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Research Article

Determinants of Appropriate Antibiotic Dosing in Patients with Chronic Kidney Disease in a Kenyan Referral Hospital

Mary A. Onyango [a, b], Faith A. Okalebo [c, *], David G. Nyamu [b], George O. Osanjo [c], and Kipruto arap Sinei [c]

[a] *Jaramogi Oginga Odinga Teaching and Referral Hospital, Kisumu, Kenya*
[b] *Department of Pharmaceutics and Pharmacy Practice, School of Pharmacy, University of Nairobi, Kenya*
[c] *Department of Pharmacology and Pharmacognosy, School of Pharmacy, University of Nairobi, Kenya*

* **Corresponding author:** Department of Pharmacology and Pharmacognosy, School of Pharmacy, University of Nairobi, P.O. Box 19676-00202, Nairobi, Kenya. **Tel**: +254-73-7434204; **Email**: faith.okalebo@uonbi.ac.ke

Background: Reduced renal function in chronic kidney disease (CKD) necessitates appropriate dose alterations to avoid drug accumulation.

Objectives: The main objective of the study was to determine the prevalence of inappropriate antibiotic dosing in patients with CKD in the largest referral hospital in eastern Africa. Variables associated with inappropriate dosing were identified.

Methods: The design was a retrospective review of patients' records. The study population was adult patients, with CKD admitted between January, 2006 and December, 2010. Data was abstracted from patient files. Logistic regression was used to determine variables associated with appropriate antibiotic dosing.

Results: Ceftriaxone and amoxicillin-clavulanic acid were the most frequently prescribed antibiotics. Dose adjustment was required for 379 (59.9%) antibiotic prescriptions. Of these, 105 doses (27.7% [95% CI: 23.2 – 32.2%]) were appropriate and 274 (72.3% [95% CI 67.8 – 76.8%]) were inappropriate. The resultant dosing errors were: 271 (98.9%) and 3 (1.1%) cases of over and under dosing respectively. Key explanatory variables for appropriate dosing were: stage of renal disease (adjusted odds ratio (OR) 0.159 [95% CI: 0.082, 0.309]); administration; (adjusted OR 1.724 [95% CI:1.185, 2.508]); and treatment with amoxicillin-clavulanic acid (adjusted OR 0.101 [95% CI 0.024, 0.420].

Conclusion: Antibiotic doses in patients with CKD were often inappropriate.

Keywords*:* Antibiotic, dose adjustment, chronic kidney disease

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1. Introduction

Irrational, improper or inappropriate antibiotic use consists of improper practices such as unwarranted use with no clear indication, incorrect choice for a given infection, improper timing and improper or unnecessary combinations (Kunin et al, 1973; Ozkurt et al, 2005).Incorrect antibiotic dosing, also termed inappropriate dosing, is the administration of doses that are above or below the recommended dosage and frequency (Seyler et al, 2011). An inadequate dosing regimen is failure to attain the minimum therapeutic concentration in plasma (Seyler et al, 2011). Dose adjustment is the practice of changing a dose on the basis of patient or disease related factors such as body mass index or renal function. It may be done correctly or incorrectly. Patients with chronic kidney disease (CKD) are particularly prone to treatment failure and

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adverse drug reactions resulting from administration of inappropriate doses of antibiotics (Seyler et al, 2011).

Kidney diseases are a global public health problem (Levey et al, 2007). Sub-Saharan African countries have an increasing burden of chronic kidney renal disease. For instance, Sumaili et al (2009), found that the prevalence of chronic kidney disease (CKD) among Congolese study subjects was 36%. In Kenya, patients with reduced renal function are often encountered in clinical practice (Wools-Kaloustian, 2007; Ogeng'o et al, 2011).

Decreased renal function affects the pharmacokinetic disposition as well as the pharmacodynamic effects of drugs. Careful dose adjustment and therapeutic drug monitoring are essential in patients with renal insufficiency to prevent accumulation of administered drugs and/or toxic metabolites (Myrna et al, 2007; Hassan et al, 2009). Appropriate dose adjustment reduces the incidence of adverse drug reaction, improves treatment success and reduces hospital admission and even mortality. It reduces costs associated with drug related toxicity and resultant increased hospital stay (Bonapace et al, 2002).

Drugs that are largely excreted by the kidney as active compounds require dose adjustment (Verbeeck and Musuamba, 2009). Dose adjustment with CKD is dependent on the degree of renal impairment and the half life of the drug (Swan and Bennet,1992).Patients with CKD are particularly prone to developing sepsis and other infections. Antibiotics are therefore inevitably widely used by renal patients. For most antibiotics, the loading dose may not require adjustment but the maintenance dose may need adjustment (Myrna et al, 2007; Hassan et al, 2009).

There is paucity of literature regarding the practice of antibiotic dose adjustment in Kenyan patients with CKD. This study was conducted to evaluate the practice of antibiotic dose adjustment for patients with chronic kidney in Kenyatta National Hospital which is the largest teaching and referral hospital in Eastern Africa. Patients with CKD are referred from all over the country for dialysis and follow up. The practices in this referral hospital influence practice in the rest of the country and in the region. The hospital has no written protocol for antibiotic drug prescribing for patients with CKD. The main objective of the study was to determine the proportion of patients with CKD who received inappropriate doses of antibiotics as per standard international guidelines for dose adjustment. Drug and patient related explanatory variables for inappropriate dosing were also identified.

2. Methods

2.1 Study design and population

The design was a cross sectional study that involved a retrospective review of patient files. It was conducted in Kenyatta National Hospital (KNH) which is the largest referral, teaching and research hospital in East Africa. The hospital receives approximately 5 new patients with CKD every week. The patients were drawn from two clinical sites within the hospital: the medical wards and the specialized renal unit of KNH. The study population was adult patients aged 18 years and above with a diagnosis of CKD and admitted in the hospital between January, 2006 to December, 2010.

2.2 Inclusion criteria

The inclusion criteria were: diagnosis of CKD, an antibiotic prescription and a documented serum creatinine concentration at the time the antibiotic prescription was written.

2.3 Sampling

Sample size was calculated using the equation for cross sectional studies described by Browner et al (2007). The expected prevalence of inappropriate antibiotic dose s was 75 % which was the figure reported by Arlicot et al (2007). Alpha was set at 0.05 and the width of the confidence interval was 0.10. The calculated sample size was adjusted upwards by 10% to allow for missing information in the files. The targeted minimal sample size was 317.

A list of all patients with a diagnosis of CKD seen between January 2006 and December 2010 was obtained from the Medical Records department. From the list, simple randomization with replacement (Altaman and Bland 1999) was performed to obtain a sample of 500 files. The files were selected by picking a paper a pile of papers that each a file. The pile was shuffled before each draw. All files that met the inclusion criteria were included in the study.

2.4 Data collection

A pre-tested data collection form was used to abstract the following information from patient files: patient demographics, co-morbidities and serum creatinine concentration. Data was also collected on antibiotics prescribed, their doses, frequency and durationof administration. For patients who had more than three prescriptions during the study period, data abstraction was restricted to the latest three antibiotic prescriptions. Prescriptions were first assessed to determine if they contained antibiotics for drugs for which dose adjustment is routinely required in CKD. Those that contained drugs that did not require dose adjustment were not analyzed further.

The prescribed antibiotic doses were compared with those that are recommended in the dosing guidelines for adults with CKD by the American College of Physicians (Aronoff, 2007). For drugs not listed in this guideline, the recommendations of the British National Formulary were used to judge the appropriateness of dose adjustment (British National Formulary, 2010). The guidelines required calculation of the estimated glomerular filtration rate (eGFR) to determine the appropriate dose.

Serum creatinine levels, age and sex were used to calculate eGFR using the Modification of Diet in Renal Disease four variable (MDRD) equation (National Kidney Foundation, 2002;Coreshet al, 2002).Disparities between the recommended and prescribed dose were noted.

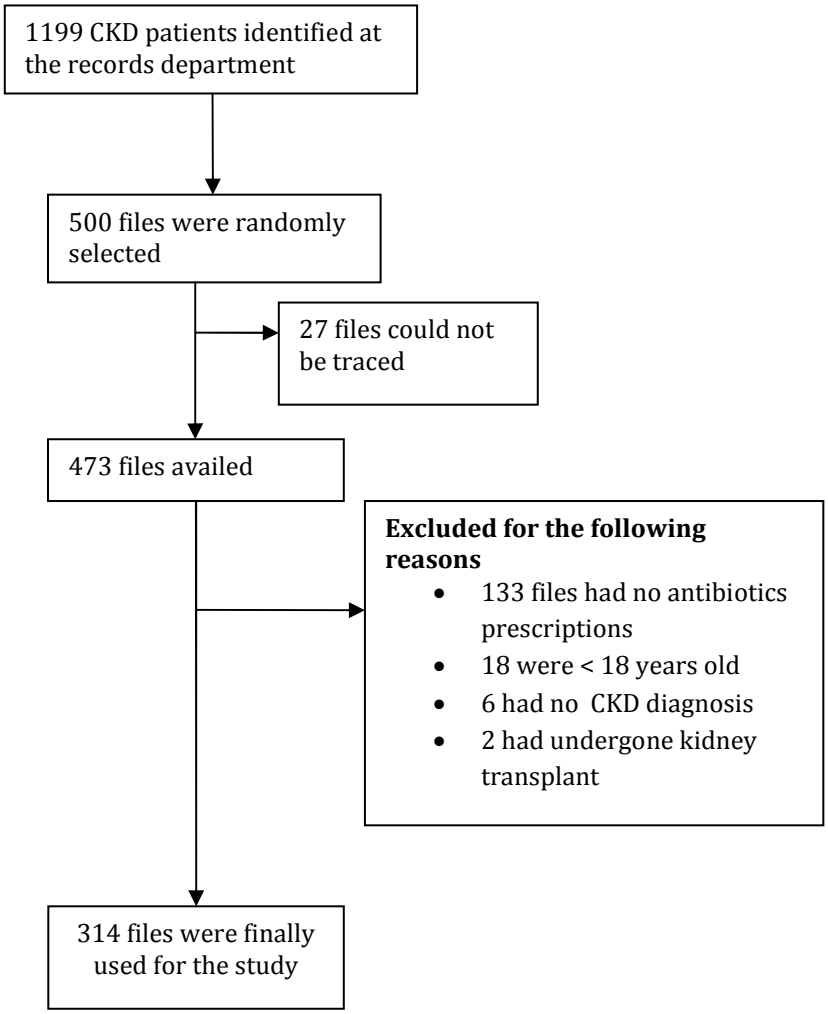

Figure 1: Consort diagram of selection of adult patient with chronic kidney disease for inclusion in study

2.5 Case definition

Where a prescription had more than one antibiotic, each was treated as a separate antibiotic prescription. Appropriate dose was defined as the agreement of the prescribed dose and frequency with the guideline recommendations taking into consideration the degree of comprised renal function. Where there was a disparity in the prescribed and calculated doses, the prescribed dose was considered to be inappropriate. An overdose was defined a dose or frequency of administration that was greater than that calculated on the basis on the guideline recommendations. An under dose was defined a dose or frequency of administration that was less than that calculated on the basis on the guideline recommendations.

2.6 Variables

The main outcome of interest was appropriateness of the antibiotic dose. 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.

2.7 Data analysis

Data analysis was conducted using STATA version 9 statistical software. Shapiro-Wilk test for deviation of continuous variables from normality showed that all the continuous variables did not follow normal distribution. The medians and interquartile ranges were therefore reported.

Proportions were used to summarize categorical variables. Patient, disease and drug related variables of prescriptions with inappropriate and appropriate doses were compared.

Pearson's Chi-square test was used to test for the presence of association between categorical variables and compare their distribution across groups. The two sample Wilcoxon rank-sum test was used for inferential data analysis of continuous variables.

Logistic regression was carried out to adjust for cofounding. Manual forward stepwise model building was done to identify the most important risk factors for prescriptions with inappropriate antibiotic doses. P values of less than 0.05 were considered to be statistically significant.

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2.8 Ethical considerations

Permission to carry out the research was obtained from the KNH/University of Nairobi Research and Ethics Committee as the letter of approval of 11th of March, 2011, reference number KNH-ERC/A/52. Information regarding the patient identity was kept confidential by the using the files within the confines of the hospital, limiting access to the files to the investigators and exclusion of patient identifying information such as patient names from the data collection form. Study numbers were assigned to each patient. All the filled data collection forms was filed and stored in lockable drawer.

Table 1: Demographic characteristics and baseline renal function of the study participants

Variable	n (%)	Variable	n (%)
Sex		**Baseline Stage of CKD[a]**	
Female	134 (42.7%)	1	3 (1.0%)
Male	180 (57.3%)	2	6 (1.9%)
		3	14 (4.5%)
Age group		4	29 (9.2%)
≥ 45 years	166 (52.9%)	5	262 (83.4%)
Below 45 years	148 (47.1%)		
		Cause of CKD[a]	
Age (median, years)	46 [32, 60], n=313	Unknown	62 (20%)
		Diabetes mellitus	32 (10.2%)
Marital status		Hypertension	50 (15.9%)
		Diabetes and hypertension	35 (11.1%)
Married	249 (79.3%)	Primary glomerular disease	57 (18.2%)
Single	63 (20.1%)	HIV associated nephropathy	27 (8.6%)
Missing	2 (0.6%)	Obstructive uropathy	45 (14.3%)
		Drug induced	2 (0.6%)
Highest level of education		Other	4 (1.3%)
No education	34 (10.8%)		
Primary School	118 (37.6%)		
Secondary School	104 (33.1%)	**Co-morbidity**	
Tertiary	38 (12.1%)		
Missing	20 (6.4%)	None	46 (14.7%)
		Diabetes mellitus	82 (26.1%)
Employment		Hypertension	115 (36.6%)
		HIV/AIDS[b]	31 (9.9%)
Unemployed	193 (61.5%)	Heart disease	11 (3.5%)
Employed	50 (15.9%)	BPH[c]	12 (3.8%)
Self employed	67 (21.3%)	Prostate cancer	5 (1.6%)
Missing	4 (1.3%)	Cervical cancer	3 (1%)
		Breast cancer	1 (0.3%)
Weight (kg)	62 [56, 70], n=59	Others	8 (2.6%)

[a]Chronic Kidney Disease; [b]Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome; [c] Benign Prostrate Hypertrophy.

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3. Results

3.1 Baseline characteristics of the study participants

The Medical Records Department provided a list of 1199 patients who had a diagnosis of CKD over the 4 year study period. Five hundred patients were randomly selected from this list. From the list, 473 files were availed for the study. Of these, 314 met the eligibility criteria and were used in the study. Of the remaining files, 133 files had no antibiotic prescriptions within the study period, 18 of the files were for patients aged below 18 years of age, 6 had no documented diagnosis of CKD and 2 had had kidney transplantation (**Figure 1**).

The baseline demographic characteristics of the patients are presented in **Table 1**. The median age at diagnosis of CKD in the study population was 46 years. There were slightly more male (n=180, 57.3%) than female patients. There was limited data on weight with only 59 entries at baseline.

Most of the patients were married (n=249, 79.3%) and 142 (45.2%) had attained secondary or tertiary education.

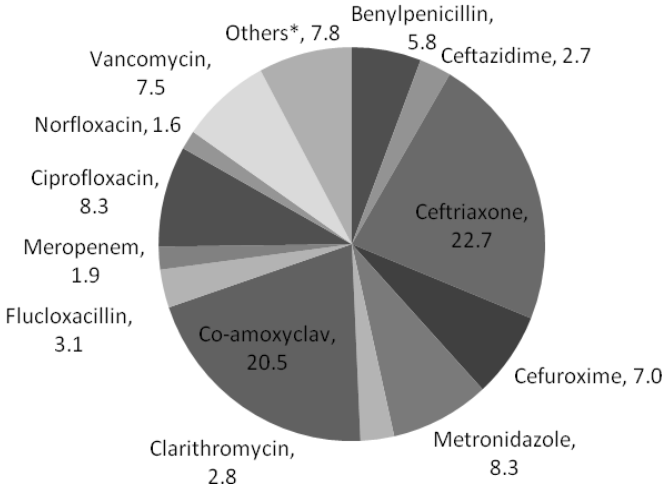
3.2 Patterns of antibiotic prescription in patients with chronic kidney disease

Out of the 473 files obtained from the records department, 18 belonged to patients aged below 18 years and were therefore excluded from the study. The rest of the files number belonged to adult patients. Out of 455 adult patients, 314 (69.0%) had a prescription for an antibiotic. Some patients had received more than one antibiotic prescription during the study period. There were a total of 639antibiotic prescriptions. Twenty four different types of antibiotics were prescribed. The proportions of the different types of antibiotics prescribed are presented in **Figure 2**.The most frequently prescribed drugs were ceftriaxone (n=145, 22.7%) and amoxicillin-clavulanic acid (n=131, 20.5%). Five prescriptions (0.78%) had nitrofurantion which is contraindicated in patients with CKD.

Table 2 presents the indication, duration, frequency and routes of antibiotic administration. The clinical sites where the prescribing was done as well as selected renal parameters at the time the prescription was generated are presented. All patients seen in the renal unit had stage 5 disease and most of them (97.1%) were on dialysis. The most common indication was respiratory tract infection (n= 104, 16.3%). There was no written indication for antibiotic use for 297 (46.5%) prescriptions. Patients seen in the clinical wards had less severe renal disease (P<0.000).Most antibiotics were administered intravenously (n**=**485, 75.9%). Most antibiotics were administered 12 hourly (twice daily) or 8 hourly (three times daily). There was no written duration of administration for 224 (35.1%) prescriptions.

3.3 Appropriateness of doses of antibiotics prescribed to patients with chronic kidney disease

The prescriptions were scrutinized to determine if they contained antibiotics for which dose adjustment is not routinely required. Five prescriptions (0.78%) had nitrofurantion which is contraindicated in patients with CKD and therefore were not evaluated. Out of the 634 prescriptions that were evaluated, 379 (59.9%) had antibiotics for which dose adjustment is routinely required and 255(40.1%) did not require dose adjustment.



**Others: Gentamicin (1.3%); Amoxicillin (1.1%); Cotrimoxazole (1.1%); Amikacin (0.8%); Nitrofurantion (0.8%); Imipenem/cilastatin (0.8%); Levofloxacin (0.8%); Linezolid (0.5%); Doxycycline (0.3%); Clindamycin (0.2%); Piperacillin/tazobactam (0.2%); and Erythromcyin (0.2%)*

Figure 2: Antibiotics prescribed to patients with chronic kidney disease in Kenyatta National Hospital (N=639)

Table 2: Patterns of antibiotic prescribing and renal parameters of patients with chronic kidney disease at Kenyatta National Hospital

Indications for the antibiotic	**n (%)**
None documented	297 (46.5)
RTI[a]	104 (16.3%)
Catheter site infection	14 (2.2%)
Sepsis	85 (13.3%)
Urinary Tract Infection	51 (8.0%)
Gastroenteritis	46 (7.2%)
Surgical prophylaxis	9 (1.4%)
CNS[c] infection	3 (0.5%)
Bone and soft tissue infections	5 (0.8%)
Others	25 (3.9%)

Clinical setting where the prescription was generated	**n (%)**
General Wards	533 (83.4%)
Renal Unit	105 (16.4%)
Missing	1(0.2%)

Serum Creatinine (µmol/L)	778
Median (IQR),	(434,1141), n=639
eGFR[b](ml/min/1.73m^2)	7.486
Median (IQR), n	(4.782, 14.96), n=639

Patients on dialysis at the time of prescribing	
Not on dialysis	303 (47.4%)
On dialysis	336 (52.6%)

Route of drug administration	
Intravenous	485 (75.9%)
Oral	152 (23.8%)
Missing	2 (0.3%)

Duration of antibiotic administration (days)	
Not written	224 (35.1%)
1 to 4	18 (2.8%)
5	179 (28.0%)
7	163(25.5%)
9 to 12	34 (5.3%)
14	14 (2.2%)
15 to 21	3 (0.5%)
28 to 30	2 (0.3%)

Frequency of administration (times daily)	
Start dose	19 (3.0%)
Once	95 (14.9%)
Twice	246(38.5%)
Thrice	193(30.2%)
Four	55 (8.6%)
5 to 10	30 (4.7%)
Missing	1 (0.2%)

[a]RTI - Respiratory Tract Infection , [b]GFR - Glomerular Filtration Rate, [c]CNS – Central Nervous System

3.3 Appropriateness of doses of antibiotics prescribed to patients with chronic kidney disease

The prescriptions were scrutinized to determine if they contained antibiotics for which dose adjustment is not routinely required.

Five prescriptions (0.78%) had nitrofurantion which is contraindicated in patients with CKD and therefore were not evaluated. Out of the 634 prescriptions that were evaluated, 379 (59.9%) had antibiotics for which dose adjustment is routinely required and 255(40.1%) did not require dose adjustment.

Out of the 379 prescriptions for which dose adjustment is routinely required, 105 doses (27.7%, (95% CI 23.2 – 32.2%) were appropriate according to the degree of renal insufficiency and 274 (72.3%) were inappropriate. The errors that resulted from prescribing inappropriate doses were: 271 (98.9%) cases of overdose and only 3(1.1%) cases of under dosing.

According to the dosing guidelines for adults with CKD by the American College of Physicians (Aronoff, 2007), seven of the prescribed antibiotics that did not require dose adjustment were: ceftriaxone (n=145, 22.9%); metronidazole (n=53, 8.4%); flucloxacillin (n=20, 3%);

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linezolid (n=3, 0.5%); doxycycline (n=2, 0.3%); erythromycin (n=1, 0.2%); and clindamycin (n=1, 0.3%).

The antibiotics for which dose adjustment is routinely required are listed in **Table 3**. Amoxycillin-clavulanic acid, ciprofloxacin and benzyl penicillin were the most frequently prescribed antibiotics that required dose adjustment. **Table 3** includes some antibiotics that were administered as single loading doses, and therefore, dose adjustment was not required. Cefuroxime axetil which is the oral formulation of cefuroxime does not routinely require adjustment.

All patients treated will levofloxacin (n=5), cotrimoxazole (n=7) and piperacillin/tazobactam (n=1) received inappropriate doses. Over 75% of patients treated with amoxicillin-clavulanic acid (118, 91.5%), cefuroxime (27, 79.4%), meropenem (9, 75%) and amikacin (3, 75%) received inappropriate doses. Vancomycin (23, 69.7%) was the only antibiotic for which over 50 % of treated patients received the appropriate dose.

About half of the patients treated with benzylpenicillin (18, 48.6%) received the appropriate dose.

Table 3: Appropriateness of prescribed doses of antibiotics for which dose adjustment is routinely required in patients with chronic kidney disease

Antibiotic	Need for dose adjustment*		Appropriateness of prescribed doses	
	Not required	Adjustment required	Dose not appropriate n (%)	Dose appropriate n (%)
Aminoglycosides				
Amikacin	1	4	3(75.0%)	1 (25.0%)
Gentamicin	0	8	5(62.5%)	3(37.5%)
Betalactams				
Amoxicillin-clavulanic acid	2	129	118(91.5%)	11(8.5%)
Benzyl penicillin	0	37	19(51.4%)	18(48.6%)
Amoxicillin	1	6	4(66.7%)	2(33.3%)
Piperacillin/tazobactam	0	1	1(100%)	0(0.0%)
Monobactams				
Imipenem/cilastatin	0	5	3(60.0%)	2(40.0%)
Meropenem	0	12	9(75.0%)	3(25.5%)
Cephalosporins				
Ceftazidime	0	17	11(64.7%)	6(35.3%)
Cefuroxime	11	34	27(79.4%)	7(20.6%)
Fluoroquinolones				
Ciprofloxacin	0	53	33(62.3%)	20(37.7%)
Norfloxacin	0	10	7(70.0%)	3(30.0%)
Levofloxacin	0	5	5(100.0%)	0(0.0%)
Miscellaneous				
Cotrimoxazole	0	7	7(100.0%)	0(0.0%)
Clarithromycin	0	18	12(70.6%)	6(29.4%)
Vancomycin	15	33	10(30.3%)	23(69.7%)
Total	**30 ()**	**379(59.9%)**	**274(72.3%)**	**105 (27.7%)**

**If a single dose was administrated, dose adjustment was not considered necessary*

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3.4 Risk factors for prescriptions with inappropriate antibiotic doses for patients with chronic kidney disease

Table 4 (Supporting information) presents the results of bivariable analysis which was carried out to determine if there was an association between each of the covariates and appropriate dose administration. The crude and adjusted odd ratios for the association between inappropriate dosing and predictor variables are presented in **Table 5** (Supporting information). On bivariable analysis, the statistically significant predictors of appropriateness of the antibiotic dose: were dialysis status, severity of renal disease, type of antibiotic, frequency and duration of drug administration (**Table 4,** Supporting information). Severity of renal disease was measured using three parameters: serum creatinine, estimated GFR and the CKD stage. All these variables remained significant on adjusting for confounding (**Table 5**, Supporting information). The association between age group and appropriate dosing was not statistically significant on bivariable analysis but was significant on multivariable analysis. There was a negative association between appropriate antibiotic dose and the following variables: stage of renal disease (adjusted OR 0.159 [95% CI: 0.082, 0.309]) and age below 45 years (adjusted OR 0.422 [95% CI: 0.198, 0.898]).

Although the association between dialysis status and appropriate antibiotic dose was not statistically significant, it is notable that there was a strong negative association (adjusted OR 0.458 [95% CI: 0.192, 1.090]).

Benzylpenicillin was selected as the reference drug because a sizeable number of patients were treated with this drug and there is a lot of clinical experience with use of this drug. Secondly about equal proportions of the patients on benzyl penicillin received appropriate and inappropriate doses. The odds of receiving a wrong dose of amoxicillin-clavulanic acid were about ten times the odds of receiving a wrong dose of benzylpenicillin (adjusted OR 0.101 [95% CI: 0.024, 0.420]).The only antibiotics for which the odds of receiving a correct dose were greater than that of benzylpenicillin were: vancomycin; meropenem; imipenem/cilastatin; metronidazole and gentamicin. However these findings were not statistically significant because of the small numbers of patients treated with these drugs.

There was also a statistically significant positive association between the presence of heart disease and the correct dose administration.

4. Discussion

The key finding of our study is that, only 27.7% of the prescribed antibiotic doses were appropriate. A number of surveys show that dose adjustment of drugs used by patients with CKD is often incorrect and may not be done at all (van Dijk et al, 2006; Arlicot et al, 2007; Sweileh et al, 2007; Markota et al, 2009). These studies show a wide variation in the prevalence of inappropriate dose administration ranging from 25 to 68%. Our study is in agreement with published studies. The proportion of inappropriately prescribed antibiotics in our study setting (72.3%) was very similar to that reported in a study conducted in France where prevalence of inappropriate antibiotic dose prescribing was at 75% (Salomon et al, 2003).The investigators in the French study noted that the antibiotics were prescribed according to protocols for use in patients with normal renal function. A similar practice was observed in our study. A study done in South Africa also reported a similar prevalence of 68% of inappropriate (Decloedt et al, 2010).

The problem of inappropriate dose adjustment in renal insufficiency seems to be widespread. The key barrier to dose adjustment in many clinical settings is a high physician and clinical pharmacist workload which makes it difficult to attend to detail (Vogtländer et al 2002). In addition, many clinical centers electronic support prescribing systems which have the potential of improving prescribing practice (Vogtländer et al 2002).

The most common error was over dosing because doses that were prescribed to patients with CKD were those recommended for individuals with normal renal function. Over dosing may cause drug accumulation which increases the risk of adverse events and 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 events (Bonapaceet al 2002).

Severity of renal disease had an inverse relationship with the probability of correct dosing. This poses a challenge because patients with severe loss of renal function are particular at risk of drug accumulation. In mild disease, the doses used in normal subjects may be appropriate, thus lessening the need for dose reduction.

The only patient factor that had an effect on appropriate dosing was age. Patients aged below 45 years were less likely to get an appropriate doses compared to older patients (adjusted OR 0.422 [95% CI: 0.198, 0.898]). This could probably be attributed to the fact that prescribers were more likely to pay greater attention to older patients were may be sicker.

Drug characteristics such as the type of antibiotic, its duration and frequency of administration were significant determinants of appropriateness of the prescribed dose. Vancomycin was the only drug for which more than half the prescribed doses were appropriate. Out of the 48 prescriptions of vancomycin (**Table 3**), 33 required dose adjustment and 23 (69.7%) were appropriate dose. Though empiric doses of 1g every 4-7 days were prescribed for most patients, it was difficult to ascertain if the doses were adequate because therapeutic drug monitoring (TDM) is not routinely done in hospital. Therapeutic drug monitoring (TDM), which is not routinely done in the referral, is required for drugs such as vancomycin. 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 (Ye et al, 2013).

The other antibiotics for which the odds of receiving a correct dose were greater than that of benzylpenicillin were: ceftazidime; meropenem; imipenem/cilastatin; metronidazole and gentamicin. The nephrotoxicity of gentamicin is well known and this could have contributed to the tendency to prescribe correct doses.

In the case of ceftazidime, imipenem/cilastatin and meropenem, prescribers probably had good knowledge of the potential adverse consequences of inappropriate dosing in renal insufficiency.

Drug were prescribed at a high frequency per day (adjusted OR 1.724 [95% CI: 1.185, 2.508]) were more likely to be prescribed appropriately. This could be attributed to the fact that prescribers were more cautious about the risks of accumulation and adjusted the dose appropriately.

Most patients treated with the older penicillins, such as amoxcyllin, benzylpenillin and amoxycillin-clavulanic acid received inappropriate doses. Penicillins have very wide therapeutic index and are may perceived by most prescribers to be safe. This could have promoted the tendency to neglect dose adjustment the doses in renal disease. Only 11(8.5%) out of 129 cases that required dose adjustment, received the appropriate dose of amoxycillin-clavulanic acid. All patients treated with amoxicillin received inappropriate doses. The pharmacokinetic profile of amoxicillin-clavulanic acid is altered in patients with renal disease (Horber et al, 1986) and there is likelihood of accumulation in CKD. Accumulation may lead to crystalluria (Labriola et al, 2003).

Strategies to alert prescribers of the need for dose adjustment should be considered. These strategies may include simplified aids to guide dose adjustment, automated systems for computation of GFR and adjustments to treatment sheets to highlight information on renal parameters.

One of the limitations of the study was data on prescriber traits was not collected. Consequently, it was not possible to determine the effect of prescriber traits on appropriate dose selection in patients with CKD. Secondly, GFR was calculated using the MDRD equation but not the gold standard which requires use of an exogenous filtration marker (National Kidney Foundation, 2002). Furthermore, the study was retrospective in nature and therefore the information obtained from the records could not be verified.

5. Conclusion

Antibiotic dose adjustment in patients with CKD was often not done appropriately. This highlights the need to study barriers to dose adjustment to inform the design of interventions to promote safe prescribing.

Conflict of Interest declaration

The authors declare no conflict of interest

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