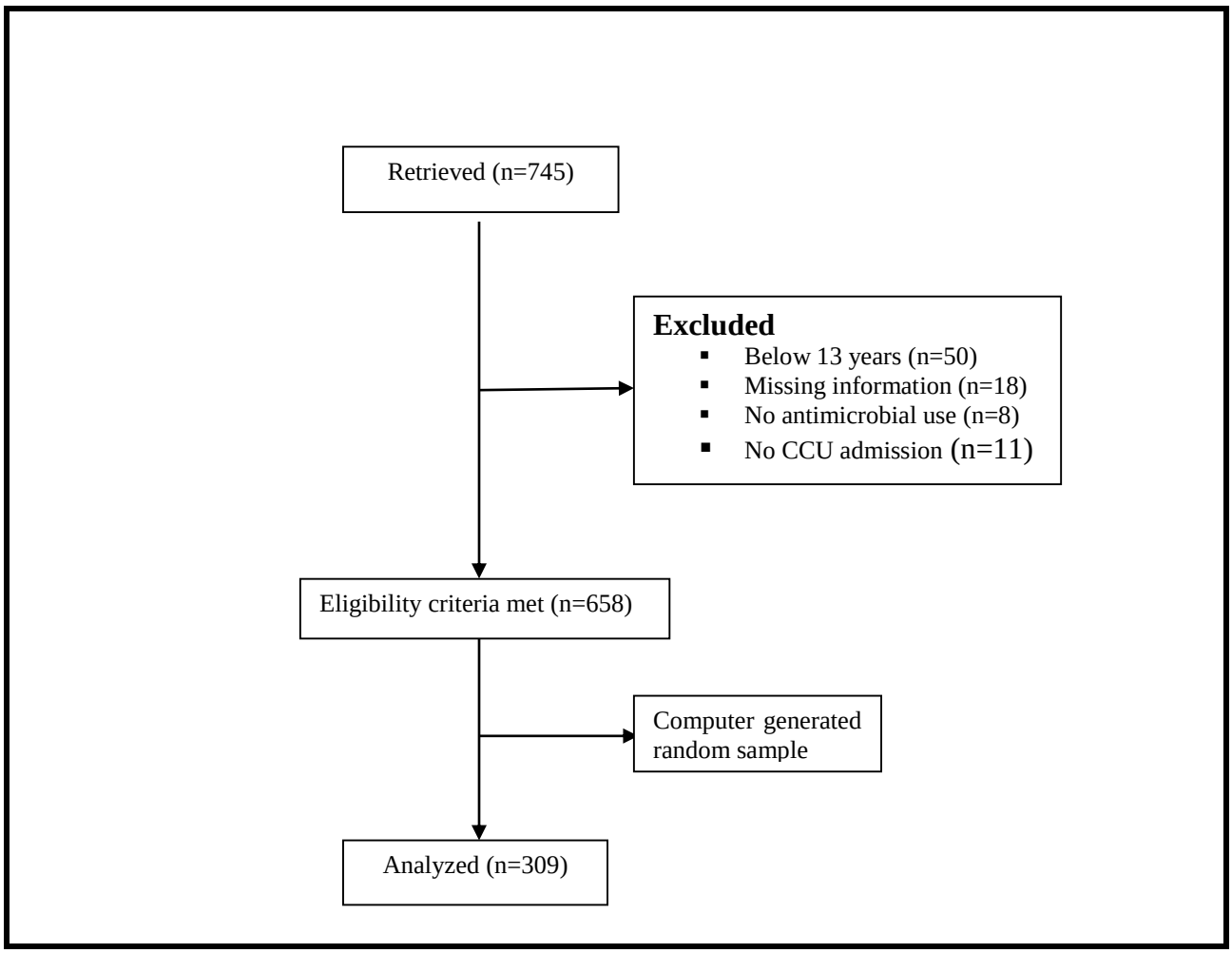


Figure 4. 1: Consort diagram of patients in the study at Kenyatta National Hospital

4.2 Demographic characteristics of the study participants.

The total number of patients included in this study was 309. As shown in table 4.1, there were 158 (51.1%) males and 151 females (48.9%).

Table 4. 1: Demographic characteristics of critical care patients at Kenyatta National Hospital

Background Information of the Study Patients		
Characteristic	**n**	**(%)**
Age group in years		
13 to 20 years	37	11.97
21 to 30 years	63	20.39
31 to 40 years	78	25.24
41 to 50 years	46	14.89
51 to 60 years	35	11.33
61 to 70 years	32	10.36
Above 70 years	18	5.83
TOTAL	**309**	**100**
Mean(SD)=40.61(17.47)		
Gender		
Male	158	51.13
Female	151	48.87
TOTAL	**309**	**100**
Direct admission into CCU		
Yes	92	29.77
No	217	70.23
TOTAL	**309**	**100**
Ward admitted		
Main CCU	182	58.9
Medical 7A	37	11.97
Medical 8A	90	29.13
TOTAL	**309**	**100**

The main CCU had 182 (58.9%) patients in the study population followed by the medical CCU 8A which had 90 (29.1%) and the medical CCU 7A had only 37 (12.0%) patients included in this study.

The 31 years to 40 years age category had the largest number of patients 78 (25.24%) admitted to the CCU, followed by 46 (14.89%) patients in age category 41 years to 50 years old as shown in table 4.1. The mean length of stay across the CCUs was 7.3 days [IQR=1-37]. The inpatient department of KNH was the source of most patients into the CCU. There were 217(70.23%) patients who were admitted to the CCU from other wards in KNH and referrals from another health care facility while the other 92 (29.77%) patients were admitted to the CCU directly from the community. The mean age of the study patients was 40.61 years and standard deviation of 17.47. The main CCU admitted 182 (58.9%) patients who participated in the study, while the medical CCU 8A admitted 90 (29.1%) and the medical CCU 7A admitted 37 (12.0%).

4.3 Clinical characteristics of the study patients.

More than half (54.43%, n=162) of the patients had been admitted to a health facility 90 days before the present admission. The proportion of patients that had undergone intubation was 81.88% (n=253) as shown in table 4.2.

A majority of patients were catheterized 291 (94.17%); 277 (95%) had a urinary catheter, 209 (71.8%) had a peripheral vascular catheter, 112 (38.4%) had a central vascular catheter and 26 (8.9%) had a hemodialysis catheter.

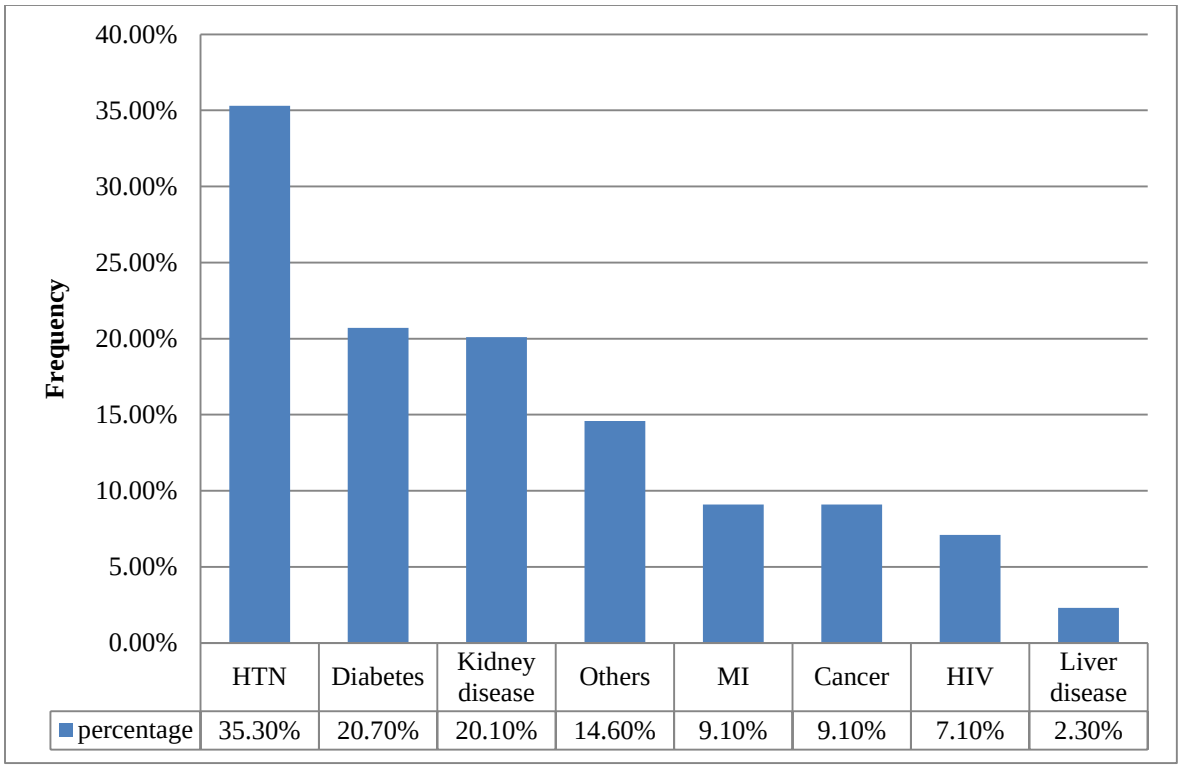
Table 4. 2: Clinical characteristics of critical care patients at the Kenyatta National Hospital

Characteristic	n	(%)
Hospitalized in last 90 days(N=309)	162	52.43
Use AMA* in last 90 days (N=309)	159	51.46
Referral from other KNH wards	129	59.45
Referral from other health facilities	88	40.55
TOTAL	**217**	**100**
Co-morbidity		
Yes	229	74.11
No	80	25.89
TOTAL	**309**	**100**
catheterization	291	94.17
intubation	253	81.88

***AMA-antimicrobial agent**

4.3.1 Co-morbidities among the study patients

A majority 229 (74.11%) of study patients had at least one co-morbidity. The most common co-morbidity was hypertension with 81(35.30%) patients, 47 (20.7%) patients had diabetes while 46 (20.1%) had kidney disease as shown in figure 4.2. There were 33 (14.6%) patients with co-morbidities that were classified under others. These included asthma, anemia, gastric ulcers, epilepsy, myasthenia gravis, psychosis and systemic lupus erythromatosus (SLE)

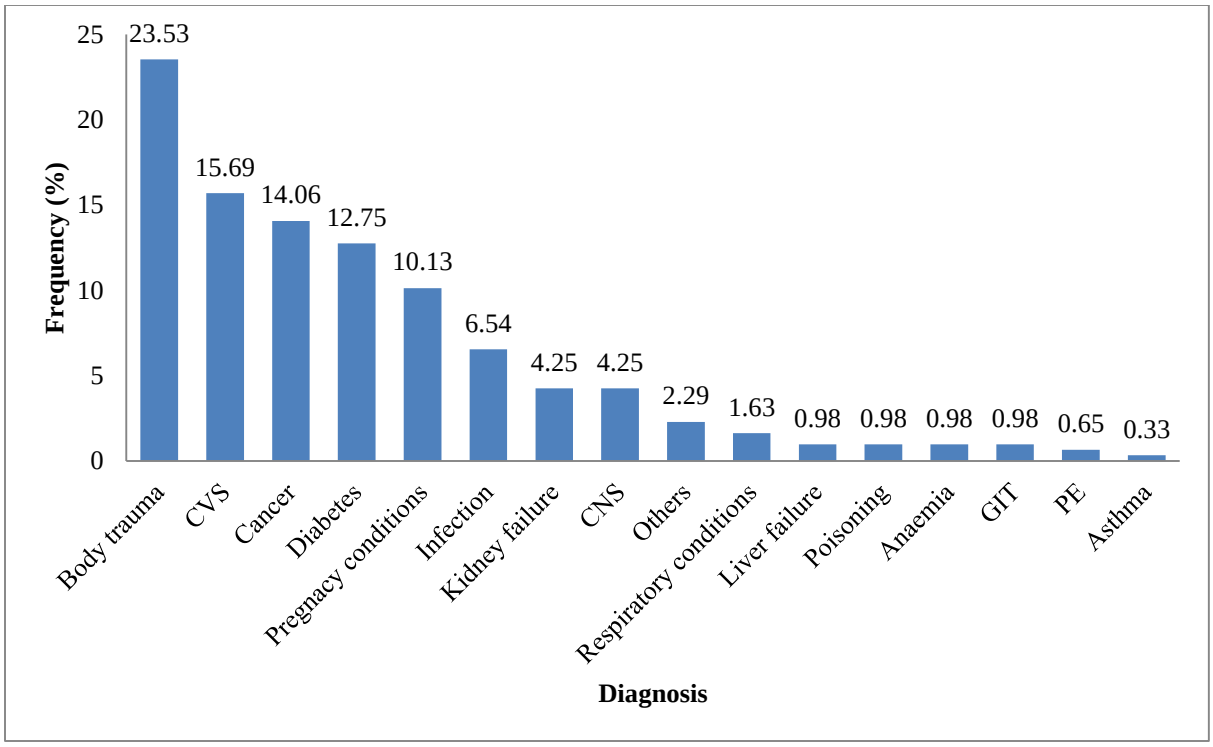


***HTN-Hypertension, MI-Myocardial Infarction, HIV-Human Immunodeficiency Virus**

Figure 4. 2: Co-morbidities in critical care patients at Kenyatta National Hospital.

4.3.2 Diagnosis at admission among the study patients.

The CCUs at KNH admits patients with various conditions. The most common diagnosis at admission in the study population was trauma (consisting of motor vehicle accidents, fights, gunshot wounds, and domestic violence) with 72 (23.53%) patients. The patients who presented with cardiovascular-related conditions were 48 (15.69%), whereas 43 (14.06%) patients presented with cancer, 39 (12.75%) patients had been admitted due to diabetes and lastly 31(10.13%) patients were admitted to the CCU due to pregnancy-related conditions (Figure 4.3). The majority of patients admitted due to trauma were male 72 (87.5%) whereas more females 39 (69.2 %) had diabetes.



***CVS-Cardio-vascular system, CNS- Central nervous system, GIT-Gastro-intestinal tract, PE-Pulmonary Embolism**

Figure 4. 3: Diagnosis in critical care patients at the Kenyatta National Hospital.

4. 4 Prevalence of antimicrobial prescribing at the Critical Care Unit

Antimicrobial agents were prescribed for 304 (98.4%) of the study patients with 150 (49.5%) patients receiving more than one antimicrobial agent at admission. Empiric prescribing was practiced for all the 304 patients at admission into the Kenyatta National Hospital.

4.4.1 Types of antimicrobial agents prescribed

There were 235(36.83%) prescription encounters containing ceftriaxone followed by 108 (16.93%) with metronidazole and 79(12.38%) with meropenem as shown on Table 4.3.

Table 4. 3: Antimicrobial agents prescribed in critical care at Kenyatta National Hospital.

Antimicrobial agent	**n**	**(%)**
Ceftriaxone	235	36.83
Metronidazole	108	16.93
Meropenem	79	12.38
Amoxicillin clavulanic acid	57	8.93
Cefuroxime	32	5.02
Amikacin	19	2.98
Clarithromycin	13	2.04
Ceftazidime	13	2.04
Vancomycin	12	1.88
Ciprofloxacin	12	1.88
Flucloxacillin	10	1.57
Clindamycin	8	1.25
Fluconazole	8	1.25
Piperacillin/Tazobactam	7	1.10
Gentamycin	6	0.94
Erythromycin	4	0.63
Linezolid	4	0.63
Nitrofurantoin	4	0.63
Levofloxacin	3	0.47
Cefazolin	3	0.47
Benzylpenicillin	1	0.16
Total	**638**	**100**

4.4.2 Class of antimicrobial agents prescribed

The most prescribed antimicrobial class was the cephalosporins with 283(44.36%) prescription encounters of which the third generation ceftriaxone accounted for 83%. The second most prescribed class was the nitroimidazoles (mainly metronidazole; 108 (16.93%) followed by the carbapenems (mainly meropenem 79 (12.38%).

Figure 4.4 shows the classes of antimicrobials prescribed with the furadontoins 4 (0.63%) and oxazolidinones 4 (0.63%) having the least proportion of prescribing.

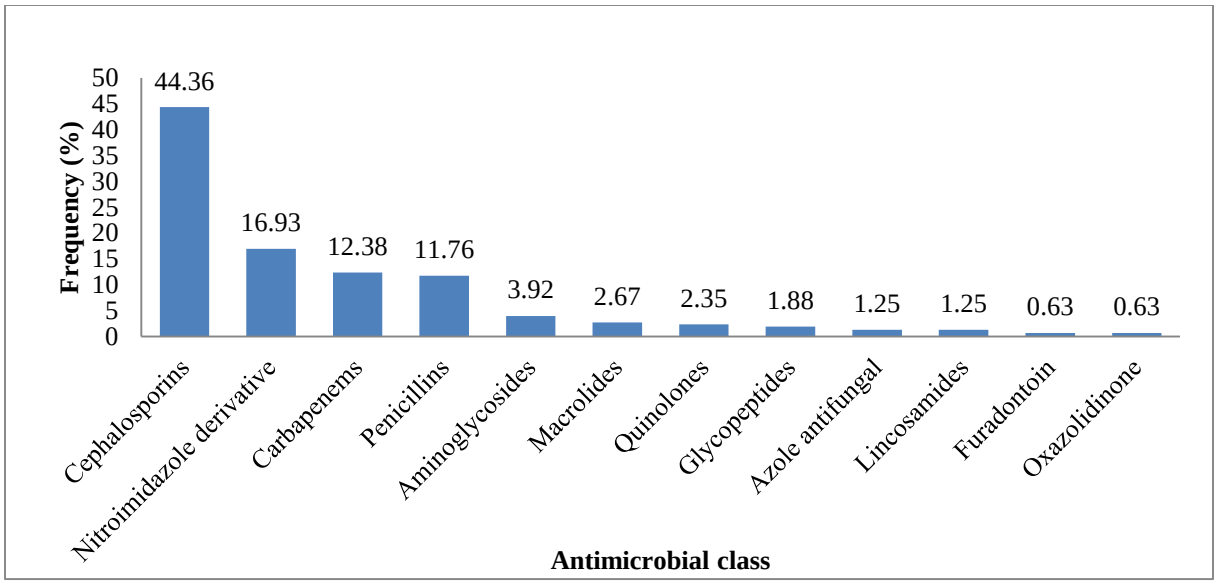


Figure 4. 4: Classes of antimicrobial agents prescribed at Kenyatta National Hospital.

4.4.3 Number of antimicrobial agents prescribed

The number of antimicrobial agents prescribed per patient varied between one and six throughout the hospital stay. The number of patients who received one antimicrobial agent was 108 (34.95%) while 111 (35.92%) patients received two antimicrobial agents.

More than half of patients were on one or two antimicrobial agents (n=219, 70.9%). Few patients 30 (9.7%) were prescribed for four (4) to six (6) antimicrobial agents. The number of antimicrobial agents prescribed per patient throughout the hospital stay is shown in figure 4.5.

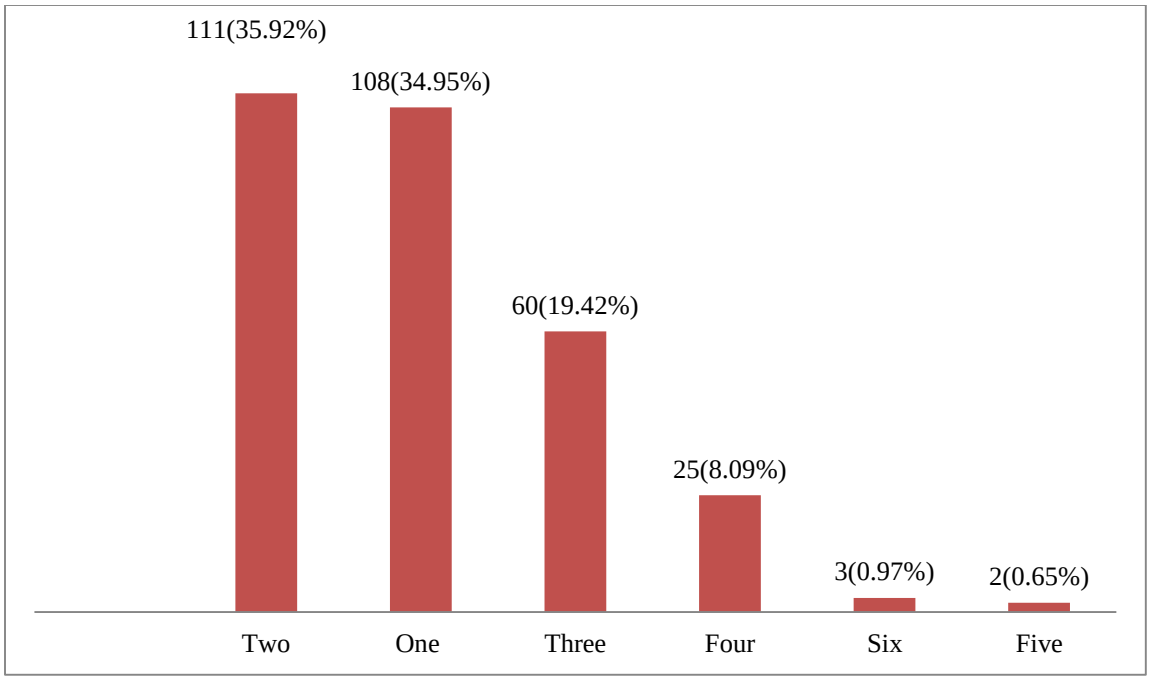


Figure 4. 5: Number of antimicrobial agents prescribed at Kenyatta National Hospital

4.5 Culture and sensitivity tests

At admission to the CCUs, a culture and sensitivity test (CST) was performed for 158 (51.1%) patients. A further 29 (9.4%) patients, had a second CST requested while only 5 (17.9%) patients had a third request for CST. It took 72 hours [IQR=24-336] on average before a request for CST was made by the health care providers.

The turnaround time for the CST report to be received in the ward was 24 hours [IQR=24-48]. In 142 (89.3%) patients, the CST report was received in the ward in 24 to 48 hours while in 5 (3.2%) patients; it took 120 to 192 hours.

4.5.1 Micro-organisms isolated from patient samples.

The positivity rate from the first CST was 42.7%. A micro-organism was isolated in 67(42.7%) of the first CST requested. The most commonly isolated microorganisms were *Klebsiella pneumonia* (23.9 %) followed by *Acinetobacter baumanii (*16.4%) and *Escherichia coli* (10.5%) (Figure4.6).

Other micro-organisms isolated included *Staphylococcus hominis, Staphylococcus sciuri, Citrobacter freundii, pseudomonas stutzeri, and staphylococcus haemolyticus*.

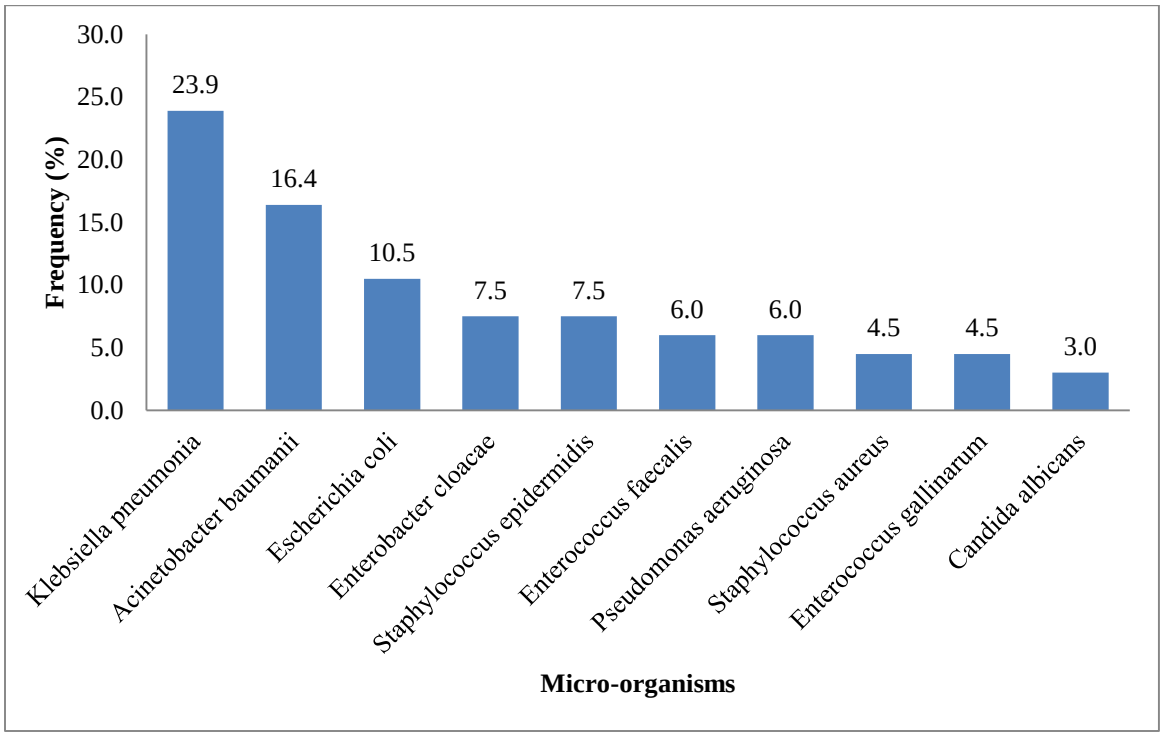


Figure 4. 6: Micro-organisms isolated from critical patients at Kenyatta National Hospital.

4.5.2 Sensitivity patterns of microorganisms isolated in culture and sensitivity testing.

A micro-organism was isolated in 67(42.7%) of the first CST requested. The sensitivity profile of these microorganisms is shown in Table 4.4. The top three microorganisms isolated were *Klebsiella pneumonia 16* (23.9%), *Acinetobacter baumanii* 11(16.4%), *and Escherichia coli* 7(10.4%). A large proportion of the *Klebsiella pneumonia* isolates 11(67%) were sensitive to meropenem, 9(56%) isolates were sensitive to amikacin and 7(44%) isolates were sensitive to ciprofloxacin.

Of the *Acinetobacter baumanii* isolated 9 (82%) were sensitive to amikacin while 6 (55%) were sensitive to meropenem. Only 3 (27%) isolates were sensitive to ceftazidime and cefepime respectively. All the *A. baumanii* isolates were resistant to the following antimicrobials agents: amoxicillin-clavulanic acid, ceftriaxone, cefuroxime, cefotaxime and these three reserve antimicrobials; tigecycline, linezolid and teicoplanin.

Most of the *Escherichia coli* isolates were sensitive to meropenem 6(86%), amikacin 5(71%), and 3(43%) to gentamycin. None of the *E. coli* isolates were sensitive to ceftazidime, cefepime, ceftriaxone, cefuroxime, and levofloxacin among other antimicrobial agents tested against.

All the 3 (100%) *Staphylococcus aureus* isolated were sensitive cotrimoxazole, levofloxacin, clindamycin, gentamycin, erythromycin, teicoplanin, tetracycline, and linezolid while only 1 (33%) isolate was sensitive to tigecycline. Among the organisms isolated,only *Staphylococcus epidermidis* was sensitive to tigecycline, levofloxacin, and colistin. None of the *K. pneumonia* isolate was sensitive to linezolid, ceftazidime, ceftriaxone, and cefuroxime.

Table 4. 4: Sensitivity of microorganisms from critical patients at Kenyatta National Hospital.

Microorganism	Isolates n	Sensitive antimicrobial agents	n (%)	Resistant antimicrobial agents
Klebsiella pneumonia	16	Meropenem Amikacin Ciprofloxacin Piperacillin/Tazobactam Gentamycin Amoxicillin clavulanic acid	11(69%) 9(56%) 7(44%) 5(31%) 4(25%) 3(19%)	Ceftriaxone Ceftazidime Cefuroxime Clindamycin Linezolid Erythromycin Benzyl penicillin
Acinetobacter baumanii	11	Amikacin Meropenem Ceftazidime Cefepime	9(82%) 6(55%) 3(27%) 3(27%)	Ceftriaxone Cefuroxime Cefotaxime Levofloxacin Amoxicillin clavulanic acid Clindamycin Benzyl penicillin
Escherichia coli	7	Amikacin Meropenem Nitrofurantoin Gentamycin	6(86%) 5(71%) 4(57%) 3(43%)	Ceftriaxone Ceftazidime Cefuroxime Cefepime Levofloxacin Benzyl penicillin
Enterobacter cloacae	5	Meropenem Ciprofloxacin Amikacin	5(100%) 5(100%) 3(60%)	Ceftriaxone Ceftazidime Benzyl penicillin Ciprofloxacin
Staphylococcus epidermidis	5	Levofloxacin Teicoplanin Gentamycin Clindamycin Tigecycline Vancomycin Linezolid Erythromycin Clindamycin	4(80%) 4(80%) 4(80%) 3(60%) 3(60%) 3(60%) 3(60%) 3(60%) 3(60%)	Ceftriaxone Ceftazidime Cefuroxime Ciprofloxacin Amoxicilline clavulanic acid Meropenem Amikacin Colistin

4.6 Risk categorization of study participants.

None of the patients in this study was categorized according to the KNH guideline to antimicrobial therapy from the patients' medical records. However, for the sake of conducting the analysis, it was necessary to categorize the patients based on the criteria in the KNH guideline. The matrix on Table 3.2 (page 25) was developed based on the existing guideline and was used to derive the patient risk categories. The patients were categorized into the four classes namely; risk category one for patients with no risk for infections, risk category two for patients with at least one co-morbidity but with no infection. Patients in risk category three have co-morbidity and a risk factor for infection and lastly risk category four patients are those with a confirmed infection at admission. Figure 4.7 shows the distribution of the patients according to the four risk categories.

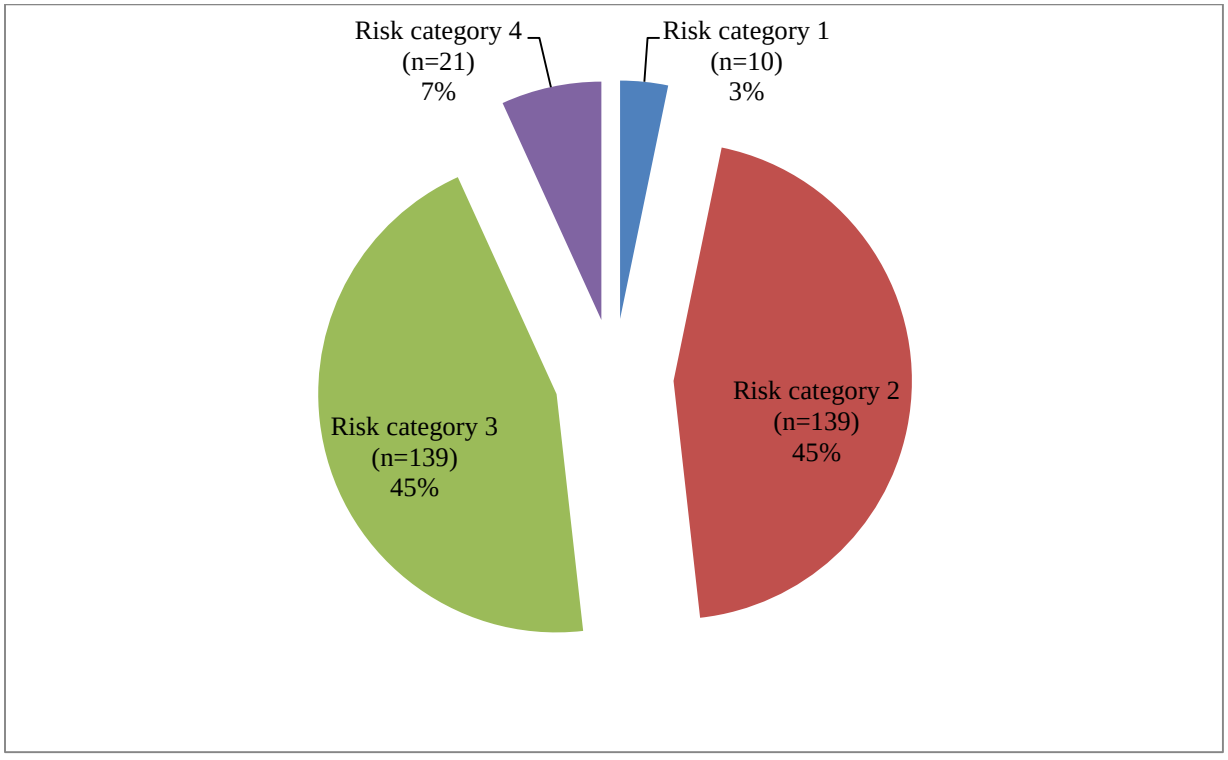


Figure 4. 7: Risk categorization of critical care patients at Kenyatta National Hospital

4.6.1 Socio-demographic characteristics of patients on risk categorization.

The main CCU admitted 182 (58.9%) of the study patients, while medical CCU 8A and medical CCU 7A admitted 90 (29.1%) and 37 (12%) respectively. There were more males 158 (51.13%) than females 151 (48.87%) admitted in the CCU and the difference was statistically significant **(P<0.032).** There were 76 (50.3%) females that were classified under risk category two which was higher than that of males 63 (39.9%). This was also observed in risk category four (4) where the number of females 14 (9.3%) was more than that of males 7 (4.4%). There were more males than females classified under risk categories one (1) and three (3) as shown in Table 4.5. The main CCU admitted 116(63.7%) patients that were classified under risk category three (3) while the medical CCUs (7A &8A) admitted a larger proportion of patients under risk category two.

Table 4. 5: Demographic characteristics on risk categorization at Kenyatta National Hospital

Characteristic	Risk Category 1	Risk Category 2	Risk Category 3	Risk Category 4	Total	P
Gender						
Male	7 (4.4%)	63(39.9%)	81(51.3%)	7(4.4%)	158	**0.032**
Female	3(2.0%)	76(50.3%)	58(34.4%)	14(9.3%)	151	
Age category						
13 to 20 years	2(5.4%)	17(46%)	14(37.8%)	4(10.8%)	37	
21 to 30 years	1(1.6%)	23(36.5%)	31(49.2%)	8(12.7%)	63	
31 to 40 years	4(5.1%)	36(46.2%)	31(39.7%)	7(9%)	78	
41 to 50 years	3(6.5%)	14(30.4%)	29(63%)	0	46	**0.019**
51 to 60 years	0	19(54.3%)	15(42.9%)	1(2.9%)	35	
61 to 70 years	0	19(59.4%)	12(37.5%)	1(3.1%)	32	
Above 70 years	0	11(61.1%)	7(38.9%)	0	18	
Ward						
Main CCU	5(2.8%)	46(25.3%)	116(63.7%)	15(8.2%)	182	
Medical CCU 7A	3(8.1%)	23(62.2%)	9(24.3%)	2(5.4%)	37	0.067
Medical CCU 8A	2(2.2%)	70(77.8%)	14(15.6%)	4(4.4%)	90	

4.6.2 Clinical characteristics and patient risk category.

Risk category one (1) is assigned to patients who have no clear risk factors for infections hence may not require an antimicrobial agent. Such patients should not have been hospitalized or used an antimicrobial agent in the recent past (90 days) prior to the hospitalization at Kenyatta National Hospital (KNH). The main source of patients to the CCU was the inpatient wards of KNH. A majority of the patients 217(70.23%) were admitted to the CCU from other KNH wards and referrals from other health facilities. Only 92 (29.77%) patients were admitted directly to the CCU (Table 4.6).

The difference in characteristics of patients' hospitalization in the last 90 days and use of antimicrobial agents prior to CCU admission across the four risk categories was statistically significant **P<0.001.** The presence of comorbidities in the critical care patients across the risk categories was also statistically significant **P<0.001.**

Table 4. 6: Patients medical characteristics across risk categories

Characteristic	Risk Category 1	Risk Category 2	Risk Category 3	Risk Category 4	Total	P
Hospitalized in last 90 days	0 (0.0%)	86 (53.1%)	60 (37.0%)	16 (9.9%)	162	**<0.001**
Use AMA use in last 90 days	0 (0.0%)	82 (51.6%)	61 (38.4%)	16 (10.0%)	159	**<0.001**
Direct admission to CCU	4 (4.4%)	38 (41.3%)	44 (47.8%)	6 (6.5%)	92	0.739
Co-morbidity	0 (0.0%)	127 (55.7%)	88 (38.6%)	13 (5.7%)	228	**<0.001**
Patient catheterized	7 (2.4%)	133 (45.7%)	131 (45.0%)	20 (6.9%)	291	**0.007**
Patient intubation	7 (2.8%)	111 (43.9%)	117 (46.3%)	18 (7.1%)	253	0.565

4.6.3 Antimicrobial prescribing patterns at admission across risk categories

The proportion of critical care patients prescribed for an antimicrobial agent at admission across the risk categories is shown in figure 4.8. The total number of patients put on at least one antimicrobial agent at admission was 304 (98.4%). Those who got a second antimicrobial agent at admission were 143 (49.5%). There was no statistically significant difference in the patterns of antimicrobial prescribing at admission across the four risk categories (p=0.851).

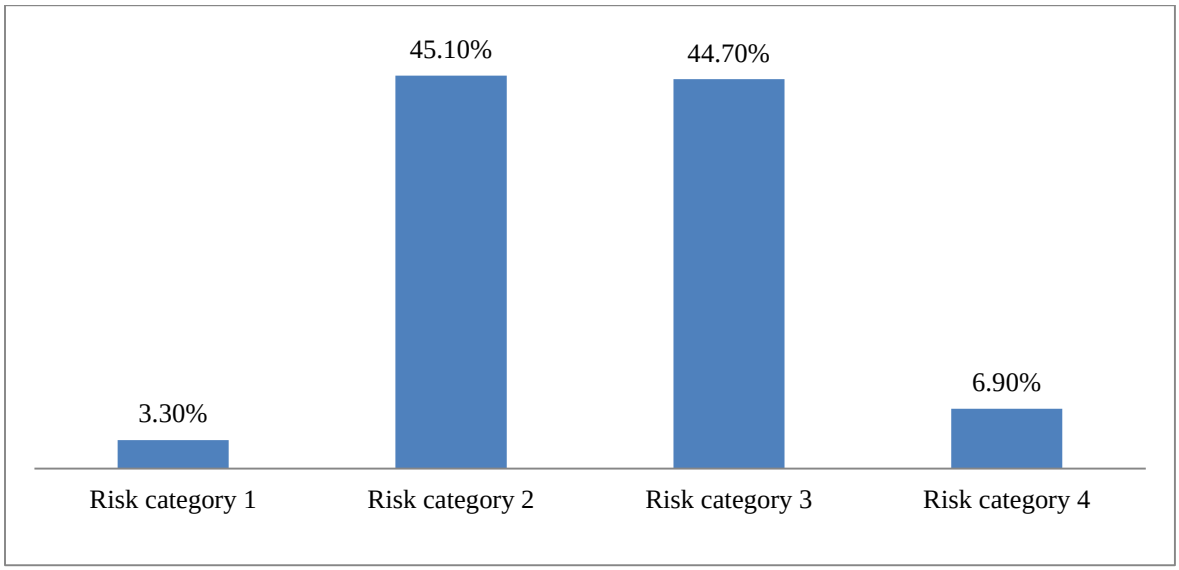


Figure 4. 8: Antimicrobial prescribing patterns at admission across patients risk categories.

4.6.4 Types of antimicrobial agents prescribed across risk categories

Ceftriaxone was the most commonly prescribed antimicrobial agent 185 (59.9%), followed by amoxicillin-clavulanic acid 39 (12.6%), meropenem 24 (7.8%), cefuroxime 20 (6.5%) and metronidazole 13 (4.2%) as shown in table 4.7. None of the participants in risk category one (1) was prescribed for amoxicillin-clavulanic acid, amikacin, cefuroxime, and meropenem at admission.

Table 4. 7: Types of antimicrobial agents prescribed at admission across risk categories.

Characteristic	Risk Category 1	Risk Category 2	Risk Category 3	Risk Category 4	TOTAL
Ceftriaxone	7(3.8%)	79(42.7%)	88(427.6%)	11(6.0%)	185
*Amoxicillin clavulanic	0(0.0%)	17(45.6%)	20(51.3%)	2(5.1%)	39
Meropenem	0(0.0%)	13(54.2%)	7(29.2%)	4(16.7%)	24
Cefuroxime	0(0.0%)	8(40.0%)	11(55.0%)	1(5.0%)	20
Metronidazole	1(7.7%)	6(46.2%)	6(46.2%)	0(0.0%)	13
Ceftazidime	0(0.0%)	5(83.3%)	1(16.7%)	0(0.0%)	6
Flucloxacillin	0(0.0%)	3(60.0%)	0(0.0%)	2(40.0%)	5
Gentamycin	0(0.0%)	2(66.7%)	1(33.3%)	0(0.0%)	3
Ciprofloxacin	1(33.3%)	1(33.3%)	1(33.3%)	0(0.0%)	3
Cefazolin	1(33.3%)	0(0.0%)	1(33.3%)	1(33.3%)	3
Levofloxacin	0(0.0%)	1(50.0%)	1(50.0%)	0(0.0%)	2
Amikacin	0(0.0%)	1(100.0%)	0(0.0%)	0(0.0%)	1
Clarithromycin	0(0.0%)	1(100.0%)	0(0.0%)	0(0.0%)	1

* **Amoxicillin clavulanic acid**

4.7 Indicators for antimicrobial prescribing

4.7.1 Documentation of antimicrobial indication in patient records

The indication for prescribing an antimicrobial agent was documented in only 66 (21.4%) of the patients sampled. The distribution of the patents is as shown in table 4.8. The difference in documenting the indication across the wards was not statistically significant. P=0.898

Table 4. 8: Antimicrobial indication for critical patients at Kenyatta National Hospital.

Ward	Documented indication	P-value
Main CCU	33(50%)	0.898
Medical CCU 8A	22(33.3%)	
Medical CCU 7A	11(16.7%)	

4.7.2 Use of generic name in prescribing

There were 651 prescribing encounters in this study, 434 (66.7%) of which the generic name was used while in 217 (33%) the brand names of the antimicrobial agents was used. There were antimicrobial agents that were most commonly prescribed using brand names. These were metronidazole with 96 (85%) of the prescriptions made using the brand name and amoxicillin-clavulanic acid with 58 (98%). (Table 4.9)

Table 4. 9: Prescribing using generic name for critical patients at Kenyatta National Hospital.

Antimicrobial agent	Number of prescriptions	Use of INN n, (%)
Ceftriaxone	231	201(87%)
Metronidazole	113	17(15%)
Meropenem	77	60(78%)
*Amoxicillin clavulanic	59	1(2%)
Cefuroxime	40	26(86.7)
Amikacin	20	19(95%)
Clarithromycin	18	18(100%)
Ceftazidime	15	15(100%)
Vancomycin	13	13(100%)
Ciprofloxacin	13	12(92.3%)
Flucloxacillin	10	6(60%)
Piperacillin/Tazobactam	8	2(25%)
Nitrofurantoin	8	8(100%)
Fluconazole	7	7(100%)
Clindamycin	6	6(100%)
Gentamycin	6	6(100%)
Erythromycin	4	4(100%)
Cefazolin	4	4(100%)
Linezolid	4	4(100%)
Levofloxacin	3	3(100%)
Benzylpenicillin	2	2(100%)
Total	**651**	**434(66.7)**

* **Amoxicillin clavulanic acid**

4.7.3 Documentation of antimicrobial therapy review in the patients' records.

Only 36 (11.7%) patients had a review or stoppage of antimicrobial therapy documented in their medical records. In a majority of the patients, 272 (88.3%) there was no documented instruction to stop the use of an antimicrobial agent even when a new prescription had been issued (Figure 4.9). In the medical CCU 8A, 16 (44%) patients had antimicrobial therapy reviews documented followed by 14 (38.9%) in the main CCU and finally 6 (16.7%) in the medical CCU 7A. The variation in the frequency of documentation across the 3 wards sampled was statistically significant. **P=0.031**.

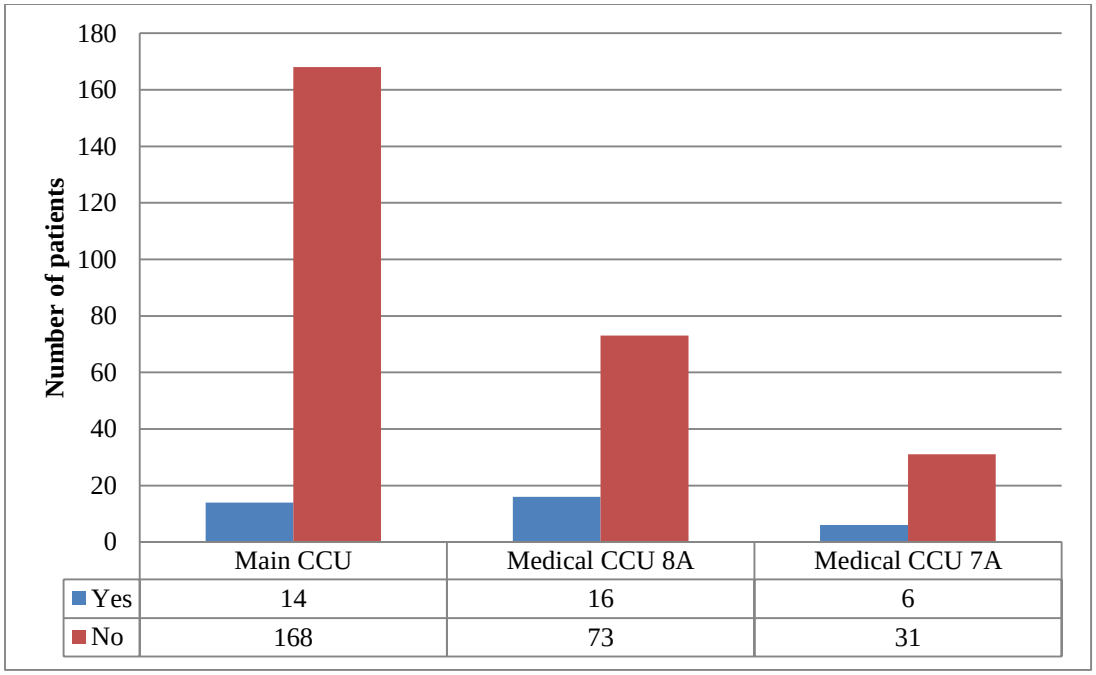


Figure 4. 9: Documented therapy review for critical patients at Kenyatta National Hospital.

4.7.4 Prescribing based on culture and sensitivity testing

A culture and sensitivity test (CST) was requested for 158 (51.1%) of patients at admission to the CCU. In 106 (67%) patients, the choice of the antimicrobial agent prescribed was informed by the result of CST whereas for 42(33%) patients, the results did not inform the choice of antimicrobial agent prescribed (Figure 4.10).

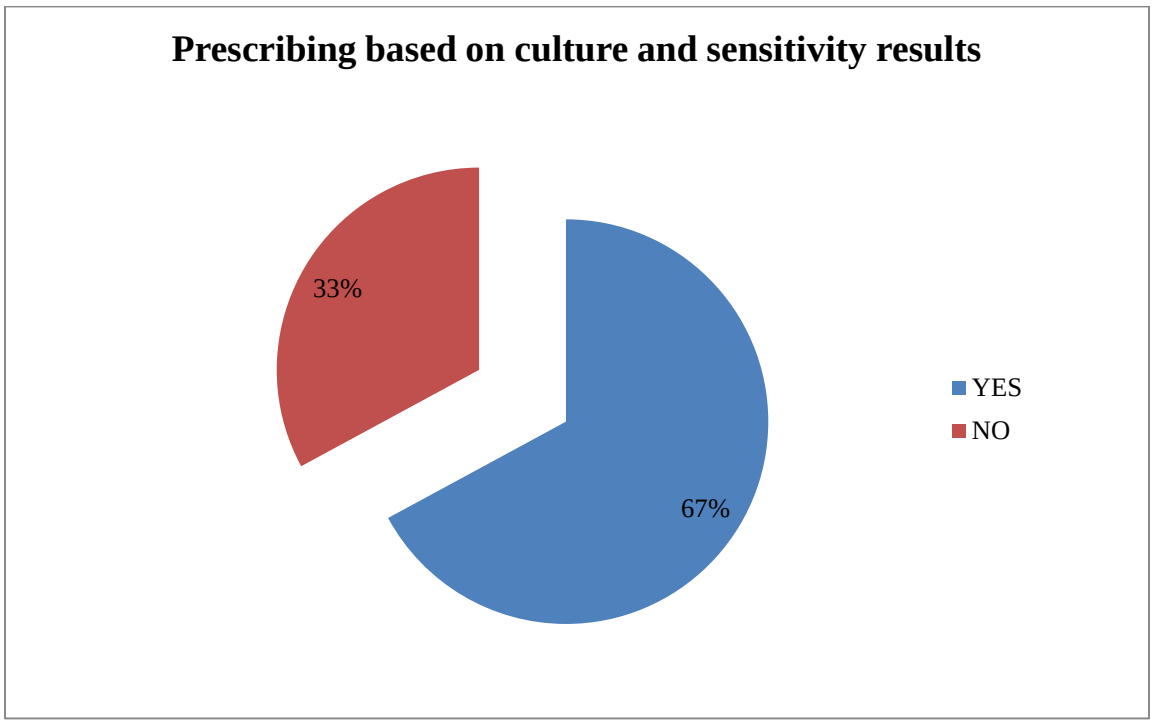


Figure 4. 10: Prescribing on culture and sensitivity testing at Kenyatta National Hospital

There was a statistically significant difference in the way the results of the culture and sensitivity testing was used to influence the choice of antimicrobial agent to prescribe across the three (3) CCUs in the study. **P>001**. In the main CCU, 47 (47.5%) CST results guided antimicrobial agent prescribing while in the medical CCU 8A, the results influenced the choice of antimicrobial agent for 39 (38.6%) patients (Table 4.10).

Table 4. 10: Prescribing based on sensitivity testing at Kenyatta National Hospital wards.

	Antimicrobial choice based on CST results		P-Value
Ward	Yes	No	
Main CCU	49 (46.2%)	23 (44.2%)	**>0.001**
Medical CCU 8A	41 (38.7%)	20 (38.5%)	
Medical CCU 7A	17 (16.0%)	7 (17.4%)	
TOTAL	**107**	**50**	

4.8 Guideline compliance

The antimicrobial agent prescriptions were compared with the KNH guide to antimicrobial therapy at CCU to determine compliance. Compliance was assessed based mainly on the choice of antimicrobial agent for empiric management at admission and targeted treatment in the CCU if the patient was previously admitted in the other KNH wards.

4.8.1 Compliance of targeted antimicrobial prescribing to guideline in Critical Care Unit

The first antimicrobial change at admission to the CCUs was used to assess compliance of antimicrobial prescribing for targeted treatment to the KNH guide for antimicrobial therapy. There was change of antimicrobial therapy for 125(40.5%) of patients at admission into the CCU. Of the 125 patients who had a new prescription for antimicrobial therapy at CCU, compliance was observed in 52(41.6%) patients. Only 14 (4.5%) patients had a further change of antimicrobial therapy with compliance being observed in 6 (42.9%) patients.

4.8.2 Compliance of empiric prescribing to guideline

At admission 304 (98.4%) patients were prescribed for an antimicrobial agent. There was compliance of empiric prescribing to guideline in 76 (25%) of the study patients as shown in figure 4.11.

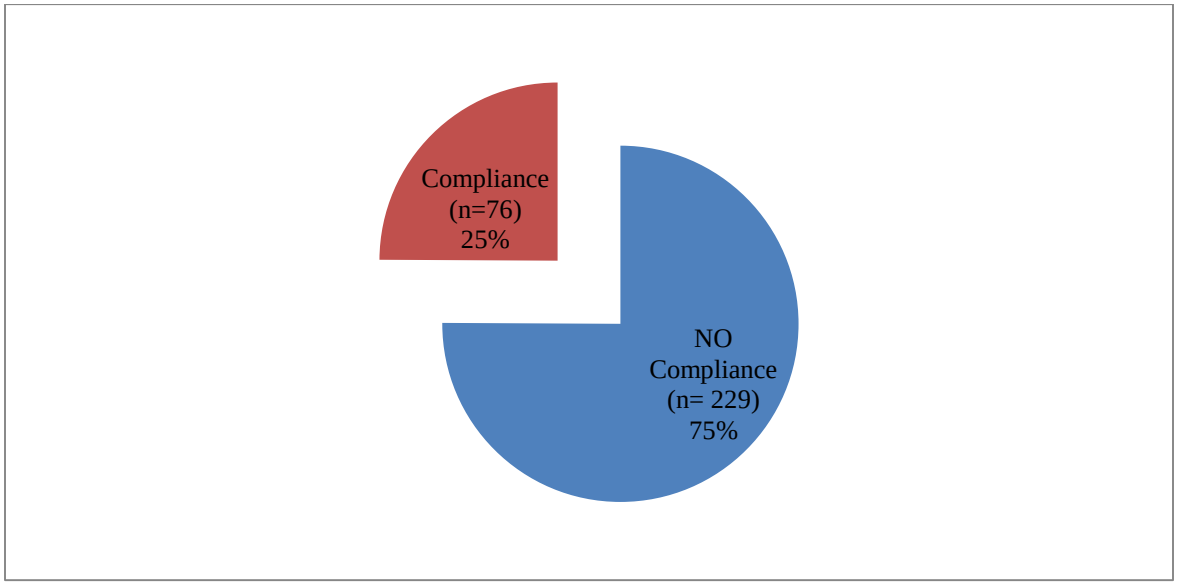


Figure 4. 11: Compliance of antimicrobial empiric prescribing at Kenyatta National Hospital

4.8.3 Compliance to guideline for the micro-organism isolated.

Only 22 (21%) prescriptions complied with the guideline recommendation of the antimicrobial agent to be prescribed for the micro-organism isolated (figure4.12). The variation in compliance that was noted across the 3 CCUs was not statistically significant (P=0.736).

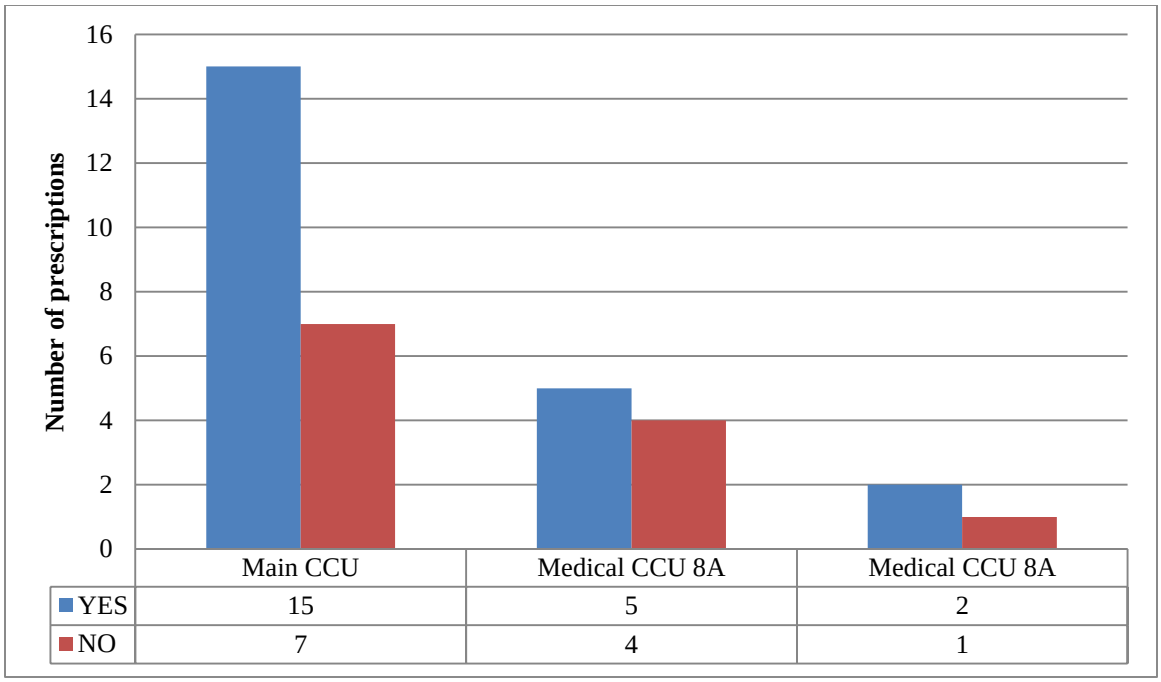


Figure 4. 12: Guideline compliance for micro-organism isolated at Kenyatta National Hospital

4.9 Factors affecting compliance to the guideline in antimicrobial prescribing.

Results in **Table 4.11** below reveals that out of 158 (51.1%) of males, 34 (21.3%) of the participants complied with the guideline while 43 (28.7%) of the females complied with the guideline out of 151 (48.9%) female participants. On age category, 8 (21.6%) of the participants complied with the guideline and were in age category 13 years old to 20 years old, 14 (22.2%) of the participants in age category 21 years to 30 years complied with the guideline, 19 (24.7%) of the participants in age category 31 years to 40 years complied with the guideline, 9 (19.6%) of the participants were in age category 41 years to 50 years old and complied with the guideline. Only 9 (27.3%) participants in age category 51 years to 60 years, 11 (35.5%) participants in age category 61 years to 70 years old and 6 (33.3%) participants in category 71 years and above complied with the guideline.

A large majority of patients 224 (73.9%) had a co-morbidity of which 61 (27.2%) complied with the guideline. For the 287 (95.1%) patients who had at least one form of catheter on them, 72 (25.1%) complied with the guideline. Those who were admitted direct to CCU were 92 (29.8%) and of these participants, 17 (18.5%) complied with the guideline. Those who were admitted from other wards in KNH were 129 (59.4%) and of those 41(31.5%) participants complied with the guideline. The results further reveal that those who were in risk category three were less likely (UOR=0.4; 95%CI, 0.14-0.97; p-value=**0.043**) to comply with the guideline as compared to risk category four. Bivariate analysis in Table 4.11 showed a significant association between compliance to guideline with the patients in risk category three, those who were recently on antimicrobial agents, had comorbidity and a recent hospital stay.

Table 4. 11: Factors affecting compliance to guideline on antimicrobial prescribing in CCU.

Variables	Total n (%)	Compliance No n (%)	Compliance Yes n (%)	UOR(95%CI)	P-value
Gender					
Male	158(51.1)	124(78.7)	34(21.3)	ref	
Female	151(48.9)	108(71.3)	43(28.7)	1.5(0.88-2.51)	0.138
Age Category					
13-20 years	37(12.0)	29(78.4)	8(21.6)	ref	
21-30 years	63(20.4)	49(77.8)	14(22.2)	1.1(0.39-2.77)	0.944
31-40 years	78(25.3)	59(75.3)	19(24.7)	1.2(0.46-3.03)	0.720
41-50 years	46(14.9)	37(80.4)	9(19.6)	0.9(0.30-2.56)	0.818
51-60 years	35(11.3)	25(72.7)	9(27.3)	1.4(0.46-4.06)	0.583
61-70 years	32(10.3)	21(64.5)	11(35.5)	1.9(0.68-5.83)	0.208
Above 70 years	18(5.8)	12(66.7)	6(33.3)	1.8(0.52-6.35)	0.353
Comorbidity					
No	79(26.1)	65(82.3)	14(17.7)	ref	
Yes	224(73.9)	163(72.8)	61(27.2)	1.7(0.91-3.32)	0.095
Risk categorization					
Risk Category one	10(3.3)	7(70.0)	3(30.0)	0.7(0.14-3.49)	0.660
Risk Category two	139(44.9)	98(70.8)	41(29.2)	0.7(0.26-1.74)	0.411
Risk Category three	139(44.9)	114(81.8)	25(18.2)	0.4(0.14-0.97)	**0.043**
Risk Category four	21(6.9)	13(61.9)	8(38.1)	ref	
Catheterization					
No	15(4.9)	12(80.0)	3(20.0)	0.8(0.21-2.72)	
Yes	287(95.1)	215(74.9)	72(25.1)	ref	0.658
Intubation					
No	55(18.0)	45(81.8)	10(18.2)	0.6(0.29-1.29)	0.205
Yes	250(82.0)	184(73.6)	66(26.4)	ref	
Direct Admission to CCU					
No	217(70.2)	156(72.0)	61(28.0)	ref	
Yes	92(29.8)	75(81.5)	17(18.5)	0.6(0.32-1.07)	0.082
Admitted from to CCU					
Other wards in KNH	129(59.4)	88(68.5)	41(31.5)	1.8(0.95-3.47)	0.073
Transfer in from another HF	88(40.6)	70(79.8)	18(20.2)	ref	

****Statistically significant at P-value<0.05; ref, Reference Category; UOR, Bivariate logistic regression****

4.10 Assessing the predictors of guideline compliance

The results in Table 4.12 below show that there was no factor which was associated with guideline compliance.

Table 4. 12: Predictors of guideline compliance in antimicrobial prescribing at KNH

Variables	Overall N (%)	Compliance n (%)	UOR(95%CI)	P-value	AOR(95%CI)	P-value
Gender						
Male	158(51.1)	34(21.3)	ref		ref	
Female	151(48.9)	43(28.7)	1.5(0.88-2.51)	0.138	1.6(0.78-3.15)	0.210
Age Category						
13-20 years	37(12.1)	8(21.6)	ref		ref	
21-30 years	63(20.7)	14(22.2)	1.1(0.39-2.77)	0.944	0.9(0.29-3.16)	0.961
31-40 years	78(25.3)	19(24.7)	1.2(0.46-3.03)	0.72	0.8(0.26-2.42)	0.676
41-50 years	46(15.1)	9(19.6)	0.9(0.30-2.56)	0.818	1.2(0.32-4.73)	0.605
51-60 years	35(11.3)	9(27.3)	1.4(0.46-4.06)	0.583	2.4(0.66-8.63)	0.757
61-70 years	32(10.3)	11(35.5)	1.9(0.68-5.83)	0.208	2.4(0.49-10.86)	0.184
Above 70 years	18(5.8)	6(33.3)	1.8(0.52-6.35)	0.353	2.3(0.49-10.86)	0.289
Comorbidity						
No	79(26.1)	14(17.7)	ref		ref	
Yes	224(73.9)	61(27.2)	1.7(0.91-3.32)	0.095	1.7(0.63-4.41)	0.301
Risk categorization						
Risk Category one	10(3.3)	3(30.0)	0.7(0.14-3.49)	0.66	2.1(0.21-20.03)	0.532
Risk Category two	139(44.9)	41(29.2)	0.7(0.26-1.74)	0.411	0.7(0.17-2.53)	0.539
Risk Category three	139(44.9)	25(18.2)	0.4(0.14-0.97)	0.043	0.5(0.11-1.85)	0.273
Risk Category four	21(6.9)	8(38.1)	ref		ref	
Catheterization						
No	15(4.9)	3(20.0)	0.8(0.21-2.72)		0.5(0.09-2.65)	0.400
Yes	287(95.1)	72(25.1)	ref	0.658	ref	
Intubation						
No	55(18.0)	10(18.2)	0.6(0.29-1.29)	0.205	0.5(0.21-1.28)	0.154
Yes	250(82.0)	66(26.4)	ref		ref	
Direct Admission to CCU						
No	217(70.2)	61(28.0)	ref		ref	
Yes	92(29.8)	17(18.5)	0.6(0.32-1.07)	0.082	NA	NA
Admitted from to CCU						
Other wards in KNH	129(59.4)	41(31.5)	1.8(0.95-3.47)	0.073	1.8(0.87-3.67)	0.117
Transfer in from another HF	88(40.6)	18(20.2)	ref		ref	

****Statistically significant at P-value<0.05; ref, Reference Category; AOR, Bivariate logistic regression****

CHAPTER FIVE: DISCUSSION

This study assessed the patterns of antimicrobial prescribing in the CCUs at Kenyatta National Hospital. The results showed that the vast majority of critically ill patients were exposed to an antimicrobial agent before admission to the CCU. The study also assessed the compliance of antimicrobial therapy prescribing to the CCU guideline and this was noted to be low at 40.9%. Lastly, the use of culture and sensitivity testing to promote rational antimicrobial prescribing was described.

5.1 Prevalence of antimicrobial prescribing

This study observed a high prevalence (98.4%) of antimicrobial prescribing at admission. This is consistent with the results of studies conducted in Nigeria where the prevalence was 88.9% (45) and North Ireland and Jordan where the prevalence was observed to be 78.2% (46). The point prevalence surveys done here in Kenya at Jaramogi Oginga Odinga Teaching and Referral hospital (39) and Rift Valley Provincial Hospital (Now Nakuru Level V) (47) in 2017 reported a prevalence of 67.7% and 100% respectively. Similar results were observed in other parts of the world such as Canada 79% (34), China 81.8% (35) and Vietnam which reported a high prevalence of 84.8% in the Critical Care Unit (36). This high prevalence can be attributed to the critical condition of patients admitted to this unit and the importance of early initiation of an effective antimicrobial agent to reduce patient morbidity and mortality (3).

Empiric antimicrobial selection is influenced by the presenting symptoms of the patient, the likely causative organisms and local resistance patterns (37). The patients admitted to the CCU are critically ill and are at a high risk of developing life-threatening infections. Therefore, they require early and effective initiation of antimicrobial therapy for their survival because any delay would lead to an increase in mortality (13).

This practice is shown by the high prevalence of antimicrobial use in the CCU. The use of microbiological investigations is therefore important in refining the empiric therapy to the most appropriate and cost-effective antimicrobial agent.

5.2 Quality Indicators for antimicrobial prescribing

This study adopted the European Surveillance of Antimicrobial Consumption (ESAC) indicators that are employed to assess the performance of interventions meant to improve patient outcomes. The indicators assessed in this study included the documentation of the reasons for antimicrobial prescribing, a stop or review of antimicrobial therapy and compliance to the existing guideline. In addition to these indicators, use of INN in prescribing and empiric versus targeted prescribing were also assessed in the study.

There was poor documentation of instruction on stoppage or review of antimicrobial therapy. The stop or review instructions was documented in 11.7% (n=36) cases of the antimicrobial agents prescribed. This was much lower than 27.8% and 36.6% which were reported in a study of antimicrobial prescribing in a Nigerian hospital (45) and in the adult 2015 Global Point Prevalence survey (GPPS) (8) respectively. Documentation of any stop or review in antimicrobial therapy is one way of ensuring appropriate antimicrobial prescribing. It demonstrates communication between clinicians in order to improve patient outcomes (47).

Documenting the indication for antimicrobial therapy ensures that the clinician has information to modify therapy as needed and/ or discontinue the antimicrobial therapy in a timely manner (7). In this study, only 16.5% of the patients had an indication for antimicrobial therapy documented in the medical records.

This is in contrast with 37.3% reported at the Rift Valley Provincial Hospital intensive care unit (47), 61.8% in a study on antimicrobial prescribing in four Nigerian tertiary hospitals and 70.4% that was reported in the adult 2015 global PPS (8).

There are concerns across many countries with the adherence to guidelines on antimicrobial use (39). In Kenya, a survey of public hospitals found only 40% were adherent to the national Standard Treatment Guidelines (STG). Compliance to the KNH guide to antimicrobial therapy was observed to be 41.6% which was very low as compared to 77.4% established in a global point prevalence survey conducted in 53 countries(8). This low level of compliance could be due to unavailability or lack of awareness about the guideline. When compared to other low and middle income countries (LMIC), the compliance at KNH Critical Care Unit was higher as compared to 7.1% which was observed in Uganda (32). This could be attributed to the established antimicrobial stewardship program in the hospital.

However, more concerted effort is required by the KNH antimicrobial stewardship committee because of the below-average compliance. Compliance to a guideline has been shown to improve patient clinical outcomes for example shortening of the duration of treatment and hospital stay and reducing the development of antimicrobial resistance (8). The use of generic names also known as International Nonproprietary Name (INN), ensures rational prescribing of medicines. The INN was used in 66.7% of the prescription in this study. These findings are similar to 62.5% observed in the point prevalence survey conducted at the Rift Valley Provincial Hospital in Kenya (47).

A majority of critically ill patients had been exposed to an antimicrobial agent before admission to the Critical Care Unit (CCU). One of the major contributors to the increase in AMR is antimicrobial agent use prior to CCU admission (48). In this study, most (98.4%) of the patients

had already been initiated an antimicrobial agent before CCU admission. This shows that empiric prescribing of antimicrobial agents is widely practiced at KNH which is a well-known cause of increased resistance. This is in contrast to 28% reported in a prospective study in 41 French hospitals and 83% in a medical CCU in Turkey (48).

5.3 Culture and sensitivity testing

Appropriate antimicrobial use is aided by using culture and sensitivity tests to confirm infection, identify the causative organism and the susceptibility patterns to the antimicrobial agents available (49). The use of diagnostic support such as culture and sensitivity testing before selecting an antimicrobial agent fosters rational use of antimicrobial agents (47) by refining empiric therapy to the most appropriate narrow-spectrum agent (37). In this study, only 158 (51.1%) of the study patients had a microbiological test performed at admission to the CCU. This can be attributed to a lack of capacity to perform investigations on every case and/or lack of or unclear policies for antimicrobial prescribing (50). This is in contrast to the high level (75%) reported in a medical CCU in Turkey (48). The culture positivity for this study was 42.7% differing from the 70% positivity reported by the European study to investigate the prevalence of Infection in Intensive Care (EPIC II) and the medical CCU in Turkey where the frequency of positive culture was 66% (48).

5.4 Organisms isolated

The most common isolated micro-organism in this study was *Klebsiella pneumonia* (23.9 %,) followed by *Acinetobacter baumanii (*16.4%), *Escherichia coli* (10.5%), *Pseudomonas aeruginosa* (6.0%) and *Staphylococcus spp* (12%). These observations are consistent with other studies conducted to investigate the causes of infections in the CCU that lead to the acronym ESKAPE (20). However, these results differed slightly from a study done by Njiru et al (2013) at the KNH

laboratory which showed that *Escherichia coli* was the most isolated organism at 46% followed by *Klebsiella pneumonia* (19.5%) and *Citrobacter spp* (15.9%) (14).

The patterns of infection-causing microorganisms observed in this study were also similar to studies conducted previously at KNH with the most predominant organism being *Klebsiella pneumonia, Acinetobacter baumanii* and *Escherichia coli* (16,51). The most commonly isolated microorganism were gram-negative bacteria (50.8%) such as *Klebsiella pneumonia (23.9%), Acinetobacter baumanii (16.4%)* and *Escherichia coli (10.5%)* a trend that had been previously reported in KNH (14) and in a surgical ICU in Canada.(41)

5.5 Pattern of antimicrobial susceptibility

The microorganisms that cause infections in the CCUs have reduced susceptibility to a number of commonly used antimicrobial agents. This leaves clinicians with limited antimicrobial agents to prescribe in the management of these infections (29). While ceftriaxone (59.9%) was the most common antimicrobial agent prescribed for patients in the CCUs, it is noteworthy that none of the most commonly isolated organisms were susceptible to it. The increasing antimicrobial resistance is a threat to the health of the patient and the health system worldwide. AMR leads to increased costs of treatment such as forcing a change to antimicrobial agents that are more expensive and broader spectrum (52).

The *Acinetobacter baumanii* isolated in this study showed high susceptibility to amikacin 82% and meropenem 55%. The *Klebsiella pneumonia* isolated was most sensitive to amikacin 56%, imipenem 69% and ciprofloxacin 44% a pattern that is consistent with the results of a similar study conducted in Iran (53). Majority of the *Escherichia coli* isolated (86%) was sensitive to

meropenem differing from what was observed in the study in Iran where only 22% of the *E.Coli* was sensitive to imipenem.

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

The prevalence of antimicrobial prescribing in the KNH CCU was high which is consistent with findings from CCUs across many hospitals. Ceftriaxone was the most common antimicrobial agent prescribed despite most micro-organisms isolated showing resistance. Compliance with the antimicrobial guideline was suboptimal. The indication for antimicrobial use was not recorded in majority of cases. The study observed that even when the culture and sensitivity report was available; it informed antimicrobial prescribing in only a few cases. AMR is an increasing threat to the health of individuals and the health system worldwide. Therefore, there is a need to strengthen the stewardship programs to improve antimicrobial prescribing in KNH. It is therefore intended that the information from this study will be used by KNH antimicrobial stewardship committee to develop strategies to improve antimicrobial use in the Critical Care Unit.

6.2 Recommendations

1. Antimicrobial resistance patterns compiled by the laboratory should be communicated to the hospital formulary team quarterly so as to ensure that the guideline and formulary are regularly updated.

2. Since the culture and sensitivity tests are carried out regularly in the CCU but the results are not used effectively, the antimicrobial stewardship committee should develop an intervention to ensure these results are utilized to inform antimicrobial therapy.

3. There is a need for an antimicrobial stewardship ward round every 48 hours to review patient antimicrobial treatment.

4. The KNH guideline to antimicrobial therapy should be available and accessible for use. Therefore, the antimicrobial stewardship committee should develop charts and posters, have them well displayed in the clinical areas for use by the health care providers.

5. At risk categorization in the KNH guide to Antimicrobial Therapy in Critical Care Units is not user-friendly. The risk classification is too complex and provides for both empirical and targeted treatment in the same context giving room for inappropriate antimicrobial use.

This study has developed an improved risk category algorithm (figure 6.1) to be considered by the KNH AMS committee.

Consider the following cascade of questions in risk categorization of patients at admission.

> **Question 1:** Does the patient have a confirmed infection that is life-threatening or difficult to treat at admission?
>
> **If yes, assign risk category 4 and start antimicrobial agent immediately.**
>
> **Question 2:** Has the patient undergone trauma or invasive surgical procedure? Does have HIV or is immune-compromised?
>
> **If yes, assign risk category 3: Implication: Consider prophylactic antimicrobial use.**
>
> **Question 3**: Does the patient have co-morbidity such as diabetes, hypertension, and kidney disease etc. but there is no evidence of an established infection? The patient has no trauma or has not undergone any invasive procedure?
>
> **Assign risk classification 2.**
>
> **Question 4:** Assign risk classification 1 for patients with no clear risk factors for infection, without any recent hospitalization or antimicrobial use hence may not require an antimicrobial.

Proposed Risk classification algorithm

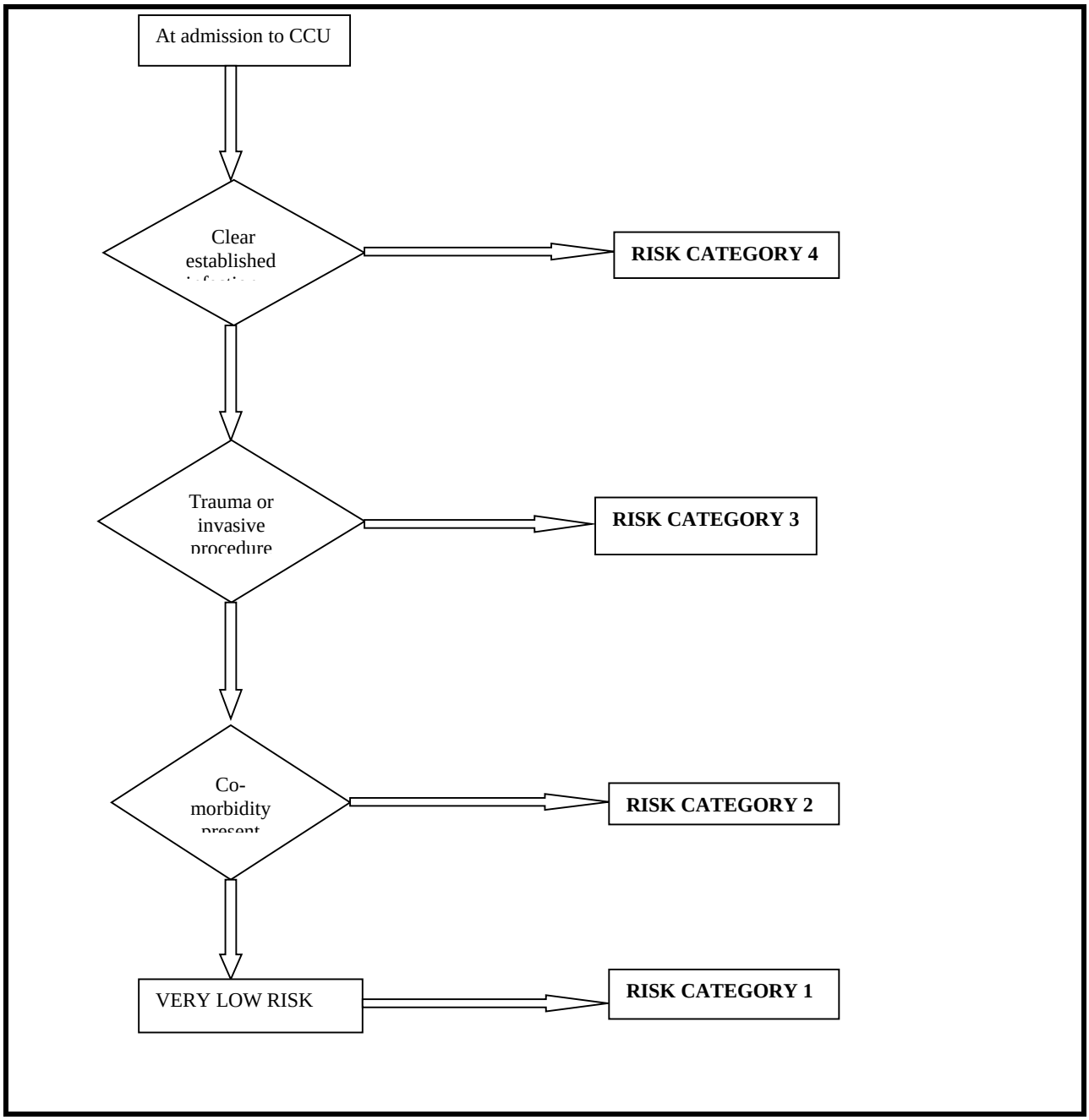


Figure 6. 1: Risk categorization algorithm for Critical Care at Kenyatta National Hospital

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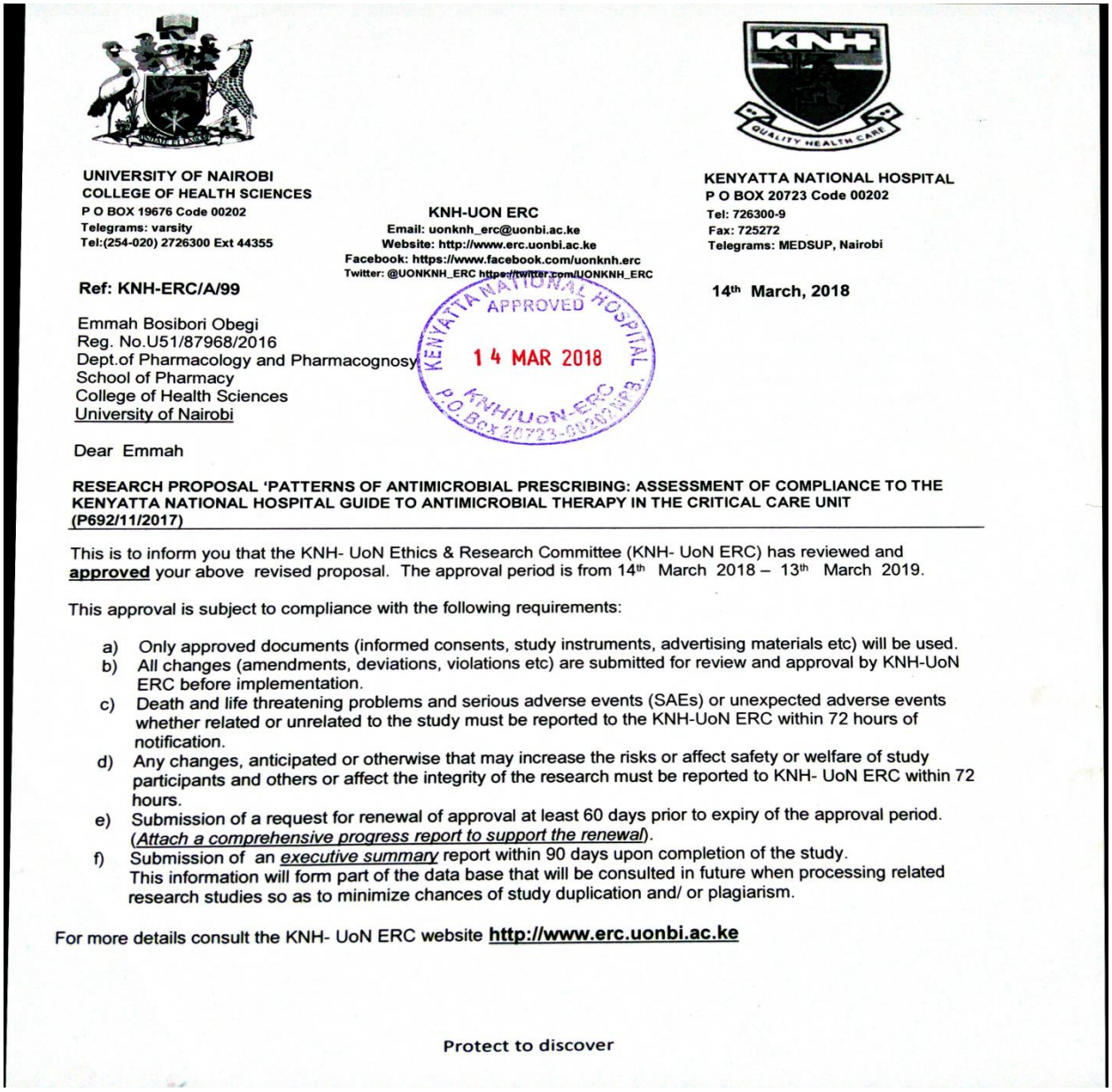
APPENDICES

Appendix A: Kenyatta National Hospital ERC Approval



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Ref: KNH-ERC/A/99

14th March, 2018

KENYATTA NATIONAL HOSPITAL APPROVED 14 MAR 2018 KNH/UoN-ERC P.O. Box 20723-00202 NAIROBI

Emmah Bosibori Obegi
Reg. No.U51/87968/2016
Dept.of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Emmah

RESEARCH PROPOSAL 'PATTERNS OF ANTIMICROBIAL PRESCRIBING: ASSESSMENT OF COMPLIANCE TO THE KENYATTA NATIONAL HOSPITAL GUIDE TO ANTIMICROBIAL THERAPY IN THE CRITICAL CARE UNIT (P692/11/2017)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above revised proposal. The approval period is from 14th March 2018 – 13th March 2019.

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) 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*).
f) 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.

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

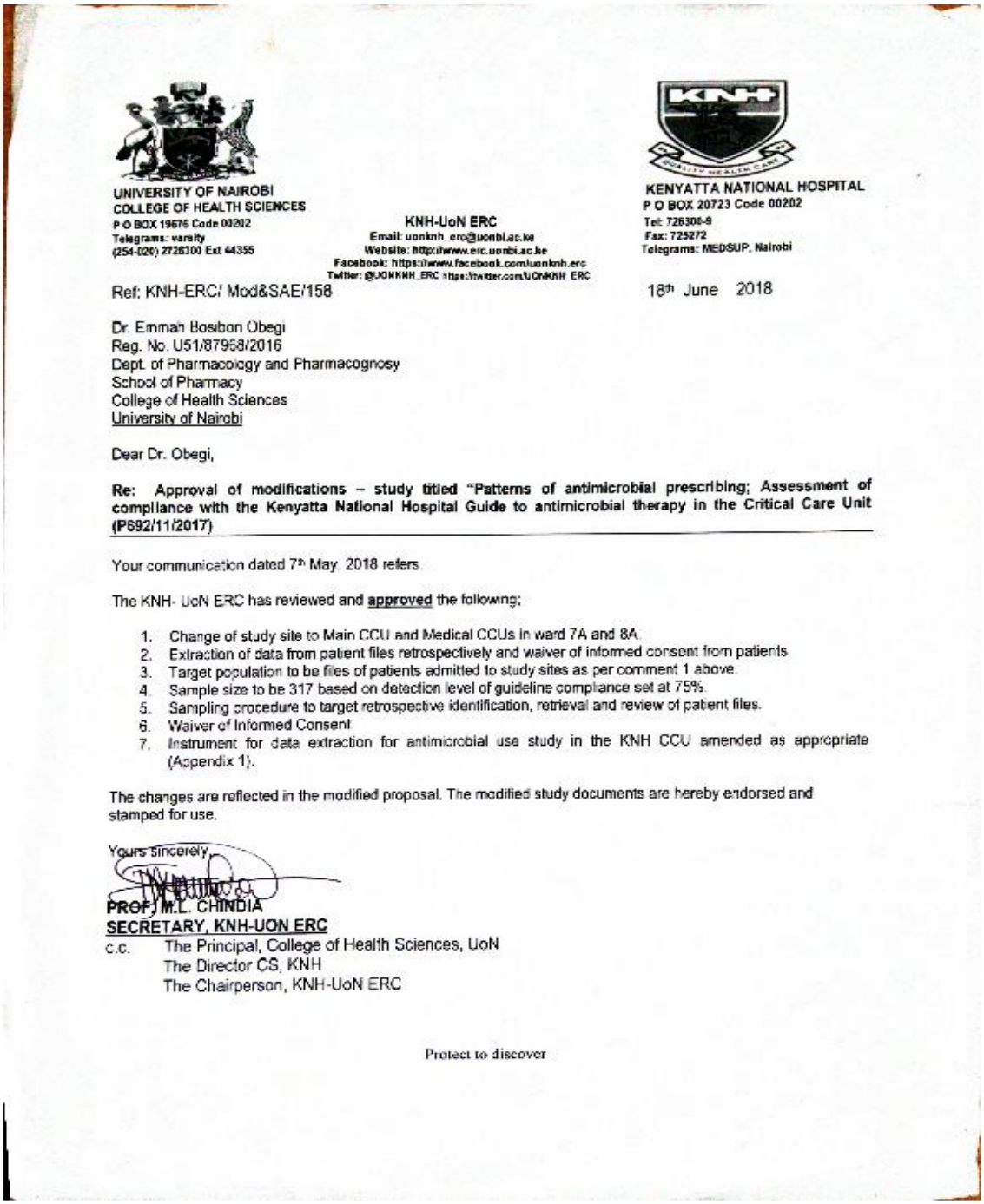
Protect to discover

Yours sincerely,

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

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director, CS, KNH
The Chairperson, KNH-UON ERC
The Dean, School of Pharmacy, UoN
The Chair, Dept.of Pharmacology and Pharmacognosy, UoN
Supervisors: Dr. Margaret Oluka, Dr. Sylvia Opanga, Dr. Dorothy Aywak

Appendix B: Kenyatta National Hospital ERC Approval of Modifications



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18th June 2018

Dr. Emmah Bosibori Obegi
Reg. No. U51/87958/2016
Dept. of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Dr. Obegi,

Re: Approval of modifications – study titled "Patterns of antimicrobial prescribing; Assessment of compliance with the Kenyatta National Hospital Guide to antimicrobial therapy in the Critical Care Unit (P692/11/2017)

Your communication dated 7th May 2018 refers.

The KNH- UoN ERC has reviewed and **approved** the following:

1. Change of study site to Main CCU and Medical CCUs in ward 7A and 8A.
2. Extraction of data from patient files retrospectively and waiver of informed consent from patients
3. Target population to be files of patients admitted to study sites as per comment 1 above.
4. Sample size to be 317 based on detection level of guideline compliance set at 75%.
5. Sampling procedure to target retrospective identification, retrieval and review of patient files.
6. Waiver of Informed Consent
7. Instrument for data extraction for antimicrobial use study in the KNH CCU amended as appropriate (Appendix 1).

The changes are reflected in the modified proposal. The modified study documents are hereby endorsed and stamped for use.

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

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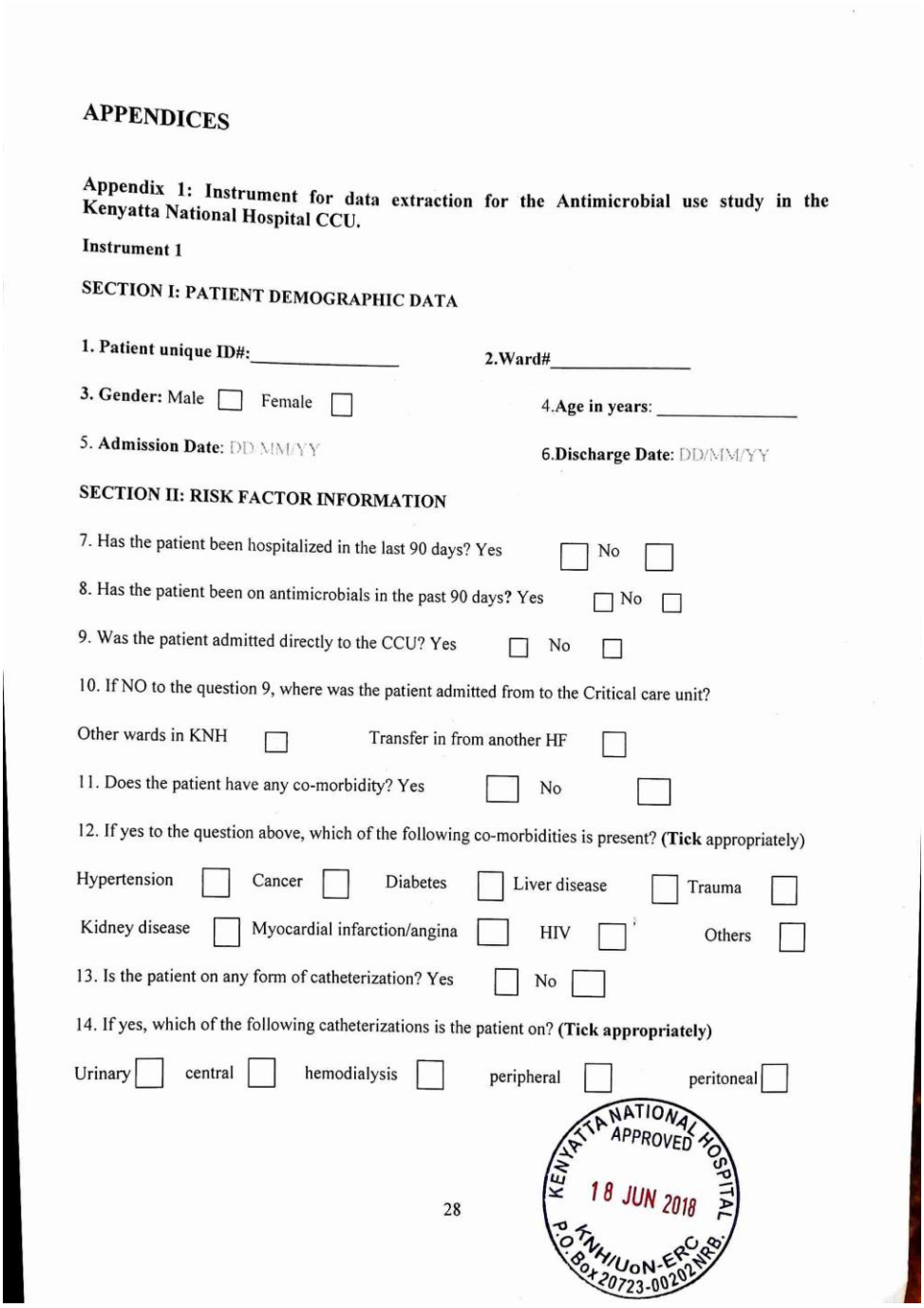
Appendix C: Instrument for data extraction for the Antimicrobial use study in the Kenyatta National Hospital CCU.



APPENDICES

Appendix 1: Instrument for data extraction for the Antimicrobial use study in the Kenyatta National Hospital CCU.

Instrument 1

SECTION I: PATIENT DEMOGRAPHIC DATA

1. Patient unique ID#:_____ **2.Ward#**_____

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

5. **Admission Date**: DD/MM/YY 6.**Discharge Date**: DD/MM/YY

SECTION II: RISK FACTOR INFORMATION

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

8. Has the patient been on antimicrobials in the past 90 days? Yes ☐ No ☐

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

10. If NO to the question 9, where was the patient admitted from to the Critical care unit?

Other wards in KNH ☐ Transfer in from another HF ☐

11. Does the patient have any co-morbidity? Yes ☐ No ☐

12. If yes to the question above, which of the following co-morbidities is present? **(Tick** appropriately)

Hypertension ☐ Cancer ☐ Diabetes ☐ Liver disease ☐ Trauma ☐

Kidney disease ☐ Myocardial infarction/angina ☐ HIV ☐ Others ☐

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

14. If yes, which of the following catheterizations is the patient on? **(Tick appropriately)**

Urinary ☐ central ☐ hemodialysis ☐ peripheral ☐ peritoneal ☐

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KENYATTA NATIONAL HOSPITAL APPROVED 18 JUN 2018 KNH/UoN-ERC P.O.Box 20723-00202 NRB

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

16. If yes, which of the following? **(Tick appropriately)**

Endotracheal ☐ Suction ☐ Tracheostomy ☐ Nasogastric/feeding ☐ Gastroduodenal ☐

SECTION III: INFORMATION ON PRESENT MANAGEMENT

17. Was the patient initiated on an antimicrobial agent at admission? Yes No ☐ ☐

18. If yes, which antimicrobial agent(s) was prescribed?

Medicine	**Dose strength mg**	**Duration days**	**Dose Frequency OD,BD,TDS,QID**	**Route of Admin (P,R,O,IV)**	**INN Used (Y/N)**

19. Is the treatment empirical or targeted? Yes ☐ No ☐

20. If empirical, was the therapy in compliance with the guideline? Yes ☐ No ☐

21. What is the main reason for admission to Kenyatta National Hospital?

_____

22. What type of infection has the patient been diagnosed with? **(Tick in the appropriate box)**

Bloodstream ☐ Intra-abdominal ☐ Urinary tract ☐ Skin and soft tissue ☐

23. Was Risk categorization done on the patient? Yes ☐ No ☐

24. If yes, in which risk category is the patient? 1 ☐ 2 ☐ 3 ☐ 4 ☐

25. Is the risk categorization in compliance to the guideline? Yes ☐ No ☐

SECTION IV: ANTIMICROBIAL USE INFORMATION

26. Has a request for culture and susceptibility test been made? Yes ☐ No ☐

27. On which day of admission was the first CST requested? _____

28. After how long (days) was the report received in the ward? _____

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

30. If yes to question 29, what micro-organism/s was isolated?

_____

29. If yes to question 29, what is the antimicrobial susceptibility profile for the micro-organism isolated?

Antimicrobial	Resistant	Susceptible

30. If CST report is available, did it inform the choice of antimicrobial agent? Yes ☐ No ☐

31. Is there a stop/review date for antimicrobial therapy in the patient file? Yes ☐ No ☐

32. Is there any change in antimicrobial therapy for the patient? Yes ☐ No ☐

33. What is the reason for change of antimicrobial therapy as written in the patient file?

CST report ☐ Initial inappropriate antimicrobial agent ☐ Fever ☐

Worsening of the patients' condition ☐ No reason is written ☐

Others (specify) _____

34. What antimicrobial has been prescribed?

Medicine	Dose strength mg	Duration days	Dose Frequency OD,BD,TDS,QID	Route of Admin (P,R,O,IV)	INN Used (Y/N)

35. Does the prescribed antimicrobial agent comply with the guideline recommendation?

Yes ☐ No ☐

36. Does the prescription comply with the 1st line recommended for organism? Yes ☐ No ☐

37. If No, does it comply with the alternative/2nd line recommendation? Yes ☐ No ☐

38. Is the type of indication for antimicrobial therapy written in the patient records? Yes ☐ No ☐

39. What type of antimicrobial therapy change was made?

Dose escalation ☐ Dose de-escalation ☐ Antimicrobial agent stop ☐

Change of frequency ☐ New antimicrobial agent prescribed? ☐

Others (specify) _____

40. Was another culture and susceptibility test request made? Yes ☐ No ☐

What was the result? **(LIST UP TO 2 ADDITIONAL TESTS WITH ISOLATED MICRO-ORGANISM)**

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

42. What micro-organism/s was isolated? _____

43. Antimicrobial susceptibility profile for isolated micro-organism isolated?

Antimicrobial	Resistant	Susceptible

44. Is there any change of antimicrobial therapy for the patient? Yes ☐ No ☐

45. If yes, what antimicrobial agent has been prescribed?

Medicine	Dose strength mg	Duration days	Dose Frequency OD,BD,TDS,QID	Route of Admin (P,R,O,IV)	INN Used (Y/N)

46. Does the prescribed antimicrobial agent comply with the guideline recommendation?

Yes ☐ No ☐

47. Does the prescription comply with the 1st line recommended for organism? Yes ☐ No ☐

48. If No, does it comply with the alternative/2nd line recommendation? Yes ☐ No ☐

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

50. What micro-organism/s was isolated? _____

51. Antimicrobial susceptibility profile for isolated micro-organism isolated?

Antimicrobial	Resistant	Susceptible

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comply with the guideline as

52. Is there any change of antimicrobial therapy for the patient? Yes ☐ No ☐

53. If yes, what antimicrobial agent has been prescribed?

Medicine	Dose strength mg	Duration days	Dose Frequency OD,BD,TDS,QID	Route of Admin (P,R,O,IV)	INN Used (Y/N)

54. Does the prescribed antimicrobial agent comply with the guideline recommendation?

Yes ☐ No ☐

55. Does the prescription comply with the 1st line recommended for organism? Yes ☐ No ☐

56. If No, does it comply with the alternative/2nd line recommendation? Yes ☐ No ☐

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