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Original Article

PRESCRIPTION PATTERN OF ANTIBIOTICS AND THEIR APPROPRIATENESS IN PATIENTS WITH CHRONIC KIDNEY DISEASE-AN OBSERVATIONAL STUDY IN A TERTIARY CARE TEACHING HOSPITAL IN SOUTH INDIA

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ABSTRACT

Objective: The primary objective of the study was to assess the prescribing pattern of antimicrobial agents in patients with chronic kidney disease. The secondary objectives of this study are to assess antibiotic appropriateness and dose optimization in patients with chronic kidney disease in relation to their comorbidities.

Methods: A retrospective study was conducted, and medical records of all patients with CKD who were admitted in the nephrology department of Sri Venkateswara Institute of Medical Sciences, Tirupati, during Jan 2018-Dec 2018 were reviewed for antibiotic prescriptions. A total of 200 medical records were selected and assessed for antimicrobial prescriptions. A p-value <0.05 was considered significant throughout the statistical analysis.

Results: Analysis showed that overall 163 drugs were prescribed to CKD patients, of which nearly 96 (58.9%) required dosage adjustment. Of those 163 drugs, the majority N= 25 (26%), were unadjusted, and the remaining N = 71 (74%) were properly adjusted. The length of hospitalization of CKD patients was below 7 was 13.5%, above 7 was 86.5%. Mean and SD was 10.27±7.18 d, (Range: 1–35 d). The Chi-square analysis confirmed that out of the seven studied variables, two i.e. Length of stay days; p<0.001.

Conclusion: It is concluded that the occurrence of medication dosing errors was moderate in hospitalized chronic kidney disease patients in our study. Nearly 20% of patients who had prolonged stays were prescribed antibiotics for a prolonged period. The predictors of medication dosing errors in CKD patients were the severe-to-end stages of chronic kidney disease, the number of prescribed antibiotics, and the length of hospitalization.

Keywords: Chronic kidney disease, GFR, Antibiotics, Prescription

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INTRODUCTION

Chronic Kidney Disease (CKD) is a serious public health concern that affects nearly 10 to 15%of the adult population worldwide. CKD is defined as a reduced GFR (glomerular filtration rate) <60 ml/minute for>3 mo that may or may not be coupled with kidney damage and classified into several stages based on GFR [1]. When GFR falls below 15 ml/min, it is Kidney failure and the patient requires dialysis. More than 800 million people worldwide, more than 10% of the overall population, have chronic kidney disease [2], between 1990 and 2017; in India, there was a 38% increase in deaths attributable to kidney failure between 2001–03 and 2010–13 [3]. The global all-age prevalence and mortality from CKD increased by 29.3 and 41.5%, respectively [4]. CKD alters the pharmacokinetic and pharmacodynamics response of various drugs mainly excreted from the body through the renal route [5]. Reduction in GFR causes accumulation of drugs that are excreted unchanged via the kidney, accumulation of active metabolites of drugs causing prolonged action, change in drug distribution-protein binding and a decrease in renal drug metabolism. Kidney dysfunction influences the pharmacokinetic parameters of at least 50% of all essential drugs. The response to a drug can be altered by pathologic conditions (acute and chronic illness and kidney disease) by Decreased receptor number (E_{max}) and sensitivity (EC50), Decreased receptor binding and altered signal transduction. It was found that vancomycin with a time-dependent antibacterial effect showed increased efficacy and decreased toxicity when administered by prolonged infusion rather than short-term infusion [6]. Similar effect is noted with Meropenem and Piperacillin, where the dosage was based on pharmacodynamics regimens. The complications of CKD include increased susceptibility to Adverse drug reactions, metabolic and endocrine complications, including anemia and acidosis, increased risk for cardiovascular diseases, and a variety of other complications, including infections, frailty, and cognitive impairment. Complications may occur at any stage. Complications may also arise from adverse effects of interventions to prevent or treat the disease and associated comorbidities.

Hence normal kidney function is of utmost importance for several drugs and their metabolites to be eliminated from the body. Doses have to be reduced or adjusted in patients with renal impairment. This is often overlooked by the healthcare professions and could lead to adverse drug reactions (ADRs), drug toxicities and therapeutic failure [7].

Several studies conducted worldwide have shown that the doses of drugs that are excreted unchanged in Urine are not being adjusted appropriately among CKD patients. The most commonly prescribed medications among CKD patients are Antibiotics which account for nearly 97% of the prescriptions in patients undergoing Chronic Renal Replacement Therapy in the hospital setting. Thus the present study was conducted to assess the prescribing pattern of antimicrobial agents in patients with chronic kidney disease. The secondary objectives of this study are to assess antibiotic appropriateness and dose optimization in patients with chronic kidney disease in relation to their comorbidities.

MATERIALS AND METHODS

Study setting and study design

A retrospective study was conducted, and medical records of all patients with chronic kidney disease admitted to the nephrology department of Sri Venkateswara Institute of Medical Sciences (SVIMS), Tirupati, during Jan 2018-Dec 2018 were reviewed for antibiotic prescriptions after obtaining Ethics Committee Approval for the study (Roc. No. AS/11/IEC/SVIMS/2017/849). The study data was anonymized and deidentified to ensure the confidentiality of the patient's details. Chronic kidney disease patients were selected based on estimating the Glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) equation. Patients with eGFR<60 ml/min/1.73m^2 will be included in the study. The formula for eGFR using the MDRD equation:

$$eGFR = 175 \times (SCr)^{-1.}[15]^{4} \times (age)^{-\circ.}[20]^{3} \times 0.742 \text{ [if female]} \times 1.212 \text{ [if African American]}$$

Medical records of all patients with chronic kidney disease who were admitted to the nephrology unit for a minimum period of 24 h, having eGFR<60 ml/min/1.73m$^{2.}$ Which means patients included in the study had stages of chronic kidney disease as follows: stage 3 (CrCl 30–59 ml/min), stage 4 (CrCl 15–29 ml/min), and stage 5 (CrCl<15 ml/min) and those prescribed Antibiotics during the hospital stay were studied. All those medical charts not meeting the criteria mentioned above were excluded. A total of 200 medical records were selected and assessed for antimicrobial prescriptions. A special data collection form was designed and used to collect the required data.

MATERIALS AND METHODS

Data on the Patient's age, gender, length of Hospital stay, associated comorbidities, serum creatinine, estimated GFR, antibiotics prescribed, type and dosing pattern were recorded from the medical records. The antimicrobials were classified based on chemistry and mode of action.

The Antimicrobial prescriptions were assessed for the appropriateness and rationality in chronic kidney disease patients for their class, dose and duration of therapy according to the standard guidelines of the National Formulary of India 2021. The doses of drugs were assessed for appropriateness individually for every patient using the dose adjustment guidelines (table 1) [8].

Table 1: Dose adjustment guidelines for antimicrobials prescribed in the study

S. No.	Antimicrobials	Usual dose (Normal renal function)	CrCl (ml/min)	Dosage adjustment (In renal insufficiency)
1.	Ceftriaxone sodium	1-2g q24h in equally two divided doses as 30 min infusion Max dose: 4g	-	No dose adjustment is necessary, but serum monitoring is required in severe renal impairment and in patients with both renal and hepatic dysfunction.
2.	Piperacillin/tazobactam	Nosocomial pneumonia: 4.5g q6h plus an aminoglycoside Other Infections: 3.375g q6h as 30 min infusion	>40 20-40 <20 HD CAPD	3.375g q6h and for nosocomial pneumonia 4.5g q6h 2.25g q6h and for nosocomial pneumonia 3.375g q6h 2.25g q8h and for nosocomial pneumonia 2.25g q6h 2.25g q12h and for nosocomial pneumonia 2.25g q8h 2.25g q12h and for nosocomial pneumonia 2.25g q8h
3.	Doxycycline	100 mg/day	-	No dose change is needed with kidney/liver damage
4.	Cefixime	200 mg q12h	>50 10-50 <10	200 mg q12h Decrease dose by 75% Decrease dose by 50%
5.	Metronidazole	Prophylaxis: 500 mg before surgery; repeated 8 hourly Treatment: 500 mg q8-12h	Mild, moderate	No dose adjustment required
6.	CEF+Salbactum	3.0-4.5g q12h as 15-60 min infusion (Maximum recommended dose of cefoperazone is 8g and sulbactam is 4g)	15-30 <15 HD	3g q12h 1.5g q12h Dose to be given after dialysis
7.	Vancomycin	500 mg q6h or 1g q12h as 1h infusion	>50-90 10-50 <10/HD/CAPD	1g q12h 1g q24-96h 1g q4-7days
8.	Amoxicillin/clavulanic acid	1.2g q6-8h	>30 No dose adjustment necessary 10 <10	>30 No dose adjustment necessary 30 1.2g IV stat., followed by 600 mg q12h 1.2g IV stat., followed by 600 mg q24h
9.	Ciprofloxacin	400 mg q8-12h depending on the severity of infection as 1h infusion	>30 5-29	No dose adjustment required 200-400 mg q18-24h

Data analysis

Statistical analysis was carried out using IBM SPSS version 20. Descriptive statistics were applied on independent variables such as age, gender, stages of chronic kidney disease, the number of prescribed antibiotics, the length of hospitalization, comorbidities of patients, and the pattern of medication dosing errors. A p-value<0.05 was considered significant throughout the statistical analysis.

RESULTS

In this study, nearly 192 medical charts of chronic kidney disease (CKD) patients were assessed. Of which, nearly 71.4% of patients were males and 28.6% were females. Nearly 34 (17.7%) patients were aged between 21–40 y, followed by 98 (51%) who were aged between 41–60 y, and only 26% who had an age above 60 y. The length of hospitalization of CKD patients was below 7 was 13.5%, above 7 was 86.5%. Mean and SD was 10.27±7.18 d, (Range: 1–35 d). Furthermore, it was observed that the majority N = 160 (83.3%) of patients had CKD stage 5, followed by nearly 9.9% who had CKD stage 4, and the remaining 5.2% of patients had CKD stage 3. Hypertension 72 (37.5%), Diabetes with Hypertension 37 (19.3%) and Respiratory Illness (3.1%) were observed as the three topmost comorbidities in CKD patients (table 2). Further analysis showed that overall, 163 drugs were prescribed to CKD patients, and nearly 96 (58.9%) required dosage adjustment, of those 163 drugs, the majority N= 25 (26%) were unadjusted, and the remaining N = 71 (74%) were properly adjusted (table 3). Moreover, the descriptive statistics revealed that the most common unadjusted drugs were Inj. Amoxicillin+Clavulanic acid, Inj. Metronidazole (0.6%), Inj. Cefoperazone+Sulbactam, Tab. Amoxicillin+Clavulanic acid (0.6%), Inj. Amoxicillin+Clavulanic acid (0.6%), Tab. Amoxicillin+Clavulanic acid (4.9%), Tab. Cefixime (3.7%), Tab. Metronidazole (0.6%), Tab. Norfloxacin (0.6%). For further details, please see table 4. The Chi-square analysis was carried out to assess the predictors of medication dosing errors in CKD patients. The analysis confirmed that out of the seven studied variables, two i.e. Length of stay days; p<0.001, Antibiotics prescribed; p<0.05 was associated with medication dosing errors. reaming Age (p-0.9706), Gender (p-0.3633), CKD Stages (p-0.6275), Comorbidity present (p-0.6159), Comorbidities (p-0.2307) were not associated with the medication dosing errors at p<0.05 level (table 5).

Table 2: Patient characteristics (n = 192)

Variables		Frequency	Percentage
Age			
	<20	10	5.2%
	21-40	34	17.7%
	41-60	98	51.0%
	>61	50	26.0%
Gender			
	Female	55	28.6%
	Male	137	71.4%
Length of stay days	<7	26	13.5%
	>8	166	86.5%
CKD Stage			
	Stage 1	1	0.5%
	Stage 2	2	1.0%
	Stage 3	10	5.2%
	Stage 4	19	9.9%
	Stage 5	160	83.3%
Comorbidity present			
	Yes	125	65.1%
	No	67	34.9%
Antibiotics prescribed			
	Yes	163	84.9%
	No	29	15.1%
Comorbidities			
	HT	72	37.5%
	T2DM	3	1.6%
	HTN, T2DM	37	19.3%
	HTN, Respiratory Illness	3	1.6%
	HTN, Tropical Fever	1	0.5%
	Respiratory Illness	6	3.1%
	Tropical Fever	1	0.5%
	Av Fistula Tract Infection	1	0.5%
	GE	1	0.5%

Table 3: Frequency of adjusted and unadjusted prescribed drugs

Variable	Frequency	Percentage
Total drugs prescribed	163	100 %
Number of drugs requiring dose adjustment	96/163	58.9%
Number of drugs Not requiring dose adjustment	67/163	41.1%
Number of drugs properly adjusted	71/96	74.0%
Number of drugs unadjusted	25/96	26.0%

Table 4: Pattern of medication dosing errors in chronic kidney disease patients

Generic name	Frequency	Percentage	Dose adjusted for eGFR
Inj. Amoxicillin+Clavulanic acid, Inj. Metronidazole	1	0.6%	Un Adjusted
Inj. Cefoperazone+Sulbactam, Inj. Piperacillin	1	0.6%	Adjusted
Inj. Cefoperazone+Sulbactam, Tab. Amoxicillin+Clavulanic acid	1	0.6%	Un adjusted
Inj. Piperacillin+Tazobactam	8	4.9%	Adjusted
Inj. Amoxicillin+Clavulanic acid	1	0.6%	Un adjusted
Inj. Cefoperazone+Sulbactam	54	33.1%	Adjusted
Inj. Cefoperazone+Sulbactam, Inj. Doxycycline	1	0.6%	Adjusted
Inj. Cefoperazone+Sulbactam, Inj. Metronidazole	1	0.6%	Adjusted
Inj. Ceftriaxone	12	7.4%	Not required
Inj. Ceftriaxone+Sulbactam	48	29.4%	Not required
Inj. Ceftriaxone+Sulbactam, Inj. Ceftriaxone	1	0.6%	Not required
Inj. Ceftriaxone, Inj. Doxycycline	1	0.6%	Not required
Inj. Doxycycline	4	2.5%	Not required
Inj. Imipenem+Cilastatin	1	0.6%	Not required
Inj. Piperacillin+Tazobactam	5	3.1%	Adjusted
Inj. Vancomycin	1	0.6%	Adjusted
Inj. Vancomycin, Inj. Ceftriaxone	1	0.6%	Adjusted
Tab. Amoxicillin+Clavulanic acid	10	6.1%	Un adjusted
Tab. Cefixime	9	5.5%	Un adjusted
Tab. Doxycycline	1	0.6%	Un adjusted
Tab. Metronidazole	1	0.6%	Un adjusted
Tab. Norfloxacin	1	0.6%	Un adjusted

Table 5: Predictors of medication dosing errors in chronic kidney disease patients

Variables		Frequency	Patients with unadjusted drugs	p-value
Age	<20	10	1	0.9706
	21-40	34	4	
	41-60	98	14	
	>61	50	6	
Gender	Female	55	5	0.3633
	Male	137	20	
Length of stay days	<7	26	14	0.0001
	>8	166	11	
CKD Stage	Stage 3	13	3	0.6275
	Stage 4	19	2	
	Stage 5	160	20	
Comorbidity present	Yes	125	15	0.6159
	No	67	10	
Antibiotics prescribed	Yes	163	25	0.0368
	No	29	-	
Comorbidities	HT	72	10	0.2307
	HTN,T2DM	37	4	
	GE	1	1	

Chi-square; Significance: $p<0.05$.

DISCUSSION

The aim of the present study is to assess the type of antibiotics prescribed to CKD patients with moderate to severe renal dysfunction. Additionally, the appropriateness and the dose adjustment for these antibiotics was also studied in relation to the patient's condition and comorbidities. To date, very few studies have explored antibiotic use and appropriateness in patients having severe renal dysfunction. One hospital-based study was conducted by Hui *et al.* in Australia [9] to assess the patterns of use and appropriateness of antibiotics. The results of our study were similar to their study in terms of prescribing antibiotics like Vancomycin and Amoxicillin and their dose adjustments. It was noted that 99% (n=189) of these patients had undergone hemodialysis and antibiotics were given prophylactically as these patients are at high risk of developing infections. The antibiotics were chosen according to the ICMR treatment guidelines for antimicrobial Use in common syndromes and local antimicrobial resistance pattern. The most common antibiotics prescribed were found to be injectable Cephalosporins i.e., Ceftriaxone+Sulbactam and Inj. Cefoperazone+Sulbactam. The appropriateness included choosing the right dose and frequency for the given indication and adjusting according to the patients' estimated Glomerular Filtration Rate. The number of prescriptions having appropriate dose adjustments was 74%, and those having inappropriateness was 26%.

However, the length of stay in the hospital has matched with the duration of administration of antibiotics in our study. The average length of hospitalization was 10.27 d. Out of 192 patients, 40 (20%) had prolonged hospital stay of more than 14 d and received antibiotics throughout the stay, which is of great concern. Prolonged administration of antibiotics contributes to the selection of resistant mutants and antibiotic resistance. Out of seven variables tested, two i.e. Length of stay in days; $p<0.001$, Antibiotics prescribed; $p<0.05$ was associated with the medication dosing errors in the multivariate analysis of linear regression. It was found that patients having a comorbid illness such as respiratory illness, AV fistula tract infections were prescribed with multiple antibiotics. They were prescribed initially with unadjusted doses and dose decrement done after 3-4 d. However, the information on the reason for the change of antibiotic from one class to another could not be retrieved from the medical records. The dosing interval of orally administered antibiotics is inadequate for nearly 11 % of patients, which is similar to that of Hui *et al.* and needs further research in this aspect. The percentage of medication dosing errors in antimicrobials is found to be less in our study i.e., 26% compared to the results of a similar study done by Saleemand Masood in 2016 [10]. Establishing antimicrobial stewardship in dialysis centers has been discussed by D'Agata [11]. It may be worthwhile to provide further continuing education to doctors, community pharmacists or nurses on antibiotic prescribing and use in this particular population.

LIMITATIONS

The present study has several strengths. Firstly, the pattern and predictors of medication dosing errors of antimicrobials were studied and identified in moderate to severe renal disease patients. Despite these strengths, the study has a few limitations. First, a retrospective study design was employed, which restricted us from suggesting interventions and observing actual adverse drug reactions. Second, the MDRD equation was used due to a lack of data regarding patients' weight, which is less suitable for patients with higher muscle mass and those suffering from serious disorders such as cancer. Third, due to the lack of data, the most responsible diagnosis for hospital admission could not be identified.

CONCLUSION

It is concluded that the occurrence of medication dosing errors was moderate in hospitalized chronic kidney disease patients in our study. Nearly 20% of patients who had prolonged stay were prescribed antibiotics. The predictors of medication dosing errors in CKD patients were the severe-to-end stages of chronic kidney disease, the number of prescribed antibiotics, and the length of hospitalization. Therefore, physicians are advised to take care of these predictors of medication dosing errors while prescribing drugs to chronic kidney disease patients to minimize the risk of drug-related toxicities and limit the spread of antimicrobial resistance.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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