PATTERNS OF ANTIBIOTIC USE AND DOSE ADJUSTMENT IN CHRONIC KIDNEY DISEASE PATIENTS AT KENYATTA NATIONAL HOSPITAL

A dissertation submitted in partial fulfillment of requirements for Masters Degree of University of Nairobi (Clinical Pharmacy)

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I dedicate this work to my late father Mr. John Onyango Milenyi who, despite his short life, encouraged us to always aspire for a life guided by knowledge.
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I thank the Almighty God for strength and good health He endowed me to this very day.

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TABLE OF CONTENTS

DECLARATION ................................................................. ii
SUPERVISOR'S APPROVAL .............................................. ii
DEDICATION ................................................................... iii
ACKNOWLEDGEMENTS ................................................... iv
TABLE OF CONTENTS ..................................................... v
LIST OF TABLES ........................................................... ix
LIST OF FIGURES .......................................................... ix
ABBREVIATIONS .......................................................... x
DEFINITION OF TERMS .................................................. xii
ABSTRACT ................................................................... xiii
CHAPTER ONE .............................................................. 1
1.0 INTRODUCTION AND LITERATURE REVIEW .......... 1
1.1 INTRODUCTION ....................................................... 1
1.2 LITERATURE REVIEW .............................................. 1
  1.2.1 Chronic kidney disease ...................................... 1
  1.2.2 Assessment of kidney function ............................ 2
  1.2.3 Estimation of glomerular filtration rate (GFR) ........ 3
  1.2.4 Prevalence of renal disease ......................... 5
CHAPTER ONE

1.2.5 Co-morbidities in renal disease ................................................................. 6

1.2.6 Dosage adjustment of antimicrobial drugs in renal insufficiency .......... 7

1.2.8 Studies on drug dosage adjustment in renal failure patients ............... 8

1.3 PROBLEM STATEMENT .................................................................................. 9

1.4 RESEARCH QUESTIONS ................................................................................ 9

1.5 RATIONALE OF THE STUDY ..................................................................... 10

1.6 OBJECTIVES .................................................................................................. 11

CHAPTER TWO ........................................................................................................ 12

2.0 METHODOLOGY ............................................................................................ 12

2.1 Ethical consideration .................................................................................... 12

2.2 Study design ................................................................................................. 12

2.3 Study area description ................................................................................ 13

2.4 Study population ........................................................................................ 13

2.4.1 Inclusion criteria ................................................................................... 14

2.4.2 Exclusion criteria .................................................................................. 14

2.5 Sample size determination .......................................................................... 14

2.6 Sampling method ....................................................................................... 15

2.7 Data collection and materials ..................................................................... 16

Pre-testing of the data collection form .............................................................. 17
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.8 Data management</td>
<td>17</td>
</tr>
<tr>
<td>2.9 Data analysis</td>
<td>18</td>
</tr>
<tr>
<td>2.10 Definition of cases</td>
<td>18</td>
</tr>
<tr>
<td>2.11 Variables, confounders and outcomes of interest</td>
<td>19</td>
</tr>
<tr>
<td>3.0 RESULTS AND DISCUSSION</td>
<td>20</td>
</tr>
<tr>
<td>3.1 Baseline demographic characteristics of the study population</td>
<td>20</td>
</tr>
<tr>
<td>3.2 Severity, causes and management of renal disease</td>
<td>21</td>
</tr>
<tr>
<td>3.2.1 Stages and management of renal disease</td>
<td>21</td>
</tr>
<tr>
<td>3.2.2 Causes of chronic kidney disease in the study population</td>
<td>23</td>
</tr>
<tr>
<td>3.3 Patterns of antibiotic use in the study population</td>
<td>25</td>
</tr>
<tr>
<td>3.3.1 Types of antibiotics prescribed</td>
<td>25</td>
</tr>
<tr>
<td>3.3.2 Route of administration, frequency and duration of use of the prescribed antibiotics</td>
<td>26</td>
</tr>
<tr>
<td>3.3.3 Indications for antibiotic use</td>
<td>28</td>
</tr>
<tr>
<td>3.3.4 Comparison of prescribing patterns in the two clinical settings</td>
<td>29</td>
</tr>
<tr>
<td>3.4 Antibiotic dose adjustment</td>
<td>31</td>
</tr>
<tr>
<td>3.4.1 Antibiotic dose adjustment requirement and how they were adjusted</td>
<td>31</td>
</tr>
<tr>
<td>3.4.2 Prevalence of inappropriate dose adjustment in the study population</td>
<td>32</td>
</tr>
<tr>
<td>3.4.4 Risk factors for inappropriate dose adjustment in the study population</td>
<td>34</td>
</tr>
<tr>
<td>CHAPTER FOUR</td>
<td>41</td>
</tr>
</tbody>
</table>
4.0 CONCLUSION ............................................................................................................41
4.1 RECOMMENDATIONS .................................................................................................41
4.2 STUDY LIMITATIONS ..................................................................................................42
5.0 REFERENCE: ................................................................................................................43
6.0 APPENDICES ................................................................................................................49
Appendix 1: Study eligibility checklist ............................................................................49
Appendix 2: Reason for exclusion ......................................................................................50
Appendix 3: Data collection form ......................................................................................51
Appendix 4: Drug dosage adjustment for antibiotics in the KNH drug list according to the guideline to be used in the study ..................................................................................................................54
Appendix 5: Ethical approval ..............................................................................................58
LIST OF TABLES

Table 1: Stages of renal disease .................................................................................... 3
Table 2 Demographic characteristics of the study population .................................... 20
Table 3 Renal parameters at the antibiotic prescription episodes per clinical setting ...... 22
Table 4 Extent of dose adjustment ................................................................................ 31
Table 5 Determinants of inappropriate dose adjustment .............................................. 35
Table 6: Prescribed antibiotics as determinants of appropriate dose adjustment ........ 37

LIST OF FIGURES

Figure 1 Sampling frame ................................................................................................ 16
Figure 2 Causes of chronic kidney disease .................................................................. 24
Figure 3 Antibiotics prescribed to the study population ............................................ 25
Figure 4 Routes of administration of the prescribed antibiotics .................................. 27
Figure 5 Indications for antibiotic use ........................................................................ 29
Figure 6 Antibiotics prescribed in the two clinical settings ........................................ 30
Figure 7 Antibiotic dose adjustment practices in the study population ................. 33
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>Acquired immune deficiency syndrome</td>
</tr>
<tr>
<td>BPH</td>
<td>Benign prostatic hypertrophy</td>
</tr>
<tr>
<td>CDC</td>
<td>Center for Disease Control</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic Kidney Disease</td>
</tr>
<tr>
<td>CKF</td>
<td>Chronic Kidney Failure</td>
</tr>
<tr>
<td>CrCl</td>
<td>Creatinine clearance</td>
</tr>
<tr>
<td>ESRD</td>
<td>End stage renal disease</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular Filtration Rate</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HIVAN</td>
<td>Human immunodeficiency virus associated nephropathy</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>K/DOQI</td>
<td>National Kidney Foundation Kidney Disease Outcomes Quality Initiative</td>
</tr>
<tr>
<td>MDRD</td>
<td>Modification of Diet in Renal Disease</td>
</tr>
</tbody>
</table>
NHANES: National Health and Nutrition Examination Survey
RI: Renal Insufficiency
SADTR: South African Dialysis and Transplant Registry
Ser: Serum creatinine
$\text{t}_{1/2}$: Half life
USA/US: United States of America
WHO: World Health Organization
DEFINITION OF TERMS

Chronic Kidney Disease (CKD)  This is a pathophysiologic process with multiple etiologies, resulting in the inexorable attrition of nephron number and function and frequently leading to end stage renal disease. The pathophysiologic process has to last for more than 3 months for the condition to be defined as CKD.

Acute renal failure  This is a syndrome characterized be rapid decline in the glomerular filtration rate occurring within hours to days leading to retention of nitrogenous waste products and perturbation of extracellular volume and electrolytes and acid–base homeostasis.

Renal insufficiency  This is a state of reduced endogenous renal function, which can either be due to acute renal failure or chronic kidney disease.

End stage renal disease  A clinical state or condition in which there has been irreversible loss of endogenous renal function, of a degree sufficient to render the patient permanently dependent upon renal replacement therapy in order to avoid life threatening uremia.
ABSTRACT

Background: Patients with reduced renal function are often encountered in clinical practice. The presence of reduced kidney function in any patient alters drug disposition. This alteration necessitates appropriate individualization of drug therapy to avoid unnecessary drug accumulation and adverse drug effects. There are limited local studies on the pattern of antibiotic use and dose adjustments in renal patients and hence the basis of the current study.

Objective of the study: The objective of the study was to determine the patterns of antibiotic use and dose adjustment practices in patients with chronic kidney disease (CKD) at Kenyatta National Hospital (KNH).

Methodology: The study was hospital-based retrospective cross sectional study. A preformatted data collection form was used to collect data from patient files who met the eligibility criteria. Data was collected on antibiotics prescribed to patients with CKD between January, 2006 and December, 2010 and the laboratory parameters of renal function. The antibiotic dosage for systemic administration, which ought to have been adapted depending on the GFR, was determined from the dosing guideline and this was compared with the prescribed dosages to determine the appropriateness of the prescribed doses.

Eligibility criteria: Chronic kidney disease patients, with antibiotic prescription and aged 18 years and above during the time of antibiotic prescription attending KNH during the study period were eligible for the study.
Data analysis: Estimated glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease four variable (MDRD) equation. Data analysis was done using STATA version 9 statistical software. Data was subjected to descriptive, confounding and logistic regression analysis.

Results: The median age at diagnosis of CKD in the study population was 46 years (IQR=32 – 60 years). There were slightly more males (57.3%) than females in the study. Ceftriaxone and co-amoxiclav were the most frequently prescribed antibiotics. The most important risk factor for inappropriate dose adjustment was the severity of renal disease. Dose adjustment was indicated in 59.9% of antibiotic prescriptions; however appropriate adjustment was only done in 27.7% (95%CI 23.18 – 32.23) of the prescriptions. Co-amoxiclav was the least frequently adjusted antibiotic with only 8.5% appropriate adjustment whereas, vancomycin had the highest prevalence of correct dose adjustment at 69.7% of the prescriptions that required adjustment. Over dosage was the most common dosing error. Therapeutic drug monitoring was neither requested nor done for any of the prescribed antibiotics considered in the study.

Conclusion: Antibiotic dose adjustment in patients with CKD was often incorrect especially for co-amoxiclav. Strategies to improve prescribing of drugs such as, development of a simplified guide for dose adjustment of commonly used drugs and pharmacist involvement in drug therapy monitoring should be considered.
CHAPTER ONE

1.0 INTRODUCTION AND LITERATURE REVIEW

1.1 INTRODUCTION

Renal diseases are known to affect the pharmacokinetic disposition as well as the pharmacodynamic effects of drugs. These alter drug concentration in plasma or blood and at the site of action thereby affecting drug efficacy and toxicity. Careful dose adjustment and therapeutic drug monitoring are essential in patients with renal insufficiency to prevent accumulation of administered drugs and/or toxic metabolites. Dose adjustment reduces the incidence of serious adverse drug effects. Adverse drug effects may result in extended length of hospital admission, increased health care utilization and increased cost of healthcare. Drugs that are normally excreted by the kidney as active compound or metabolized to active or reactive metabolites before elimination by the kidney require dose adjustment to prevent the accumulation of the active drug, the toxic or reactive metabolites.

1.2 LITERATURE REVIEW

1.2.1 Chronic kidney disease

Chronic kidney disease (CKD) is a serious condition associated with premature mortality, decreased quality of life, and increased health-care expenditures. Untreated CKD can result in end-stage renal disease and necessitate dialysis or kidney transplantation. The U.S National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) defines chronic
kidney disease as the presence of kidney damage or a reduction in the glomerular filtration rate (GFR) for three months or longer.\textsuperscript{[7]}  

**1.2.2 Assessment of kidney function**  

Patients with kidney disease present with symptoms that are either directly referable to the kidney or are extrarenal. Symptoms that are directly referable to the kidney include gross hematuria and flank pain while extrarenal signs include edema and hypertension. Many patients may be asymptomatic and kidney diseases are detected during routine examination. It is typical for people with CKD not to notice symptoms until the disease has progressed considerably.\textsuperscript{[8]} Elevated serum creatinine and/or an abnormal urinalysis help to identify patients suffering from kidney disease.  

Estimation of the GFR is used clinically to assess the degree of kidney impairment and to follow the course of the disease. Radiologic studies and/or renal biopsy can be used to get additional information on the cause of renal disease.\textsuperscript{[7, 9]}  

Chronic kidney disease can be classified into various classes based on the glomerular filtration rate (Table 1)
Table 1: Stages of renal disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Glomerular filtration rate (mL/min/1.73m²)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>At increased risk</td>
<td>≥90 (with CRF risk factors, no proteinuria)</td>
</tr>
<tr>
<td>1</td>
<td>Kidney damage with normal or high GFR</td>
<td>≥ 90 with proteinuria</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild reduced GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate reduced GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severe reduced GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15</td>
</tr>
</tbody>
</table>

Accurate assessment of renal function amongst patients with CKD is important for diagnosis and interventional purposes especially drug dose adjustment. This is because half of all drugs or their metabolites are excreted by the kidney, and about 30% of all adverse effects of medications have either a renal cause or a renal effect. [10]

1.2.3 Estimation of glomerular filtration rate (GFR)

The GFR is equal to the sum of the filtration rates of all the functioning nephrons, it gives a rough measure of the number of functioning nephrons. The K/DOQI clinical practice guideline advocates the use of the traditional Cockcroft-Gault equation or the Modification of Diet in Renal Disease (MDRD) study equation (full or abbreviated) for routine estimation of GFR. [71]

The Cockcroft and Gault Equation can be used to estimate the GFR as follows: [111]
**Equation 1**

\[ X = \frac{(140 - \text{age}) \times \text{weight}}{(72 \times \text{serum creatinine})} \]

Where \( X \) is the glomerular filtration rate in mL/min and age is in years.

The equation as shown requires weight to be recorded in kg and creatinine in mg/dL, and is valid for male patients. If the patient is female, the result should be multiplied by 0.85.

Or

**Equation 2**

\[ X = \frac{(140 - \text{age}) \times \text{weight}}{\text{serum creatinine}} \]

If the serum creatinine is measured in micromoles/L, the result of the equation is multiplied by 1.23 for male patients and 1.04 for the female patients.

The Modification of Diet in Renal Disease four variables (MDRD 4 variable) equation uses age, sex, ethnicity and serum creatinine to predict the GFR. \(^{[7,12]}\)

**The MDRD 4 variable equation is as follows:**

\[ \text{GFR} = 186 \times (\text{Scr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times 1.210 \text{ in African American} \]

Where Scr is serum creatinine in mg/dl, age is age in years. Serum creatinine concentration in micromol/L is divided by 88.4 to convert it to to mg/dl. This equation has the advantage of requiring fewer variables for its calculation. A study conducted at KNH comparing the different
estimating equations concluded that the MDRD 4 equation is the least bias for estimating the GFR.\textsuperscript{113}

1.2.4 Prevalence of renal disease

Chronic kidney disease (CKD) is a widely prevalent but often silent condition. Renal disease, especially glomerular disease, is more prevalent in Africa and seems to be of more severe form than that found in Western countries. It is estimated that 2 to 3\% of medical admissions in tropical countries are due to renal-related complaints, the majority being the glomerulonephritides.\textsuperscript{114}

There are no reliable statistics for End Stage Renal Disease (ESRD) in all African countries. However, there is a general impression that CKD is at least 3–4 times more frequent in Sub-Saharan Africa than in more developed countries.\textsuperscript{114}

Review of cross sectional studies in Kinshasa, indicated that the prevalence of CKD in the Democratic Republic of Congo was 12.4\%.\textsuperscript{115} In North Africa, the prevalence of ESRF ranges from 30 to 430 patients per million population with an annual incidence of 34 to 200 per million population.\textsuperscript{116}

Data from U.S National Health and Nutrition Examination Survey (NHANES) 1999-2004 indicate that the prevalence of both albuminuria and decreased GFR increased from 1988-1994 to 1999-2004. The prevalence of CKD stages 1 to 4 increased from 10.0\% in 1988-1994 to 13.1\% in 1999-2004 with a prevalence ratio of 1.3.\textsuperscript{117, 181}
The prevalence of ESRD is increasing worldwide at an estimated annual rate of 8% and the prevalence is likely to be greater in developing countries. \(^{[19]}\)

### 1.2.5 Co-morbidities in renal disease

Many clinical conditions present in renal disease patient. These can either be the cause of progressive deterioration in renal function or be the result of renal disease. The mean number of co-morbid conditions in dialysis patients is approximately 4 per patient. \(^{[19]}\)

Earlier reports from South African registry indicated that hypertension was the most common cause of ESRD in black South Africans. \(^{[20]}\) Prevalence of diabetes mellitus has increased in Africa. Diabetes mellitus accounted for 9-15% of the causes of ESRD in Kenya. \(^{[21]}\)

Cardiovascular disease (CVD) is a leading cause of death in kidney failure. The association between CKD and cardiovascular disease has been noted. The two conditions form a feedback loop with CVD putting stain on the kidney while the injured kidney contributes to CVD. \(^{[8,19]}\)

Cognitive impairment and dementia are common in CKD patients and seem to appear early in the course of kidney disease, hence frequent monitoring is needed. \(^{[22]}\)

Infectious diseases which are the leading cause of death especially in developing countries affecting about 43% of the population also tend to affect patients with renal disease. \(^{[14,23]}\)

The chronic nature of renal disease and the occurrence of the co-morbid conditions imply that CKD patients are chronically on multiple medications for extended periods of time. Drug-related problems are therefore common in these patients as they require complex therapeutic regimens.
with 5 or more medications and 12 or more medication doses per day. These require frequent monitoring and dosage adjustment.

### 1.2.6 Dosage adjustment of antimicrobial drugs in renal insufficiency

In principle, any drug can be given to any patient, as long as the dose is adjusted in accordance with the renal function and drug pharmacokinetic profile. For antibiotics the same loading doses given to patients with normal renal function should be given to patients with CKD. Maintenance doses should be adjusted. Dose adjustment is dependent on: the degree of renal impairment, the half life of the drug and whether the effect of the antibiotics is concentration or time dependent.

Concentration dependent drugs are those for which a threshold concentration must be reached for their therapeutic effect. Aminoglycosides and fluoroquinolones are examples of antibiotics whose effect is concentration-dependent. Beta-lactams such as benzyl penicillin and valganciclovir, an antiviral drug, are examples of agents whose effect is time-dependent. For time-dependent drugs, the plasma concentration should not become lower than the threshold concentration for a given minimum duration of time for them to be effective.

After the loading dose is given, the important consideration for antibiotics which are concentration-dependent is the drug concentration at the beginning of each dosing interval. It is thus recommended that the intervals between doses are extended for patients with renal insufficiency, while the administered doses remain similar as for individuals with normal kidney function. For time-dependent agents, the drug concentration at the end of each dosing interval is
critical. The recommended dose adjustment method is reduction of the doses administered while maintaining the dosing interval. [11, 25]

1.2.8 Studies on drug dosage adjustment in renal failure patients.

Various studies show that the prevalence of inappropriate dose adjustment in renal disease is very high with values ranging from 41.1% to 75.0%. [26, 27, 28, 29, 30, 31]

The drug that were commonly prescribed in renal disease patients whose doses were often not correctly adjusted included ranitidine, antibiotic and digoxin in a study in Palestine. [26] Digoxin was also reported to be commonly inappropriately prescribed in Bosnia. Other drugs whose doses were inappropriately adjusted included, metformin, angiotensin converting enzyme (ACE) inhibitors and spironolactone. [28] Digoxin being a drug with a narrow therapeutic index could cause to adverse drug effects in these patient in appropriate dose are not administered.

Risk factors identified for prescription of wrong doses included serum creatinine greater than 1.71mg/dL, creatinine clearance less than 35ml/min/1.73m² and adverse effect of the drug if dosing guidelines are overlooked. [27] Gender was identified as a risk factor in Bosnia where incorrect dose occurred more in women. [28]

With regard to antibiotics, a retrospective study in France found the incidence of incorrect dosing to be 75.0% in an orthopedic ward. [29] This was very high considering the facts that antibiotics are frequently prescribed in this set up.
Appropriate prescribing of drugs in renal disease patients can be improved. Intervention to improve prescribing practices have been studied and shown to improve patient care. Key among the interventions is the involvements of pharmacists in drug therapy monitoring, ward round attendance by clinical pharmacist together with the nephrology team and development of a dosing program for commonly prescribed drug in patients with renal disease.

1.3 PROBLEM STATEMENT

Infectious diseases are the major causes of morbidity and mortality in Sub-Saharan Africa. Antibiotics are therefore widely prescribed to patients including those with renal diseases in most health care facilities. Appropriate dose adjustment is necessary in these patients. This would maximize efficacy and minimize toxicity. Locally there is no documented evidence of whether dose adjustment in CKD patients is done and whether it is done appropriately. The proposed study therefore aims to find out the practice of antibiotic use and dose adjustment in patients with renal insufficiency due to CKD at KNH.

1.4 RESEARCH QUESTIONS

1. What is the antibiotic prescribing pattern in patients with renal insufficiency at Kenyatta National Hospital?

2. Are antibiotic doses adjusted on the basis of the degree of renal insufficiency?
1.5 RATIONALE OF THE STUDY

Patients with chronic kidney disease are frequently encountered in clinical practice. For example in the United States of America, it is estimated that 15 million people have serum creatinine values of 1.5 mg/dl or greater.\textsuperscript{117}

Chronic kidney disease causes progressive deterioration of the kidney function and therefore, these patients present with varying degrees of renal insufficiency (RI). The patients with RI have altered drug pharmacokinetic and pharmacodynamic profile. Dosage adjustment is necessary in these patients to avoid undue toxicity and optimize therapeutic outcome. Adjustments depend to the degree of RI. Dose adjustments reduce the incidence of adverse drug reaction, improve treatment success and reduce hospital admission and even mortality. It can also have economic impact by avoidance of adverse effects which would minimize the length of hospital stay and avoiding cost associated with drug related toxicity.\textsuperscript{134}

It is necessary to study the trends of dosage adjustment locally, with the aim of instituting corrective measures if need be to avoid undue suffering of patients.
1.6 OBJECTIVES

Main objective

The main objective of the study was to determine the patterns of antibiotic use and dose adjustment in patients with chronic kidney disease (CKD) at Kenyatta National Hospital (KNH).

Specific objectives

The specific objectives were to determine:

1) The types of antibiotics prescribed to patients with chronic kidney disease (CKD) at KNH.

2) If dose adjustment of antibiotics was done depending on the degree of renal insufficiency for patients with CKD.

3) The prevalence of appropriate antibiotic dose adjustment in CKD patients at KNH.

4) Factors associated with inappropriate antibiotic dose adjustment among patients with CKD.
CHAPTER TWO

2.0 METHODOLOGY

2.1 Ethical consideration

Permission to carry out the research was sought from the KNH/U.O.N. Ethics and Research Committee before the research was conducted. (Refer to attach letter of approval on Appendix 5)

There were no risks involved for the patients since the research involved retrospective review of patient files hence no direct patient involvement.

For confidentiality, the patient files were only used within the confines of the medical records department of KNH and only the investigator with the assistance of the medical records department personnel had access to the files for purposes of the study. The patient identifying information such as the name and hospital registration numbers were not included in the data collection forms and instead study numbers were assigned to each patient. All the filled data collection forms was filed and stored in lockable drawers.

2.2 Study design

The study was a retrospective cross sectional study for the time period January 2006-December 2010.
2.3 Study area description

The study was conducted at Kenyatta National Hospital (K.N.H), which is the largest national referral, teaching and research hospital in East Africa. The hospital has a staff capacity of 6,000, bed capacity of 1800 with an average annual out-patient attendance of 600,000 visits and average in-patient numbers of 89,000 patients. It receives patients on referral from other hospitals or institutions within and outside Kenya for specialized health care. It also provides facilities for medical education for the University of Nairobi and Kenya Medical Training College (KMTC) and for research either directly, or through other collaborating health institutions. Currently, it is the only public hospital that offers dialysis to patients with renal failure in the country serving patients from all over Kenya and beyond. From anecdotal information it receives approximately 5 new patients with renal disease every week. It has well established departments including a medical records department.

It was therefore an ideal study site due to availability of renal patients from all over the country and beyond. The medical records department has a good data management system.

2.4 Study population

The study population was adult patients aged 18 years and above and diagnosed with Chronic kidney disease and attended Kenyatta National Hospital during the period January, 2006 to December, 2010.
2.4.1 **Inclusion criteria**

Patients were included into the study if they had a diagnosis of CKD, were 18 years of age and above, had antibiotic prescribed to them during the study period and had documented laboratory measurement of the serum creatinine concentration.

2.4.2 **Exclusion criteria**

Patients were excluded from the study if they either had no recorded diagnosis of chronic kidney disease, were below 18 years of age, were not prescribed for any antibiotic during the study period and had no laboratory measurement of serum creatinine was undertaken prior to the time of antibiotic prescription generation.

2.5 **Sample size determination**

Sample size was determined using the following equation.\[^{35}\];

\[
N = \frac{4z_a^2 \, P \, (1-P)}{W^2}
\]

Where;

- \(Z_a\) = Standard normal deviate at 95% Confidence interval (1.96)
- \(P\) = Expected proportion of inappropriately adjusted doses. A proportion of 0.75 was used as per findings of Arlicot and colleagues who studied antibiotic adjustment.\[^{26}\]
- \(W\) = Total width of the confidence interval (0.10)
Therefore.

\[ N = 4(1.96^2)(0.75)(1-0.75) - 0.1^2 \]

\[ N = 288 \text{ files} \]

Allowing for 10% non-completeness, the minimum sample size required was adjusted upwards to 317 files.

### 2.6 Sampling method

A simple random sample of 500 files was selected from the availed list of files of patients with CKD using a random number generator. From the sample 475 files were availed for the study. 314 patients met the eligibility criteria and were used in the study. 133 patients had no antibiotic prescriptions within the study period. 18 patients were below 18 years of age. 6 had no documented diagnosis of CKD and 2 had had prior kidney transplantation. (Figure 1)
2.7 Data collection and materials

A predesigned data collection form was pre-tested and used to collect the relevant data on patient demographics, concurrent medical condition, serum creatinine concentration and antibiotic dosing regimens prescribed to the CKD patients. Data was retrieved from the sampled patient
files. The latest three antibiotic prescriptions were considered in the study to reflect the current practices in antibiotic prescribing.

For each antibiotic prescribed to each patient, the doses prescribed and the frequency of administration was documented. The GFR was calculated for the patient in question. The prescribed dosages were compared with those that are recommended in the guideline for dose adjustment in renal failure.

**Pre-testing of the data collection form**

The data collection form was piloted by randomly sampling 10 files for patients with CKD from the medical records department. The data was entered into the form to test for its suitability in data collection. The form was then redesigned to ensure that it captured all the required information.

**2.8 Data management**

Data on patient demographics at the time of CKD diagnosis, latest three antibiotic prescription episodes and the initial laboratory serum creatinine concentration before the antibiotic prescription were retrieved from the sampled files. The retrieved data was coded and double entered into a computer database designed using MS-Excel application. Data cleaning and validation was performed to achieve a clean dataset that was then exported into a Statistical Package format, STATA version 9 program. A clean datasets was stored in a computer hard drive disks ready for analysis. Back up files were stored in a CD and flask disc. This was done regularly to avoid any loss or tampering.
2.9 Data analysis

All variables were subjected to descriptive data analysis. For continuous variables, the median and interquartile ranges (IQR) were reported. Categorical variables were reported as proportions of various components and the 95% confidence interval (95% CI). The distribution of various variables was compared across clinical setting using Pearson’s chi square test for categorical variables and kruskal-wallis test for continuous variables. P-values of less than 0.05 were considered statistically significant.

The risk factors for incorrect dose adjustment were determined using logistic regression. Stepwise model building was used to identify the most important risk factors for failure to adjust the dose correctly.

2.10 Definition of cases

The following criterion was used to define cases of appropriate dose adjustment.

**Appropriate dose adjustment;** those doses that conform to the guidelines on dosage adjustment in renal failure patients.  

Dosages were deemed appropriately adjusted if the correct doses were prescribed at the recommended frequency of administration for the degree of renal insufficiency.

Wrong doses prescribed and wrong frequencies of administration on the prescription form were considered inappropriate dosage adjustment.
For drugs with no recommendation in the guideline, the recommendations in the British National Formulary (BNF) 59th Edition 2010 were used to judge the appropriateness of dose adjustment.

2.11 Variables, confounders and outcomes of interest

The main outcome of interest was appropriate adjustment of antibiotic dose. This outcome was divided into two categories depending on whether dose adjustment was correctly done, or dose adjustment was not correctly done.

The type of dosing error for antibiotics that were inappropriately prescribed was determined and classified as either over dosage or under dosage.

The independent variables included patient demographics, antibiotic prescribed, severity of renal disease, hospital unit where the prescription was generated, prescriber trait, concurrent medical condition, duration of therapy and whether the patient is on dialysis or not and the dialysis type.
3.0 RESULTS AND DISCUSSION

3.1 Baseline demographic characteristics of the study population

The study was carried out in two clinical settings, the wards and the specialized renal unit of KNH. The baseline demographic characteristics were as in the Table 2.

Table 2 Demographic characteristics of the study population

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>NUMBER OF OBSERVATIONS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (years) [Median (IQR, n)]</td>
<td>46 (32-60, n = 313)</td>
</tr>
<tr>
<td>Weight (K) [Median (IQR),n]</td>
<td>62 (56-70, n = 59)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>180 (57.3%)</td>
</tr>
<tr>
<td>Female</td>
<td>134 (42.7%)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>63 (20.2%)</td>
</tr>
<tr>
<td>Married</td>
<td>250 (79.8%)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>Non-formal</td>
<td>34 (11.6%)</td>
</tr>
<tr>
<td>Primary</td>
<td>118 (40.1%)</td>
</tr>
<tr>
<td>Secondary</td>
<td>104 (35.4%)</td>
</tr>
<tr>
<td>Tertiary</td>
<td>38 (12.9%)</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>193 (62.3%)</td>
</tr>
<tr>
<td>Formal employment</td>
<td>50 (16.1%)</td>
</tr>
<tr>
<td>Self employment</td>
<td>67 (21.6%)</td>
</tr>
</tbody>
</table>
The median age at diagnosis of CKD in the study population was 46 years. The young age at diagnosis of CKD in the study population is consistent with the situation in Sub-Saharan Africa where the condition is reported to affect mainly the young adults aged between 20-50 years of age. In Nigeria the peak prevalence of CKD between the third and the fifth decade. This is unlike in the more developed countries where it affects mainly the middle aged and elderly patients.

The number of male and female was almost the same however, there were slightly more males (57.3%) than female patients. Gender disparities in the rate of diagnosis of CKD have been documented; this could partly explain the slightly higher number of male patients in the study. Rao and her colleagues reported that CKD was 2-fold more likely to be undiagnosed in women than in men. The rate of decline in estimated GFR has been noted to be higher in men at risk of and with CKD than the corresponding rates in women. There was limited data on weight with only 59 entries at baseline.

Most patients had attained at least primary education accounting for 88.4% of the study subjects. This is typical of the Kenyan demographics with literacy levels of 85.1% in the total population.

3.2 Severity, causes and management of renal disease

3.2.1 Stages and management of renal disease

The degrees of renal insufficiency varied amongst the study subjects. Table 3 summarizes selected renal parameters of the study group.
Table 3 Renal parameters at the antibiotic prescription episodes per clinical setting

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ward Median (IQR), n</th>
<th>Renal unit Median (IQR), n</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine(μmol/L)</td>
<td>745 (385-1141), 533</td>
<td>920 (612-1110), 105</td>
<td>0.004</td>
</tr>
<tr>
<td>Est.GFR*(ml/min/1.73m²)</td>
<td>7.7 (4.76-15.58), 533</td>
<td>7.01 (4.98-9.92), 105</td>
<td>0.012</td>
</tr>
<tr>
<td>Stage of renal disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5 (0.9%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>11 (2.1%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>28 (5.2%)</td>
<td>0 (0.0%)</td>
<td>0.000</td>
</tr>
<tr>
<td>4</td>
<td>68 (12.8%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>421 (79.0%)</td>
<td>105 (100.0%)</td>
<td></td>
</tr>
<tr>
<td>Dialysis status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient on dialysis</td>
<td>234 (43.9%)</td>
<td>102 (97.1%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Patient not on dialysis</td>
<td>299 (56.1%)</td>
<td>3 (2.9%)</td>
<td></td>
</tr>
</tbody>
</table>

*Estimated glomerular filtration rate

Patients who were seen in the renal unit had more severe renal insufficiency than those seen in the other non specialized wards (P=0.000). This was reflected by higher serum creatinine concentration, lower estimated GFR and more advanced CKD stage in those seen in the renal unit. All patients seen in the renal unit had stage 5 disease and majority of them (97.1%) were on dialysis. In the wards, all the stages of renal insufficiency were present. The trend was however towards higher frequencies of more advanced disease with a majority of patients (79.0%) being in stage 5 while only 0.9% were at stage one. The reason for this observation could be because,
the less severe cases of CKD were either more stable and were less likely to present in the wards with complications or was due to lack of aggressive screening procedures to identify those patients with mild disease.

Ideally patients in stage 5 disease should have been on renal replacement therapy (RRT) in the form of either dialysis or kidney transplantation, but only 234 patient seen in the ward were on dialysis leaving out about 187 cases who needed dialysis. The main reason for this was lack of funds to support the intervention. RRT is a very expensive intervention requiring massive financial support. In KNH, a session of hemodialysis costs about Ksh. 4500 and the patients have to pay for the costs on their own. This is a huge burden to the patients and their families hence the low uptake of the services by patients in the wards.

3.2.2 Causes of chronic kidney disease in the study population

A number of causes of CKD were identified in the study population with varying frequencies. The single most frequently documented cause of CKD was primary glomerular disease which included rapidly progressing glomerulonephritis, chronic glomerulonephritis and nephrotic syndrome. This accounted for 22.6% of all causes (Figure 2). Hypertension and obstructive uropathy were the next frequent causes accounting for 19.8% and 17.9% respectively. Patients with glomerular diseases as the cause of CKD were younger with the median age at diagnosis of CKD of 30 years (IQR= 27-36 years), whereas obstructive uropathy was a major cause of CKD in elderly males with a median age at diagnosis of 65 years (IQR= 46-74 years).
There is evidence that glomerular diseases are more prevalent in Africa and seems to be of a more severe form than that found in Western countries. Glomerular disease in Africa is characterized by poor response to treatment and progression to renal failure. Hypertension is also reported to be major cause of CKD in Sub Saharan African countries.

Diabetes mellitus has also emerged as a major cause of ESRD in Kenya with reports indicating that it accounts for between 9-15% of ESRD. Cumulatively they accounted for 46.4% of all causes of the condition, either alone or as co-existing conditions. These could have been the facts behind the higher occurrences of glomerular diseases and hypertension as the major causes of renal disease in the study population.
3.3 Patterns of antibiotic use in the study population

3.3.1 Types of antibiotics prescribed

There were 638 antibiotic prescriptions noted. Most of the antibiotics that were prescribed were those listed in the KNH formulary. The frequencies of prescriptions however differed with ceftriaxone and co-amoxiclav (combination of amoxicillin and clavulanic acid) being the most frequently prescribed antibiotics.

Most of the antibiotic prescriptions were as per the recommendations in the Kenyan clinical guideline for management and referral of common conditions in Kenya.

Ceftriaxone, a third generation cephalosporin was the most frequently prescribed antibiotic, followed by co-amoxiclav. The two most frequently prescribed antibiotics have the advantage of broad spectrum of activity against the commonly encountered infections. Historically, the β-lactam class of antibiotics consisting mainly of the penicillins and the cephalosporins has
enjoyed longer clinical experience being amongst the first class of antibiotics to be introduced into clinical use. This class of antibiotics is also readily available and generally affordable. These could have led to their preference over the other classes of antibiotics. The β-lactams are also generally perceived to be safe.

Aminoglycoside consisting of gentamicin and amikacin constituted a very small proportion of the total antibiotics prescribed with each making up less than 2%. Aminoglycoside are well known to be nephrotoxic and also ototoxic especially in conditions that can lead to drug accumulation like in renal disease. This could have been the reason for the infrequent prescription of this class of drugs in the study subjects.

Most prescribed antibiotics were not contraindicated in CKD. Only 5 (0.8%) episodes of nitrofurantion prescriptions which ought to be avoided in CKD were noted. This shows that prescribers are generally aware of the safety of the various antibiotics in patients with CKD. The 5 episodes of nitrofurantion prescription also only occurred in the wards but none in the renal unit indicating higher awareness of the contraindication in the specialized renal unit.

3.3.2 Route of administration, frequency and duration of use of the prescribed antibiotics

Two main route of drug administration were employed for systemic administration of antibiotics to the study population; the intravenous route and the oral route. The intravenous route was the most predominant route of administration accounting for 76.1% of the total routes of administration (Figure 4).
CKD is often associated with changes in gastrointestinal transit time, gastric pH and oedema of the gastrointestinal tract which have been feared to alter drug absorption. Frequent complications of severe renal insufficiency such as nausea, vomiting and diarrhea can too preclude the administration of drugs via the oral route. This may account for the frequent use of IV route of administration which bypasses the gastrointestinal tract and ensures high bioavailability.

Dosing frequency of 12 hourly (twice daily) and 8 hourly (three times daily) were the most frequent in both clinical settings. Twice daily dosing frequency was the most frequent accounting for 244 (38.9%) episodes of the 638 prescription episodes. Vancomycin was frequently dosed at lower frequencies of every three to seven days. This was appropriate since interval of administration extension, is the main recommended dose method in patients with RI of this drug (Appendix 4). Benzyl penicillin was prescribed appropriately at the highest frequency of every 6
hours. Benzyl penicillin exhibits time dependent bactericidal effect and thus requires the plasma drug concentration to be above the threshold for a given minimum duration. The recommended adjustment therefore is dose reduction while maintaining the interval of administration.

Most antibiotics were prescribed for 5 and 7 days duration. Duration of 5 days accounted for 43.1% (n=179) while 7 days duration accounted for 39.3% (n=163) of all cases. The longest duration of antibiotic use was 90 days of doxycycline for the treatment of acne. This was appropriate since it warrants prolonged treatment periods. Shorter durations of treatment of 1-4 days were noted in few instances and these accounted for 2.8%. These could have constituted inappropriate use or were due to change of antibiotics after short periods of use or use of antibiotics prophylactically before surgical procedures.

3.3.3 Indications for antibiotic use

There were 217 recorded indications for antibiotic use. For the rest of the episodes, antibiotics were prescribed without an indication in the records. This may represent irrational antibiotic use, a common practice especially in developing countries. Respiratory tract infections was the most frequently documented indication for antibiotics with 63 (29.0%) cases recorded, followed closely with sepsis with 50 (23.0%) cases. (Figure 5). The least documented infection was the central nervous system infection.
Patients with CKD commonly present with infections and there have been reports of higher incidences on respiratory tract infection and sepsis amongst them. Potential contributing factor to this include presence of concurrent medical conditions, vaccine hyporesponsiveness, immunosuppressive therapy, uremia, dialysis access and the dialysis procedure used. Because of these, the infections tend to be more severe and require longer treatment periods.

3.3.4 Comparison of prescribing patterns in the two clinical settings

There was a statistically significant difference in the antibiotics prescribed in the two clinical settings (P=0.000). In the wards, co-amoxiclav 116 (21.8%) episodes followed by ceftriaxone 115 (21.6%) and ciprofloxacin 50 (9.4%) episodes in the ward, were the most frequently prescribed antibiotics. In the renal unit the most frequently prescribed antibiotics were ceftriaxone 29 (27.7%), vancomycin 19 (18.1%), and co-amoxiclav 15 (14.3%) episode in the renal unit (Figure 6).
Figure 6 Antibiotics prescribed in the two clinical settings

Most antibiotics were prescribed in the ward setting accounting for 533 (83.5%) episodes of antibiotic prescription. Piperacillin/tazobactam combination and erythromycin were prescribed only in the renal unit though at a very low frequency of one episode each. Amoxicillin, clindamycin, doxycycline and gentamicin were also only prescribed in the wards.

Prescribers’ preferences could have accounted for the large variety of antibiotics prescribed in the wards. Most antibiotics were prescribed in the wards due to the general nature of the wards where most patients are bound to be admitted even before a decision is made to transfer them to more specialized units like the renal unit. Limited facilities and space in the renal unit could have led to admission of many of these patients in the wards. Renal unit being a specialized ward handling patients with renal diseases seemed to be more careful with regard to antibiotic selection and tended to avoid certain antibiotics such as nitrofurantoin and gentamicin.
3.4 Antibiotic dose adjustment

3.4.1 Antibiotic dose adjustment requirement and how they were adjusted

Not all antibiotics required dose adjustment. The most frequently prescribed antibiotic, ceftriaxone \( n=145 \) does not routinely require dose adjustment.\(^\text{[36]}\) Others that were prescribed and did not require dose adjustment included doxycycline \( n=2 \), flucloxacillin \( n=19 \), erythromycin \( n=1 \), clindamycin \( n=1 \), metronidazole \( n=53 \) and linezolid \( n=3 \).

Table 4 Extent of dose adjustment

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Number of cases where adjustment was not required</th>
<th>Number of cases where adjustment was required</th>
<th>Dose incorrect (%)</th>
<th>Dose correct (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>1</td>
<td>4</td>
<td>3 (75.0%)</td>
<td>1 (25.0%)</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>1</td>
<td>6</td>
<td>4 (66.7%)</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>Benzyl penicillin</td>
<td>0</td>
<td>37</td>
<td>19 (51.4%)</td>
<td>18 (48.6%)</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>0</td>
<td>17</td>
<td>11 (64.7%)</td>
<td>6 (35.3%)</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>11</td>
<td>34</td>
<td>27 (79.4%)</td>
<td>7 (20.6%)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0</td>
<td>53</td>
<td>33 (62.3%)</td>
<td>20 (37.7%)</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>0</td>
<td>18</td>
<td>12 (70.6%)</td>
<td>6 (29.4%)</td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td>2</td>
<td>129</td>
<td>118 (91.5%)</td>
<td>11 (8.5%)</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>0</td>
<td>7</td>
<td>7 (100.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0</td>
<td>8</td>
<td>5 (62.5%)</td>
<td>3 (37.5%)</td>
</tr>
<tr>
<td>Imipenem/cilastatin</td>
<td>0</td>
<td>5</td>
<td>3 (60.0%)</td>
<td>2 (40.0%)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>0</td>
<td>5</td>
<td>5 (100.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>0</td>
<td>12</td>
<td>9 (75.0%)</td>
<td>3 (25.5%)</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>0</td>
<td>10</td>
<td>7 (70.0%)</td>
<td>3 (30.0%)</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>0</td>
<td>1</td>
<td>1 (100%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>15</td>
<td>33</td>
<td>10 (30.3%)</td>
<td>23 (69.7%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>379 (59.9%)</strong></td>
<td><strong>274 (72.3%)</strong></td>
<td></td>
<td><strong>104 (27.7%)</strong></td>
</tr>
</tbody>
</table>
Some antibiotics were administered as single doses at the commencement of treatment hence dose adjustment was not necessary in such instances. Cefuroxime axetil which is the oral formulation of cefuroxime does not routinely require adjustment. Vancomycin was the most frequently adjusted antibiotic while the least adjusted was Co-amoxiclav. (Table 4)

### 3.4.2 Prevalence of inappropriate dose adjustment in the study population

Figure 7 summarizes the antibiotic dose adjustment practices in the study settings. Of the 638 prescriptions recorded in the study, 379 (59.9% 95% CI 55.9-63.7) prescriptions were indicated for use in RI required dose adjustment. Dose adjustment was not necessary in 254 (40.1% 95% CI 36.3%-44.1) prescriptions. Only 104 antibiotic prescriptions were properly adjusted depending on the degree of renal insufficiency accounting for 27.7% (95%CI 23.18-32.23) of the prescriptions that required adjustment. Dose adjustment was overlooked in 72.3% (95%CI 67.77-76.82) of prescriptions that required dose adjustment.

The most common prescribing error noted was overdosing accounting for 98.9% (95% CI 97.7-100.2) of all errors (271 out of 274 prescriptions) with only three cases of under dosing noted in the study.

Despite the need to adjust antibiotic doses in renal insufficiency, this practice is often overlooked. In the study, only 27.7% of the antibiotic prescriptions that required dose adjustment were correctly adjusted. This reflects the need to sensitize prescribers on the how to correctly adjust antibiotic doses in RI.
Over dosing was the most common error. This was because doses that were prescribed to patients with renal disease were those recommended for use in individuals with normal renal function. This translated in over dosage in CKD patients. For example, the most frequently
prescribed antibiotic that required dose adjustment, co-amoxiclav, was frequently prescribed at a
dose of 1200mg every eight hours (73.3% of the episodes).

Over dosing has the potential of having negative impact on the patients. This is in terms of drug
accumulation with potential for more adverse effects and increase cost of treatment. The cost
increases as a direct consequence of the additional doses which ought not to be administered and
also increased hospital stay and interventions to manage the adverse drug effects.

The problem of inappropriate dose adjustment in renal insufficiency seems to be widespread. A
similar study on antibiotics in France showed almost similar prevalence of inappropriate dose
adjustment at 75% inappropriate doses. The investigators noted that the antibiotics were
prescribed according to protocols for use in patients with normal renal function. A recent study
done in South Africa also indicated 68% prevalence of inappropriate dose adjustment. To
optimally manage patients with CKD great emphasis should therefore be placed on the need to
preserve and administer appropriate doses.

3.4.4 Risk factors for inappropriate dose adjustment in the study population

3.4.4.1 Demographics, renal disease related variables and concurrent medical conditions

Age, gender, severity of renal disease, clinical setting where the prescriptions were generated and
concurrent medical conditions were analyzed to determine their association with inappropriate
dose adjustment. (Table 5)
Table 5 Determinants of inappropriate dose adjustment

<table>
<thead>
<tr>
<th>variable</th>
<th>Crude OR (95% CI), P-value</th>
<th>Adjusted OR (95% CI), P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.01 (1.00-1.02), 0.167</td>
<td>0.82 (0.62-1.08), 0.163</td>
</tr>
<tr>
<td>Gender</td>
<td>0.76 (0.48 -1.19), 0.228</td>
<td>0.77 (0.38-1.56), 0.468</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>0.9989 (0.9984-0.9995), 0.000</td>
<td>0.9999 (0.9991-1.0007), 0.814</td>
</tr>
<tr>
<td>Estimated GFR (ml/min/1.73m²)</td>
<td>1.06 (1.04-1.09), 0.000</td>
<td>1.05 (0.97-1.12), 0.213</td>
</tr>
<tr>
<td>CKD stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>2.99×10⁻⁸ (7.50×10⁻⁹-1.20×10⁻⁷), 0.000</td>
<td>0.34 (0.10 - 1.21), 0.097</td>
</tr>
<tr>
<td>Stage 4</td>
<td>5.08×10⁻⁹</td>
<td></td>
</tr>
<tr>
<td>Stage 5</td>
<td>1.66×10⁻⁸ (8.58×10⁻⁹-3.22×10⁻⁹), 0.000</td>
<td></td>
</tr>
<tr>
<td>Dialysis status</td>
<td>0.52 (0.33-0.82), 0.005</td>
<td>0.36 (0.08-1.66), 0.190</td>
</tr>
<tr>
<td>Type of dialysis</td>
<td>0.60 (0.38 - 0.93), 0.024</td>
<td>1.45 (0.37-5.65), 0.590</td>
</tr>
<tr>
<td>Clinical setting</td>
<td>0.94 (0.50-1.80), 0.868</td>
<td>1.24 (0.42 - 3.67), 0.703</td>
</tr>
<tr>
<td>Concurrent medical condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.23 (0.64 - 2.37), 0.529</td>
<td>1.19 (0.44 - 3.23), 0.732</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.06 (0.59-1.89), 0.848</td>
<td>1.66 (0.71 - 3.92), 0.243</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>1.32 (0.54 - 3.20), 0.538</td>
<td>1.93 (0.51-7.36), 0.335</td>
</tr>
<tr>
<td>Heart disease</td>
<td>4.89 (1.10 - 21.67), 0.037</td>
<td>14.95 (2.10-106.40), 0.007</td>
</tr>
<tr>
<td>BPH</td>
<td>0.59 (0.16 - 2.16), 0.424</td>
<td>0.13 (0.02 - 1.07), 0.058</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>5.87 (0.51 - 67.01), 0.154</td>
<td>1.40 (0.07 - 29.02), 0.828</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>5.87 (0.51 - 67.01), 0.154</td>
<td>17.61 (0.39 - 792.16), 0.140</td>
</tr>
<tr>
<td>Others</td>
<td>0.49 (0.06 - 4.22), 0.516</td>
<td>0.40 (0.03 - 6.09), 0.509</td>
</tr>
</tbody>
</table>

On univariate analysis, the only statistically significant associations between correct dose adjustment and the covariate of interest were the dialysis status, type of dialysis and parameters that measure the severity of renal disease which included; serum creatinine, estimated GFR and the CKD stage.

On univariate analysis, clinical setting where the prescription was generated was not significant factor in determining appropriate antibiotic prescribing.
There was a negative association between dialysis status and the chances of correct dose adjustment. A similar negative association was noted for severity of CKD and serum creatinine concentration. The greater the severity of renal disease meant the lesser the probability of receiving the correct doses. For example, patients in stage 3 of the CKD were about five times less likely to receive the correct dose compared to patients with stage 1 disease. On the other hand, patients in stage 5 disease were more than hundred times more likely to receive an incorrect dose compared to those in stage 1. This observation is further confirmed by the observation that there was a strong positive association between estimated GFR and the probability of receiving the correct dose. These findings indicate that prescribers were able to more accurately determine the correct dose for patients with less severe CKD. In mild disease, the doses used in normal subject also seen to be appropriate lessening the need for dose reduction.

There was also a statistically significant positive association between the presence of heart disease and the correct dose administration. The associations were not significant for all the other concurrent medical conditions. This may be attributed to the awareness by prescribers of the vulnerability of heart disease patients to situations such as electrolyte imbalances and therefore these patients may have been more keenly managed. Conditions such as diabetes mellitus, hypertension and cancers are considered not to be immediately life threatening.

3.4.4.2 Prescribed antibiotics

Apart from the renal parameters, it was noted that there was statistically significant negative association between co-amoxiclav and the correct dose. This finding is very significant since co-
amoxiclav was the most frequently prescribed antibiotic that required dose adjustment in CKD. The odds of receiving a wrong dose of co-amoxiclav were about seven times the odds of receiving a wrong dose of amikacin. This indicates that prescribers need to be sensitized on the need to correctly adjust doses of frequently prescribed antibiotics especially co-amoxiclav. Altered pharmacokinetic profile of co-amoxiclav has been evaluated [48, 49] and its likelihood of accumulation in CKD determined. The British National Formulary lists crystalluria as a potential consequence of this. [37]

The other notable association was the strong positive association between vancomycin and correct antibiotic dose. Although this finding was not statistically significant, the magnitude of the strength of association indicates that it may be a valid observation.

Table 6: Prescribed antibiotics as determinants of appropriate dose adjustment

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>CRUDE OR (95% CI), P-VALUE</th>
<th>ADJUSTED OR (95% CI), P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic prescribed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>1.04 (1.01 - 1.08), 0.025</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>0.50 (0.03 - 8.95), 0.638</td>
<td></td>
</tr>
<tr>
<td>Benzyl penicillin</td>
<td>0.75 (0.06 - 8.83), 0.819</td>
<td>0.96 (0.01 - 65.57), 0.985</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>1.38 (0.21 - 9.52), 0.717</td>
<td>3.47 (0.17 - 71.27), 0.420</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>0.82 (0.11 - 6.34), 0.848</td>
<td>17.11 (0.72 - 406.16), 0.079</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.39 (0.05 - 2.80), 0.348</td>
<td>1.94 (0.09 - 41.12), 0.672</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>0.91 (0.14 - 5.92), 0.921</td>
<td>9.59 (0.43 - 212.33), 0.153</td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td>0.62 (0.08 - 4.96), 0.656</td>
<td>5.14 (0.18 - 148.31), 0.340</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0.14 (0.02 - 0.93), 0.042</td>
<td>0.2965 (0.01 - 5.98), 0.428</td>
</tr>
<tr>
<td>Meropenem</td>
<td>0.90 (0.09 - 8.90), 0.928</td>
<td>13.75 (0.42 - 441.05), 0.139</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>0.50 (0.05 - 4.58), 0.540</td>
<td>6.73 (0.25 - 179.89), 0.256</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>0.64 (0.07 - 6.06), 0.699</td>
<td>2.90 (0.06 - 135.99), 0.587</td>
</tr>
<tr>
<td></td>
<td>3.45 (0.50-23.94), 0.210</td>
<td>5.62 (0.19 - 166.01), 0.318</td>
</tr>
</tbody>
</table>
Out of the 48 prescriptions of vancomycin recorded in the study (Table 4), 33 required dose adjustment and this was correctly done in 23 of the prescriptions. Due to the small numbers of patients, this finding was not statistically significant. It is also notable that on adjusting for confounding, the odds ratio increased to 5.6 (95% CI 0.19 - 166.01). Though empiric doses of 1g every 4-7 days were prescribed for most patients, it was difficult to ascertain if the dose were adequate since therapeutic drug monitoring (TDM) was never done for the study population. The need for TDM to guide vancomycin dosing has been studied and shown to be essential for proper management of serious infections in CKD patients.\textsuperscript{50}

For most of the other antibiotics, there was negative association between them and the correct dose on univariate analysis. However after adjusting for confounding, there was a positive association. The strongest positive associations were observed for ceftazidime, gentamicin and meropenem. The change in direction of association may be due to the effect of confounding by severity of renal disease. On univariate analysis, the effect of inappropriate dosing in patients with severe renal disease seemed to outweigh correct dose prescribing in less severe renal disease. In cases of gentamicin, ceftazidime and meropenem, prescribers probably have good knowledge of the potential adverse consequences of inappropriate dosing in renal insufficiency.

The only antibiotics that showed persistent negative association after adjusting for confounding by severity of renal disease were amoxicillin and co-amoxiclav. The two are penicillins have very wide therapeutic index and are hence perceived by most prescribers to be safe leading to the reduced tendency to accurately adjust the doses in renal disease.
3.4.4.3 Dose adjustment of selected antibiotic classes

Beta lactams

On univariate analysis, there was a negative association between prescription of β-lactams and the correct dose adjustment with (OR 0.85, 95% CI 0.781-0.935, p = 0.001). Benzyl penicillin, ceftazidime and imipenem/cilastatin were more likely to be prescribed correctly compared to amoxicillin while cefuroxime, co-amoxiclav and meropenem were less likely to be prescribed correctly compared to amoxicillin. Piperacillin/tazobactam was always prescribed wrongly. On adjusting for confounding, there was a very strong positive association between the clinical setting where prescriptions were written and the correct dose for this class of antibiotics. In the renal unit, all the doses of benzyl penicillin, cefuroxime and co-amoxiclav were incorrect. This is unlike in the wards where 51.4% of the benzyl penicillin doses were correct (18 out of 35 prescriptions). This implies that β-lactams were more likely to be adjusted correctly in the wards. Another possible explanation for this difference is the occurrence of less severe case of renal disease in the wards. All patients seen in the renal unit were in stage 5 of CKD.

Fluoroquinolones

There was a negative association between the correctness of the prescribed doses and the fluoroquinolones but this was not statistically significant. All patients received wrong doses of levofloxacin. Patients treated with norfloxacin were more likely to receive the correct dose compared to patients treated with ciprofloxacin (OR 0.71, 95% CI 0.163-3.051, p = 0.642). The observation was however not statistically significant due to the small sample size.
From these observations, it seemed that norfloxacin was more likely to be administered correctly compared to the other members in this chemical class. This implies that clinical experience with an antibiotic affected administration of the correct dose.

Aminoglycosides

Attention was paid to aminoglycosides because they are very nephrotoxic. There were 8 prescriptions of gentamicin and 4 for amikacin. Gentamicin was more widely used because it is less costly. Unfortunately only 3 prescriptions of gentamicin and 1 prescription of amikacin were correct.

Gentamicin was more likely to be prescribed correctly compared to amikacin (OR 1.80 95% CI 0.123-26.20, p = 0.667). However, this observation was not statistically significant because of the small sample size involved.

On univariate analysis there was a very strong association between clinical setting and prescription of aminoglycosides. In the renal unit, no aminoglycosides were prescribed. They could have been avoided in this setting because of the greater awareness about the nephrotoxicity of aminoglycosides.
CHAPTER FOUR

4.0 CONCLUSION

Ceftriaxone and co-amoxiclav were the most frequently prescribed antibiotics. Consistent with the other studies, [26, 27, 28, 29, 30, 31] dose adjustment was a frequently overlooked aspect in the management of infection in patients with CKD. Dose adjustment was required in 59.9% of prescription episodes, but was done correctly in 27.7% of these episodes.

The degree of renal insufficient was an important determinant for appropriate antibiotic dose adjustment. Patients with severe renal disease were more likely to receive wrong antibiotic doses.

Co-amoxiclav which was a commonly used antibiotic requiring dose adjustment was frequently overlooked.

Therapeutic drug monitoring was neither requested nor done for any of the antibiotics that were studied.

4.1 RECOMMENDATIONS

An appropriate estimating formula should be adapted for routine use within the hospital. The GFR should be estimated for all the patients with CKD to enable all the concerned healthcare personnel to make rational intervention. If possible an automated system of reporting the estimated GFR should be adopted.
Strategies to alert prescribers of the need for dose adjustment should be considered such as, simplified aids to guide dose adjustment of the commonly prescribed drugs including antibiotics and active involvement of pharmacist in medication use monitoring.

Currently information on the patient treatment sheets does not include information on the renal parameters. These should be included so that the pharmacists and other personnel who handle antibiotic prescriptions and other drugs are aware of the renal status of the patients, so as to enable them to make the necessary adjustments and consultations with the prescribers.

The study designed to determine the outcome of inappropriate dose adjustment would be useful to give more insight in to the consequences of inappropriate dose adjustment.

4.2 STUDY LIMITATIONS

The standard for estimation of GFR in the study was based on the documented serum creatinine using the MDRD 4 equation but not the gold standard of measuring the GFR using an exogenous filtration marker.

The study was retrospective in nature and therefore the information obtained from the records could not be verified.
5.0 REFERENCE:


6.0 APPENDICES

Appendix 1: Study eligibility checklist

Date ----------------------------------------- Case Number. --------------------

Data collector's initials------------------------

File study code number-----------------------

Inclusion criteria (if any of the inclusion statement below is marked NO, the file is not included in the study)

YES ( ) NO ( ) Patient 18 years old and over.

YES ( ) NO ( ) There is a diagnoses of having chronic kidney disease.

YES ( ) NO ( ) Data regarding the serum creatinine concentration recorded.

YES ( ) NO ( ) Age and sex of the patient documented.

YES ( ) NO ( ) There is antibiotic prescription.

Exclusion criteria (if any of the statements below is marked YES, the file is not included in the study)

YES ( ) NO ( ) the patient was below 18 years of age at the time

YES ( ) NO ( ) There is no documented serum creatinine levels in the file

YES ( ) NO ( ) Age and sex are not recorded on the file

YES ( ) NO ( ) there is no antibiotic prescribed

Is the file eligible for the study?

YES ( ) NO ( )
Appendix 2: Reason for exclusion

YES ( ) NO ( ) The patient was below 18 years of age

YES ( ) NO ( ) There is no documented serum creatinine levels in the file

YES ( ) NO ( ) Age and sex are not recorded on the file

YES ( ) NO ( ) There was no antibiotic prescription

YES ( ) NO ( ) There is no antibiotic prescribed
Appendix 3: Data collection form

**Patient demographics**

Date: 
Data collector's initials: 
Patient code number: 
Age: years 
Weight: Kg 
Gender: 
   Male ( ) 
   Female ( ) 
Marital status: 
   Single ( ) 
   Married ( ) 
Education level: 
   0. None 
   1. Primary 
   2. Secondary 
   3. Tertiary 
Employment status: 
   0. Unemployed 
   1. Formally employed 
   2. Self employed 

Date of admission: 

**Concurrent illnesses**

<table>
<thead>
<tr>
<th>Medical condition</th>
<th>Date of diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Clinical history pertaining to renal disease**

**Episode of antibiotic use**

Year of diagnosis: 

---

51
Likely cause

Serum creatinine at the time of antibiotic prescription

Calculated creatinine clearance (estimated GFR) -ml/min

Severity stage of renal disease:

1 ( )
2 ( )
3 ( )
4 ( )
5 ( )

Patient on dialysis

YES ( )
NO ( )

Dialysis type:
0. Intermittent haemodialysis ( )
1. Continuous peritoneal dialysis ( )

**Details of infectious disorder**

Date of diagnosis------------------------- Indicated diagnosis --------------------------

**Antibiotics prescribed**

<table>
<thead>
<tr>
<th>Serial No.</th>
<th>Drug</th>
<th>Initial dose</th>
<th>Maintenance dose</th>
<th>frequency</th>
<th>Duration</th>
<th>Dose adjustment required</th>
<th>Was the dose appropriately adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Y/N</td>
<td>Y/N</td>
</tr>
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<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

52
Clinical setting where the prescription was written

Renal unit ( )
Inpatient medical ward ( )
Outpatient clinic ( )
Other ( ) specify------------------------

Was therapeutic drug monitoring requested for any of the prescribed antibiotics?

YES ( ) NO ( )

If YES was it done?

YES ( ) NO ( )
Appendix 4: Drug dosage adjustment for antibiotics in the KNH drug list according to the guideline to be used in the study

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose for individuals with normal renal function</th>
<th>Recommended method of dose adjustment</th>
<th>Adjustment for renal failure according to GFR in mL/min/1.73ms²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;50</td>
</tr>
<tr>
<td>Amikacin (monitor plasma levels)</td>
<td>7.5mg/kg q12h</td>
<td>Interval extension</td>
<td>100% q12h or 24h</td>
</tr>
<tr>
<td>Gentamicin (monitor plasma levels)</td>
<td>1.7mg/kg q8h</td>
<td>Interval extension</td>
<td>100% q8-24h</td>
</tr>
<tr>
<td>Kanamycin (monitor plasma levels)</td>
<td>7.5mg/kg q12h</td>
<td>Interval extension</td>
<td>100% q12-24h</td>
</tr>
<tr>
<td>Tobramycin (monitor plasma levels)</td>
<td>1.7mg/kg q8h</td>
<td>Interval extension</td>
<td>100% q8-24h</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>250-500mg q8h</td>
<td>No adjustment</td>
<td>100%</td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>0.5-1g q12h</td>
<td>Interval extension</td>
<td>100% q12h</td>
</tr>
<tr>
<td>Cefamandole</td>
<td>0.5-1g q4-8h</td>
<td>Interval extension</td>
<td>Q6h</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>250-500mg q8h</td>
<td>Interval extension</td>
<td>Q8h</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>250-500mg q24h</td>
<td>No adjustment recommended</td>
<td>100%</td>
</tr>
<tr>
<td>Cefuroxime axetil</td>
<td>250-500mg q12h</td>
<td>No adjustment recommended</td>
<td>100%</td>
</tr>
<tr>
<td>Drug</td>
<td>Dose details</td>
<td>Dose reduction</td>
<td>100%</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>----------------</td>
<td>------</td>
</tr>
<tr>
<td>Benzyl penicillin</td>
<td>0.5-4 million units q4-6h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefuroxime sodium</td>
<td>0.75-1.5g q8h</td>
<td>Interval extension</td>
<td>Q8h</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>1-2g q8h</td>
<td>Interval extension</td>
<td>Q8-12h</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0.25-2g q12-24h</td>
<td>No adjustment recommended</td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>12.5mg/kg q6h</td>
<td>No adjustment recommended</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>500-750mg(400mg if IV) q12h</td>
<td>Dose reduction</td>
<td>100%</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>150-450mg q6h</td>
<td>No adjustment recommended</td>
<td></td>
</tr>
<tr>
<td>Dapsone</td>
<td>50-100mg q12h</td>
<td>No data available</td>
<td></td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>3.375-4.5g q 6-8h</td>
<td>Dose reduction and interval extension</td>
<td>100%</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>400mg q12h</td>
<td>Interval extension</td>
<td>Q12h</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100mg q12h</td>
<td>No adjustment recommended</td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>250-500mg q6h</td>
<td>No adjustment recommended</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Dose Formulation</td>
<td>Dose Reduction and Interval Extension</td>
<td>GFR &gt; 30</td>
</tr>
<tr>
<td>----------------------</td>
<td>------------------</td>
<td>--------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Meropenem</td>
<td>0.5-2g q8h</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>0.5-1.25g q12h</td>
<td>1g q12-24h</td>
<td>1g q24-96h</td>
</tr>
<tr>
<td>Cefepime</td>
<td>250-2000mg q8-12h</td>
<td>100%</td>
<td>50-100% q24h</td>
</tr>
<tr>
<td>*Co-amoxiclav (amoxicillin + clavulanic acid)</td>
<td>Oral-875/125mg q12h or 250/125-500/125mg q8h IV 1.2g q8h</td>
<td>GFR &gt; 30: No change in doses GFR 10-30: dose q12h(oral), IV 1.2g stat then 600mg q12h GFR &lt; 10: dose q24h(oral), IV 1.2g stat then 600mg daily The 875/125mg(oral) dose is not recommended for GFR &lt; 30ml/min/1.73m2</td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>250-500mg q8-12h</td>
<td>No adjustment recommended</td>
<td></td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>50-100mg q6h</td>
<td>Avoid in RI</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>250-500mg q12h</td>
<td>100%</td>
<td>50-100%</td>
</tr>
<tr>
<td>Imipenem</td>
<td>0.25-1g q6h</td>
<td>100%</td>
<td>50%</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600mg q12h</td>
<td>No adjustment recommended</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Dose Range</td>
<td>Dose Reduction and Interval Extension</td>
<td>100% q12h</td>
</tr>
<tr>
<td>-----------------</td>
<td>------------</td>
<td>---------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Cefproxl</td>
<td>250-500mg q12h</td>
<td></td>
<td>100% q12h</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>250-750mg q24h</td>
<td>Dose reduction</td>
<td>100% q12h</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>250-500mg q12h</td>
<td>Interval extension</td>
<td>Q12h</td>
</tr>
<tr>
<td>Sulphamethoxazole</td>
<td>1g q8h</td>
<td>Interval extension</td>
<td>Q12h</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>100mg q12h</td>
<td>Interval extension</td>
<td>Q12h</td>
</tr>
</tbody>
</table>

* The BNF recommends doses recommended by the manufacturer, hence doses used in the study are those recommended by the manufacturer of the original brand of co-amoxiclav, Augmentin
Appendix 5: Ethical approval

Alieno Mary Onyango  
School of Pharmacy  
University of Nairobi

Dear Mary

RESEARCH PROPOSAL: “ANTIBIOTIC DOSAGE ADJUSTMENT IN PATIENTS WITH CHRONIC KIDNEY DISEASE AT KENYATTA NATIONAL HOSPITAL” (P407/11/2010)

This is to inform you that the KNH/UON-Ethics & Research Committee has reviewed and approved your above revised research proposal for the period 11th March 2011 – 10th March 2012.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimens must also be obtained from KNH/UON-Ethics & Research Committee for each batch.

On behalf of the Committee, I wish you a fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of the data base that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely,

PROF A N GUANTAI  
SECRETARY, KNH/UON-ERC  
c.c. The Deputy Director CS, KNH  
The HOD, Records, KNH  
Supervisor: Dr. F. A. Okaebo, Dept. of Pharmacology, UON  
Dr Osajo, Dept. of Pharmacology, UON  
Dr. Nyamu D. Dept. of Pharmaceutics & Practice, UON