



Research Article

## A Retrospective Study To Evaluate Appropriateness Of Antimicrobial Dosing In Renal Impairment In A Tertiary Care Hospital In Dakshina Kannada District

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### ABSTRACT

The effects of many drugs get altered in renal impairment. Drug doses should be modified in renal disease in accordance with creatinine clearance. The aim of the study was to analyze the antibiotics with inappropriate dosage based on patient's renal function according to distinguished guidelines and to evaluate the number of prescribed antibiotics being appropriately adjusted. A retrospective study was conducted by screening the medical records of 100 patients who fulfilled the inclusion criteria. Extent of antimicrobial dosage adjustment was determined by calculating the creatinine clearance using Cockcroft and Gault equation and comparing with Stanford health care guidelines. The mean age of the study participant was 59.8 years with 67% male and 33% female. Out of 112 antimicrobials prescribed 49 antimicrobials were dosed appropriately, 63 required dosage adjustment. When the antibiotics for dosing error were evaluated Inj. Meropenem was associated with most number of dosing error (25.39%) followed by T.Amoxicillin + Clavulanic acid was associated with second most number of dosing error (14.28%). Approximately half of the antimicrobial dosing in renal impairment were inappropriate. Drug dosing should be emphasized in patients with renal impairment. Failure to do so could result in increased morbidity, mortality and therapeutic expenses. Awareness raising and monitoring system for inappropriate dosing is critical to improve the quality of care in patients with renal impairment..

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## INTRODUCTION

The kidneys are essential for maintaining proper physiology because they serve as excretory, biosynthetic, and metabolic organs. Many medications have altered effects when renal impairment occurs, especially when the medication has renal clearance. Drug doses should be altered in renal disease in accordance with the predicted reduction in the clearance of the drug.<sup>1</sup>

The kidney is the major route of elimination for many important classes of antibiotics; correspondingly, patient renal function is the single most important factor used to individualize antibiotic dosing. Antibiotic drugs are the most frequently prescribed medications among hospitalized patients for life-saving purposes, mainly in immune compromised patient, like in patient with end stage renal disease on hemodialysis (HD) or those who had documented bacterial infection. The goal of renal dosage adjustments is to achieve equivalent exposures in patients with and without renal impairment, thereby minimizing toxicity without compromising efficacy<sup>2</sup>.

Increased drug clearance results in lower drug concentrations where as decreased drug clearance results in higher drug concentrations; which results in stronger pharmacological effects. Patients with renal illness should have their doses of renally cleared medications modified to prevent damage<sup>3</sup>.

Incidence of infection among patients with kidney disease remains high in developing countries. Provision of antibiotics to treat infection in patients with kidney disease without proper dose adjustment could result in accumulation of the parent compounds and their metabolites in the body and toxic effects on organs, including kidneys.<sup>4</sup> Therefore, appropriate dosing of antibiotics therapy for patients with kidney disease is crucial to avoid adverse drug reaction, to prevent additional renal injury, and to optimize clinical outcomes.

Hence, medication review in the management of kidney disease is the key point that should always be performed by clinical pharmacists through a structured examination of patients' medications including evaluation and analysis of antibiotic dosing to avoid adverse drug reaction, to prevent additional renal injury, to improve kidney disease management and to achieve optimal outcomes<sup>5</sup>.

## OBJECTIVE OF THE STUDY

To evaluate the extent of antimicrobial dose adjustment in renal impairment according to the Stanford Health Care Antimicrobial Dosing Reference Guide.

## METHODOLOGY

**Study design:** A retrospective observational study was carried out to check the extent of antimicrobial dosing in renal impairment in tertiary care hospital of Dakshina Kannada. Data was collected from 100 case files from MRD between January-September 2022.

**Ethical Clearance:** The study protocol was approved by the Institutional Ethics Committee (IEC) of Srinivas Institute of Medical Science and Research Centre (SIMS & RC), Mangalore. (Ref. No: SIEC/SIMS & RC/2022/10/06)

**Study criteria:**

### Inclusion Criteria:

- All the AKI, CKD patients taking antibiotics.
- Patients' files containing patient age greater than 18 years.

### Exclusion Criteria

- Patients below the age of 18years.
- Pregnant or lactating category.
- All the AKI, CKD patients not taking antibiotics.

**Source of data collection:** Data(s) for the study were collected using data collection from the medical record department (MRD) of Srinivas Institute of Medical Science and Research Centre (SIMS & RC), Mangalore.

**Study method:** The study period was divided into 3 phases;



**Phase 1:** Preparation for the study:

1) Preparation of Patient's Data Collection form:

Data collection form include the patient's details, creatinine level, antibiotic prescribed and frequency, dose of antibiotic.

2) Ethics committee approval: Ethical Clearance was obtained from the Institutional Ethics committee (IEC) of Srinivas Institute of Medical Science and Research Centre (SIMS & RC), Mangalore.

**Phase 2:**

- Selection of case files: The case files for the study was selected based on the inclusion and exclusion criteria.
- Collection of data from selected case files: Data(s) were collected using data collection form with the aid of medical records from MRD of Srinivas Institute of Medical Science and Research Centre (SIMS & RC), Mangalore.
- Filling information in data collection form: The information includes the patient's demographic details, creatinine level, creatinine clearance, antibiotic prescribed, dose of antibiotics, frequency of antibiotic prescribed.
- From the serum creatinine level, age, weight Creatinine Clearance of the patient was calculated using Cock-croft Gault (C & G) equation.

For Men:  $CrCl = \frac{[(140 - \text{Age in years}) \times \text{Weight (kg)}]}{S.Cr \text{ (mg/dl)} \times 72}$

Women:  $CrCl = \frac{[(140 - \text{Age in years}) \times \text{Weight (kg)} \times 0.85]}{S.Cr \text{ (mg/dl)} \times 72}$

After calculating creatinine clearance dose of antibiotic prescribed was compared with the SHC Antimicrobial dosing guide. Appropriateness of the dose was analysed.

**Phase 3:** Statistical analysis involves collecting and scrutinizing every data sample in a set of items from which samples was drawn and a suitable statistical test was applied to analyse the data. The

collected data was analysed using Microsoft Excel.

**RESULTS**

**Demographic and Clinical Characteristics**

We assessed 153 case files of patients with renal impairment of which 100 fulfilled the inclusion criteria. The mean age of the patients was 59.8. The study showed majority of the patients were diagnosed with CKD (56%), AKI was seen in 34% of patients and 10% AKI on CKD. Majority of the participants were of 51-70 age group (59%), 21% were of age group above 71 years, 19% were of age group 31-50, 18-30 (1%). Among 100 patients 67 were male (67%) and 33 were female (33%). Patient's mean serum creatinine was 4.27 and the mean CrCl was 21.85.

**Table 1: Demographic and clinical data of patients with renal impairment**

Demographic and clinical data	Number
Number of patients with renal impairment	100
Male	67
Female	33
Age (Mean)	59.8
CrCl (Mean)	21.85
Type of renal impairment	
AKI	34
AKI on CKD	10
CKD	56

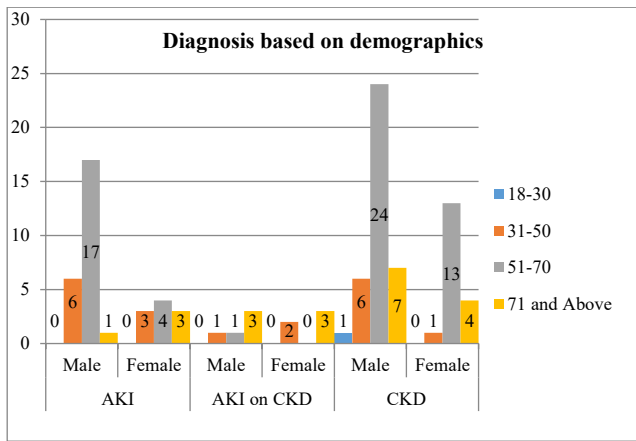


Figure 2: Co-relation between age, gender, diagnosis

**Extent of Antimicrobial Dosage Adjustment in Renal Impairment:**

The appropriateness of dosage adjustment for antimicrobial agents were assessed according to the patient’s renal function using standard guidelines and out of the 112 antibiotics prescribed, 63 antimicrobial agents were inappropriate (56.25%) and 49 antimicrobial agents were dosed appropriately (43.75%).

When the antibiotics for dosing error were evaluated Inj. Meropenem was associated with

most number of dosing error (25.39%) followed by T. Amoxicillin + Clavulanic acid was associated with second most number of dosing error (14.28%), followed by Inj. Piperacillin + Tazobactam (11.11%), T. Levofloxacin (7.93%), Inj. Cefaperazone + Sulbactam (6.34%), Inj. Amoxicillin + Clavulanic acid (6.34%), T. Ciprofloxacin (4.76%), Inj. Ceftriaxone (3.17%), Inj. Vancomycin (3.17%), T. Cefixime (3.17%), T. Cefuroxime(3.17%). On the other hand, Inj. Clindamycin, T. Azithromycin, Inj. Cefuroxime, Inj. Cefuroxime + Sulbactam, Inj. Chloramphenicol, Inj. Fluconazole, Inj. Linezolid, T. Clindamycin, T. Doxycycline had no dosing errors.

Table 3: Dose adjustment of antibiotics per patient

Number of antibiotics	Extent of dosage adjustment
1	Appropriately adjusted – 39
	Not adjusted - 49
2	At least one antibiotic adjusted – 2
	Both the antibiotics adjusted – 4
	Both antibiotics not adjusted - 6

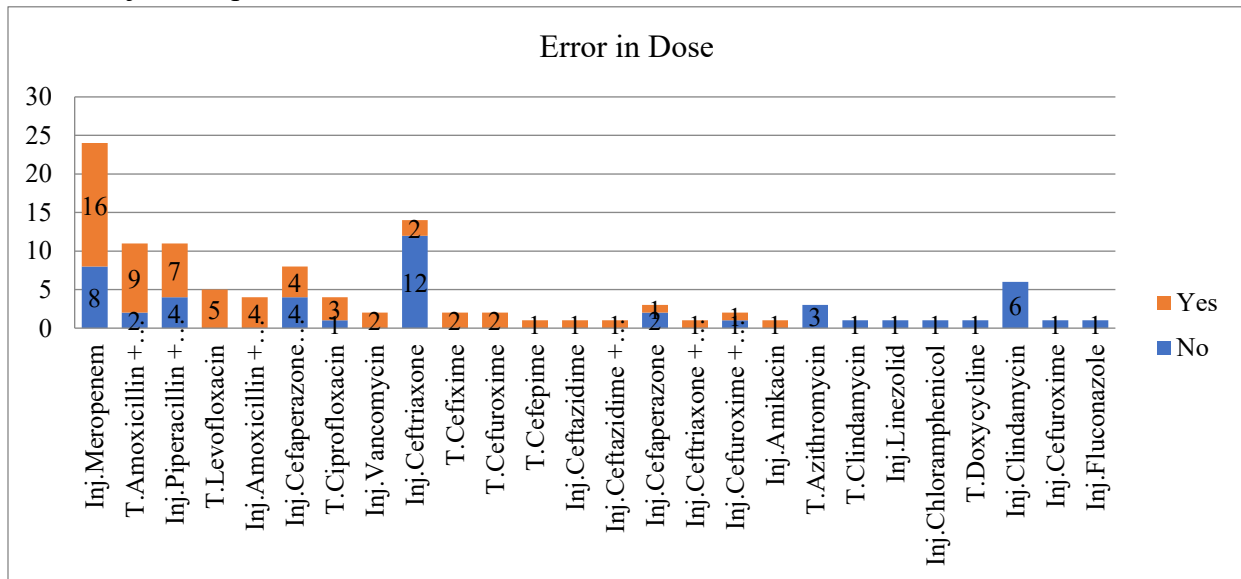


Figure 6: Proportion of antibiotics with dosing error

**DISCUSSION**

This study is primarily focused on extent of antimicrobial’s dose adjustment in renal impairment patients according to the Stanford

Health care guidelines of antimicrobial renal dose adjustment. This present study reveals that males were more affected by renal impairment than females. Similar observation was made by

Alhabadri SM *et al.*, who conducted a study on patients having moderate to severe renal impairment, where also majority of renal impairment patients were men<sup>1</sup>.

Other related research studies indicated that high testosterone levels in men which cause kidney function to decline, unhealthy living styles such as alcohol consumption and smoking, excess protein supplement intake for gym workouts as put men at increased risk for renal impairment<sup>6</sup>. Estrogen, which is more abundant in women, and also having protective effect on kidney may protect the female kidney until menopause<sup>7</sup>. Confounding variables, such as smoking, obesity, and lifestyle factors may have played a role in the observed sex difference in the incidence of renal disease<sup>8</sup>. Diabetic nephropathy is known to be more prevalent and to progress more rapidly in men than in women<sup>9</sup>.

Management of infection can be achieved with the use of antibiotics but during renal failure dose adjustment is a necessary because majority of antimicrobials are excreted via kidney and can impair drug excretion leading to toxicity<sup>10</sup> Since significant number of antibiotics are eliminated through the kidney, it is necessary to adjust dose according to renal function. Even though dosage of some antibiotics in renal impairment is necessary, studies have shown a large number of inadequate antibiotic dose in patients with renal impairment<sup>11</sup>. In the present study 57% of patients received no dose adjustment and there were proper dose adjustments only in 43% patients while it is reported by Fahimi *et al.*, that 39.3% of patients did not receive dosage adjustment and Henok *et al.*, reported that 31% of patients in their study did not receive dosage adjustment<sup>12, 13</sup>

In the present study using the creatinine clearance of each patient with renal impairment as a benchmark, all antibiotics modified dosages were found by comparing with the standard antimicrobial dosing guideline [SHC]. This study

shows that out of the total errors in dosage adjustments of antibiotics Inj. Meropenem doses were the least adjusted and it comprised of major proportion of the total errors followed by T. Amoxicillin, Inj. Piperacillin Tazobactam, T. Levofloxacin which included of total dose errors. Meropenem is filtered in glomerulus and when it reaches proximal convoluted tubule it is metabolized by brush border enzyme called dehydropeptidase. These metabolites are very toxic to PCT cells and cause tubular necrosis<sup>14</sup>. Nephrotoxicity of Amoxicillin is driven by two main mechanisms. The first is acute interstitial nephritis, a drug hypersensitivity reaction, which classically manifests after 7 to 10 days following drug exposition. The second way by which Amoxicillin may induce AKI is crystalluria. Pathophysiology of crystal formation is related to two main mechanisms. The first one is the direct precipitation of the drug due to its poor solubility in urine. The second one is the crystallization of endogenous metabolic compounds because of the drug effects. Nephrotoxic beta-lactam antibiotics cause acute proximal tubular necrosis<sup>15</sup>. While Fahimi *et al.*, in their study reported that Vancomycin doses were least frequently adjusted. There has been description of least adjustment of Amoxicillin, Levofloxacin and Ciprofloxacin also<sup>12</sup>.

In this current study 23.96% patients received adjustment for at least one drug but Henok *et al.*, reported that in their study 41% patients received adjustment for at least one drug.<sup>13</sup> A similar study was conducted by Alhabardi SM *et al.*, where in 22%, the adjustment was performed for all antibiotics requiring dosage adjustment. For 59 patients 39.3%, adjustments were not performed in any of the antibiotics requiring dose adjustment.<sup>1</sup> Though it had not been reported by other studies we found use of subtherapeutic doses of Piperacillin + Tazobactam [3.17% of dose error] and Cefepime [1.58% of dose error] in doses used





in patients with renal failure. It may lead to poor control of infection.

This study which is representative of common renal care carried out in hospitals suggested that antibiotic handling in renally impaired patients was not done according to standard guidelines and may worsen or aggravate the morbidity of patient or may even contribute to mortality of patients. Thus Clinical pharmacists must evaluate the antibiotics given to CKD patients and analyse their pharmacological logic in order to increase therapy effectiveness<sup>16</sup>.

### CONCLUSION

Errors in drug dosage could lead to toxic effects or sub therapeutic doses. It would result increased financial burden due to high dose of antibiotic and increased duration of hospitalization. Thus, Clinical pharmacists must evaluate the antibiotics given to CKD patients and analyse their pharmacological logic in order to minimize dosage error and promote rational prescribing of antimicrobial therapy in renal impaired patients by completely adhering to standard dosing guidelines available by co-operating with other medical professionals. The development of electronic calculators or convenient applications for CrCl estimation should be considered. Newer methods should be implemented or studied for the estimation of CrCl, specifically in AKI for better dosing optimization and improved clinical outcome. Also, usage of pre designed dosage adjustment charts and tables in renal wards and renal outpatient department would enable faster easier and precise dosage adjustment of drugs.

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