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" A Retrospective Study To Identify Drug Related Problems [Drp] In Antimicrobial Therapy In Renal Impairment Patients 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 objective of this study was to identify drug related problems related to dose and frequency in patients with renal impairment. 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. DRP drug related problems was analysed using Microsoft Excel. The mean age of the study participant 59.8 years with 67% male and 33% female. Majority of the patients were diagnosed with CKD (56%). Out of 112 antimicrobials prescribed 49 antimicrobials were dosed appropriately, 63 required dosage adjustment. DRP was categorized into too high dose and too low dose. Occurrence of too high dose was seen in 60 antimicrobials and too low dose in 3 antimicrobials. Too high dose will lead to toxicity and too low dose will lead to therapeutic failure. Approximately half of the antimicrobial dosing in renal impairment patients were inappropriate. Awareness raising and monitoring system for inappropriate dosing is critical to improve the quality of care in patients with renal impairment.
Key words: Antibiotics, DRP [drug related problem], renal impairment, dosage adjustments.

I. INTRODUCTION

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 haemodialysis (HD) or those who had documented bacterial infection. Antibiotics disposition and their pharmacokinetics and pharmacodynamics properties are affected in renal impairment patients which leads to antibiotic dosing errors. Several epidemiological studies found that the majority of medication error related to antibiotics occurred during the prescribing phase (30.8%). [1] Infection rates among renal disease patients are still quite high in underdeveloped nations. If antibiotics are given to people with kidney disease to treat infection without correct dose modification, the parent chemicals and their metabolites may build up in the body and have harmful effects on organs, including the kidneys. Furthermore, a small number of antibiotics' nephrotoxicity may contribute to the advancement of renal injury. Death is the ultimate bad result. Therefore, it is essential to provide antibiotics at the proper dosage for patients with kidney disease in order to minimise the risk of adverse medication reactions, stop further renal damage, and achieve the best possible therapeutic results. Therefore, clinical pharmacists should constantly monitor and adjust dose of antibiotics in renal impairment patients to prevent further renal damage, undesirable drug reactions and to obtain desired results.

II. METHODOLOGY

2.1MATERIALS AND METHODS

2.1.1 Study design:

A retrospective observational study was carried out to check DRP [drug related problems] in renal impairment in tertiary care hospital of Dakshina Kannada. Data was collected from 100 case files from MRD between January to September 2022.

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2.1.2 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)

2.13 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.

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

2.1.5 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 demographic details, creatinine level, antibiotic prescribed and frequency, dose of antibiotic.
2) Institutional 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:

1. Selection of case files: The case files for the study was selected based on the inclusion and exclusion criteria.
2. 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.
3. 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, indication, DRPs.

From the serum creatinine level, age, weight Creatinine Clearance of the patient was calculated using Cock-croft Gault (C & G) equation

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

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

After calculating creatinine clearance dose of antibiotic prescribed was compared with the SHC Antimicrobial dosing guide. Error in dose was analysed and categorised into too high dose and too low dose.
Error in frequency of prescribed antibiotic was also checked with the SHC Antimicrobial dosing guide

PHASE 3:
Analysis of data: The collected data was analysed using Microsoft Excel.
2.1.6 DATA ANALYSIS
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.

III. RESULTS

3.1 DEMOGRAPHIC AND CLINICAL CHARACTERISTICS 153 case files of patients with renal impairment were screened of which 100 fulfilled the inclusion criteria. The mean age of the patients was 59.8 years. 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.

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Demographic and clinical data	Number
Number of patients with renal impairment	100
Male	67
Female	33
Age (Mean)	59.8
CrCl (Mean)	21.85

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

3.2 ASSESSMENT OF DRP IN RENAL IMPAIRMENT

DRP related to dosage error

The DRP related to dosage error for antimicrobial agents were assessed according to the patient's renal function test and Stanford antimicrobial renal dosage adjustment guidelines and out of the 112 antibiotics prescribed, 63 antimicrobial agents had DRP related to dosage error (56.25%).

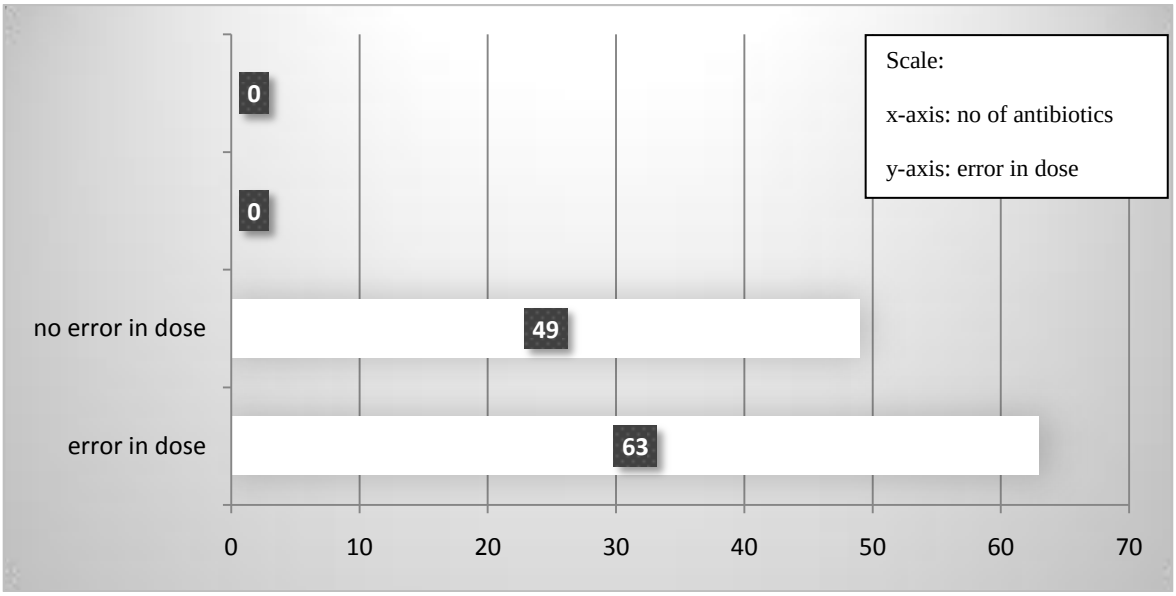

Figure 1: DRP related to dosage error

DRP related to frequency error

In-appropriate prescribing of antibiotics in relation to frequency of antibiotic was assessed. Ceftriaxone injection was prescribed with error in dosing interval (20.40%) followed by Piperacillin+Tazobactam injection (14.28%), Amoxicillin+Clavulanic acid tablet (12.24%), Meropenem injection (12.24%), Levofloxacin tablet (8.16%).

Inj. Ceftriaxone 1g was prescribed BD. The recommended dose of Inj. Ceftriaxone is 1g OD. In this case there is no dosing error but there is only frequency error but ultimately frequency error will lead to dosage error. In case of Inj. Piperacillin+Tazobactam dose error was seen in 5 cases frequency or error in dosing interval was seen in 7 cases which indicates error in dose was due to error in dosing interval.

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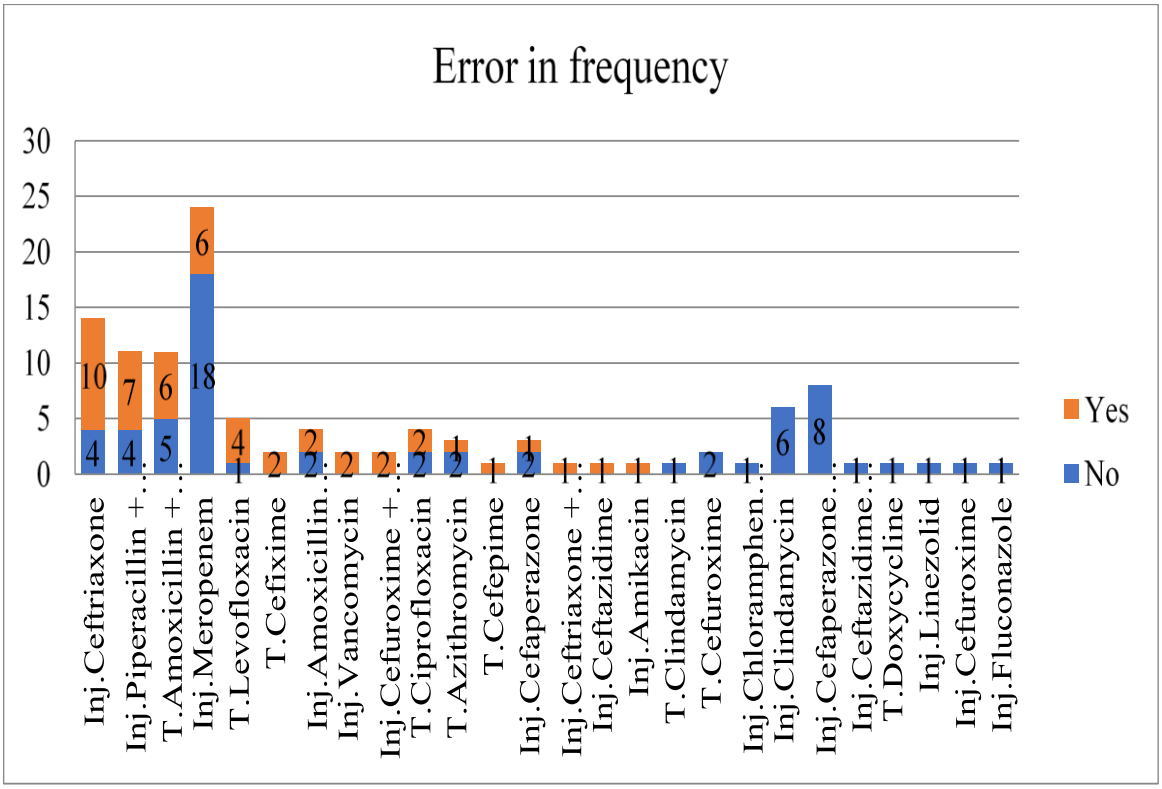

Figure 2: DRP related to frequency error

Total DRP Analysis

Based on above calculated error in dose and frequency of antibiotics DRP [drug related problems] were analysed. DRP was seen in 63 antibiotics (56.25%) in which 60 antimicrobials were prescribed with too high dose (53.57%) and 3 were prescribed with too low dose (2.67%). The most common antimicrobials associated with the occurrence of too high dose among study participants include Inj. Meropenem (26.66%), followed by T. Amoxicillin+Clavulanic acid (15%), T. Levofloxacin (8.33%), Inj. Piperacillin+Tazobactam (8.33%), Inj. Amoxicillin+Clavulanic acid (6.66%), Inj. Cefoperazone + Sulbactum (6.66%), T. Ciprofloxacin (5%), Inj. Ceftriaxone (3.33%), Inj. Vancomycin (3.33%), T. Cefixime (3.33%), T. Cefuroxime (3.33%). Too low dose was observed in only 2 antimicrobials Inj.Piperacillin + Tazobactum (66.66%) and T. Cefepime (33.33%). On the other hand, in some of the antimicrobials such as T. Doxycycline, Inj. Cefuroxime, Inj. Clindamycin, T. Azithromycin, T. Clindamycin, Inj. Linezolid, Inj. Chloramphenicol, Inj. Fluconazole there was no single DRP related to dose.

DRP related to dose	Number
No error	49
Too high dose	60
Too low dose	3

Table 2: Total DRP analysis

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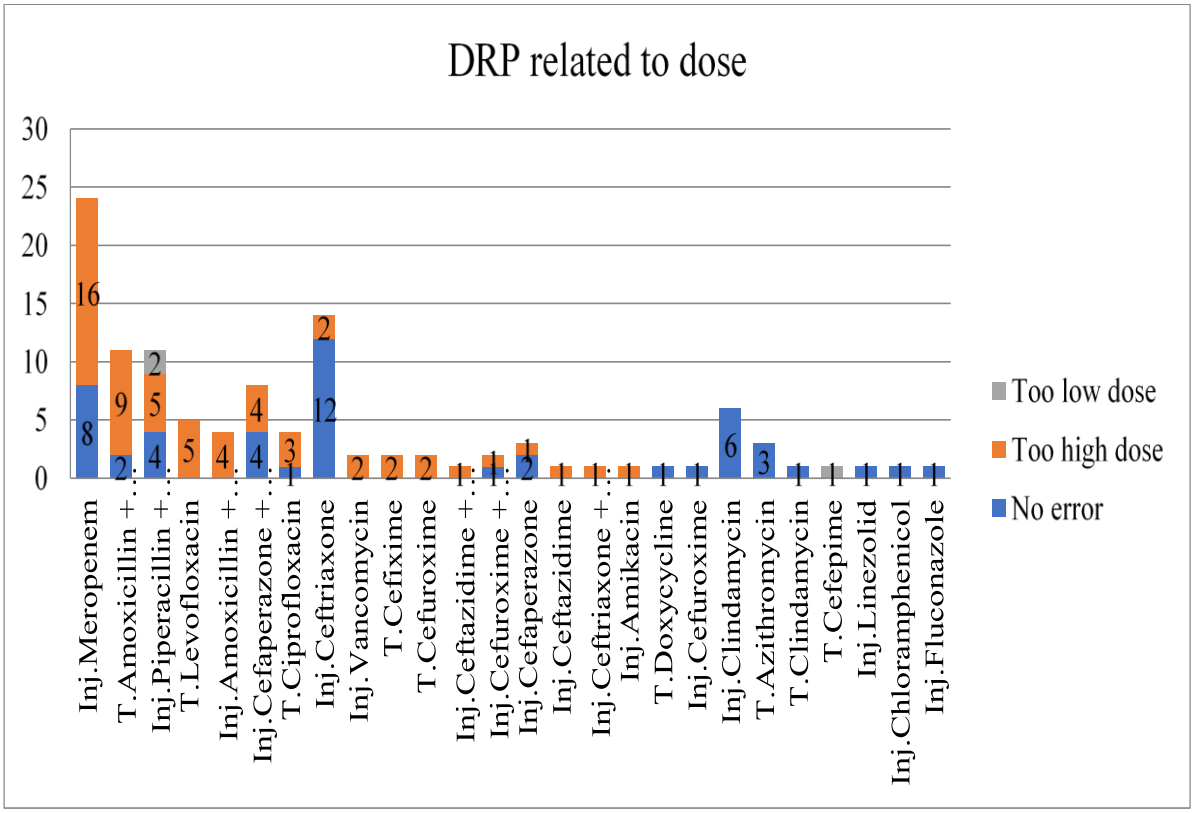

Figure:3 Drug related problems

IV. DISCUSSION

This study is primarily focused on to check DRP drug related problems in renal impairment in tertiary care hospital of Dakshina kannada 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. [2]

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.[3]Oestrogen, which is more abundant in women, and also having protective effect on kidney may protect the female kidney until menopause.[4] 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.[5] Diabetic nephropathy is known to be more prevalent and to progress more rapidly in men than in women.[6]

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.[7] 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. [8]

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. This study also revealed that 53.57% of antibiotics were prescribed to renal impairment patients with too high dose and 2.67% of antibiotics were prescribed with too less or sub therapeutic doses. In the study conducted by

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Garedow AW et al., dose too low accounted for 18% of all DRPs identified. [9]

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 tazobactum, 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. [10,11,12] Amoxicillin's nephrotoxicity is caused by two major processes. The first is acute interstitial nephritis, which typically appears 7 to 10 days after medication exposure due to a drug hypersensitivity response. Complications from medication administration can include kidney stones and crystalline nephropathy. Kidney damage develops as a result of crystal deposition inside tubules in crystalline nephropathy. Crystal formation pathophysiology is linked to two key pathways. Due to the medication's weak solubility in urine, the first one is the direct precipitation of the drug. The second one is endogenous metabolic chemicals crystallising as a result of medication actions. Acute proximal tubular necrosis is brought on by nephrotoxic beta-lactam medicines. [13,14,15] While Fahimi et al., in their study reported that Vancomycin doses were least frequently adjusted. 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. [16,17,18] A similar study was conducted by Alhabadri 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. This study also revealed that 53.57% of antibiotics were prescribed to renal impairment patients with too high dose and 2.67% of antibiotics were prescribed with too less or sub therapeutic doses. Though it had not been reported by other studies we found use of sub therapeutic 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. [19]

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. [20]

V. CONCLUSION

This study which is representative of common renal care carried out in hospitals suggested that antibiotic handling in renal 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. Drug related problems or 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. There is need to educate physicians about need of adjustment of drug dosages in patients with renal dysfunction. 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. 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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