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Original Article

Drug Dosage Adjustment of Chronic Kidney disease Patients at Nephrology Ward in Tertiary Care Hospital of Nepal

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ABSTRACT

Background: Drug dosage adjustment is essential for chronic kidney disease patients (CKD) patients. If it is not done properly, this will lead to an increase in toxicity and a decrease in the effectiveness of therapy. The objective of the present study was to assess whether appropriate dosage adjustments were made in hospitalized CKD patients.

Methods: A descriptive cross-sectional study was carried out among 80 CKD patients with stage II to V admitted in the nephrology ward of Chitwan Medical College Teaching Hospital, Nepal between 1st August to 30th November 2018. All patients with renal clearance ≤90 ml/min/1.73 m2 were included for the analysis. Data concerning patient's clinical, medications and dosages, laboratory findings were extracted from the medical record section.

Results: Total of 81 numbers of prescribed drugs was found in eighty hospitalized CKD patients. Twenty-seven were found requiring dose adjustment. Dose adjustment according to renal function was judged as necessary in 27 dose adjustment required drugs. Among these, 11 (40.7% of 27) drugs were considered appropriate in dosing, whereas 16 (59.3%) were found to be inappropriate. A total of 13 (81.3%) number of drugs were inappropriately adjusted in stage V patients.

Conclusion: Dosing errors were the most frequently observed challenge in the patient hospitalized with CKD. This study also intensified the need for strong monitoring of drug therapy which will bear in achieving the better therapeutic outcomes that improve the quality of life and decrease the various problems associated with dosing error.

Keywords: appropriateness, chronic kidney disease, dose adjustment, drug dosage adjustment, Nepal, nephrology

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INTRODUCTION

Chronic kidney disease (CKD) is one of the most widely spreading health issues which showed about 8% to 16% of prevalence.[1] Globally, hypertension and diabetes are the most leading cause of the renal problem.[2] CKD is simply defined as kidney damage or Glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 for ≥3 months which means abnormalities in pathological condition or markers of deterioration, involving blood abnormalities or urine tests or imaging studies [3]. The best way to measure kidney function is by measuring the GFR rate.[4] The age, gender, and body size are the factors that alter the normal value of GFR, which value in a healthy adult is about 120 to 130 mL/min/1.73 m^2. [5]

The alteration of renal excretion leads to the accumulation of drug metabolites in the case of patients with renal failure.[6] Besides, the pharmacokinetic parameters like distribution and elimination were affected by significantly decreasing the plasma protein binding of drugs. Finally, these changes will happen due to altering in metabolizing enzymes and drug transporters in CKD patients.[6] The proper monitoring of drug therapy is important for CKD patients to prevent drug dosage related problems like accumulation and toxicity, drug elimination is directly linked with the GFR rate so that it is logical to use eGFR or eCrCl for monitoring dosages in that case.[7] The main aim of drug individualization is to optimize the therapeutic outcome and to reduce the drug-related toxicity in CKD patients, there are two important methods for achieving this is either to lengthen the dosing interval or by reducing the dose. Firstly the loading dose needs not to be adjusted. Sometimes both the method needs to the adjusted.[8] The proper dosage monitoring can help to reduce the morbidity rate and save the cost which also prevents the drug dosage related toxicity.[9] In the case of patients with CKD if the dosage is not appropriate given which leads to an increase in toxicity and ineffective therapy.[10] The elderly population is at a high risk of developing multiple advance diseases and associated adverse events, which may due to age-related decline in kidney function and the use of polypharmacy to treat their comorbid conditions.[11-13]

The limited number of studies[14,15] that evaluate drug dosage adjustment in CKD patients were conducted in Nepal. Therefore, this study was initiated to assess drug dosage adjustment among hospitalized patients with renal impairment at Chitwan Medical College Teaching Hospital (CMCTH), Chitwan, Nepal.

MATERIALS AND METHODS

Study design: The study design was a descriptive cross-sectional study.

Study area: The study was conducted in the nephrology ward of Chitwan Medical College Teaching Hospital (CMCTH), located in Bharatpur Chitwan, Nepal which is affiliated to Tribhuvan University and it is the first ISO certified Medical College, which has a 750-bed hospital.

Study Population, inclusion and exclusion criteria: The study population was all CKD patients admitted to the nephrology department of CMCTH. Patients older or equal to eighteen years of age, patients hospitalized for at least one day were included in the study. Patients undergoing kidney transplantation, patients who were critical in condition and unable to respond, mentally retarded and psychiatric patients and pregnant women of any trimester were excluded from the study.

Sample size determination: Census sampling was taken during the data collection period.

Duration of study: The data collection period was for 3 months from 17th August 2018 to 16th November 2018.

Data collection procedures: Data were collected using a structured questionnaire and patient medication profile form. The purpose of the structured questionnaire was to document a patient-related variable that includes, socio-demographic details of the patients (age, gender, marital status, religion, ethnic group, family type, education, source of income, average investment, insurance policy, etc. Patients medication profile form was designed to document subjective observation (chief complaints, medical history, family history, social history), objective observation (physical examination, vital sign, known allergies), lab investigation, hematology, urine Analysis, presenting complaints, stage of CKD, list of comorbidities, drug regimen (generic name of medications, number of medication used, dose, frequency, route, duration).

GFR was estimated based on creatinine clearance from serum creatinine (SCr) using the Cockcroft

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Gault equation.[16] All of the information was tabulated for analysis. Appropriateness was determined by comparing practice with the guideline "The Renal Drug Handbook".[17]

Ethical Considerations: The ethics approval was obtained from the Institutional Review Committee (IRC) of Pokhara University (Reference number IRC 21-075-76). Permission to conduct the study at the hospital was also obtained from the Department of Nephrology, Chitwan Medical College Teaching Hospital, Chitwan, Nepal. Before the data collection, formal permission was obtained from each participant and the respondents were informed about the purpose and objectives of the study. Privacy and confidentiality were maintained by not disclosing the name of the participants and ensuring them, that collected information was used only for the research purpose.

Data analysis: Data were entered and analyzed using Statistical Package for Social Science (SPSS) version 20. The data were summarized and described using tables and graphs. Descriptive statistics were used to describe demographic and disease characteristics of the patients. Percentages and frequencies were used for categorical variables, and means and standard deviations were calculated for continuous variables. Inferential statistics were used to evaluate the association of socio-demographic status with stages of CKD.

RESULTS

The socio-demographic and clinical characteristics of the patients. Eighty patients identified as having moderate to severe renal impairment, 32 (40%) were male and 48 (60%) were female. The patients had an average age of 58.90 years. Regarding educational status, the majority of patients (57.5%) were illiterate and only 36.3% had gain School Level/SLC level education. The majority were in normal Body Mass Index (BMI) of 63.80%. More than half (61.3%) respondents had spent their 1-5 days of hospital staying period (table 1). The presenting complaints (complications) of CKD patients are shown in Table 2. Majority of patients (n=19) (21.25%) had hyperuricemia followed by UTI (n=13) (16.25%), edema (n=12) (15%), hyponatremia (n=11) (13.75%). (table 2)

Figure 1 shows the appropriateness of prescribed drugs for CKD patients. Out of 81 number of prescribed drugs, 27 (33.33%) required for the dose adjustment. Among them, 11 (40.74%) were

Table 1: Socio-demographic and clinical characteristics of the patients

Variable	Frequency	Percentage
Age		
18 – 28	4	5.0
29 – 38	5	6.3
39 – 48	18	22.5
49 – 58	14	17.5
> 59	39	48.8
Gender		
Male	32	40.0
Female	48	60.0
Education		
Illiterate	46	57.5
School Level/SLC	29	36.3
Intermediate	4	5.0
Bachelor or above	1	1.3
BMI		
Underweight	24	30.0
Normal weight	51	63.8
Overweight	5	6.3
Length of hospital stay		
1-5	49	61.3
6-10	25	31.3
11-15	6	7.5
Patients with a stage of renal Impairment		
Stage II	3	3.8
Stage III	4	5
Stage IV	20	25
Stage V	53	66.3

Figure 1: Appropriateness of prescribed drug for CKD patients

Table 2: Presenting complaints of CKD patients

Complication	Frequency	Percent
Hyperuricemia	19	23.75
Urinary Tract Infection	13	16.25
Edema	12	15
Hyponatremia	11	13.75
Seizure	6	7.5
Lower Respiratory Tract Infection	8	10
Chronic Obstructive Pulmonary Disease	4	5
Upper Respiratory Tract Infection	3	3.75
Hyperkalemia	2	2.5
Hypoglycemia	2	2.5
Total	80	100

Table 3: Commonly prescribed drug

Therapeutic Category	Frequeny	Percentage
Antihypertensive	139	22.24
Haematinics	78	12.48
Proton Pump Inhibitor	69	11.04
Antimicrobials	47	7.52
Antacids	37	5.92
Phosphate Binder	36R	5.76
Antiemetic	35	5.6
Anticoagulant	33	5.28
Hypoglycemic Drugs	31	4.96
Antigout	30	4.8
Nonsteroidal Anti-Inflammatory Drug	20	3.2
Antihyperlipidemic	14	2.24
Corticosteroids	14	2.24
Anticonvulsant	12	1.92
Antihistamine	9	1.44
Antispasmodic	7	1.12
Anti-thyroid	7	1.12
Analgesic	5	0.8
Anthelmintics	2	0.32
Total	625	100

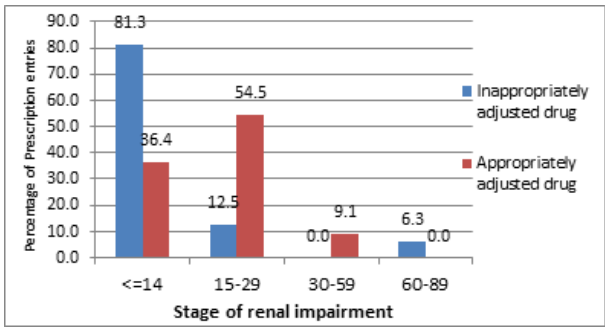
appropriately adjusted drug and the remaining 16 (59.25%) items were inappropriately adjusted.

Table 3 shows the commonly prescribed medications for CKD patients. This table showed that antihypertensive was the most commonly used medication (n=139) (22.24%) which was followed by drugs for anemia and dietary supplements (n=78) (12.48%) and proton pump inhibitor (n=69) (11.04%).

Regarding stage-wise appropriateness of drugs, a higher number of drugs 13 (81.3%) were inappropriately adjusted in stage V while among appropriately adjusted 11 drugs, 6 (54.54%) of drugs were found appropriately adjusted for stage IV (Figure. 2).

Figure 2: Appropriateness of drugs by stage of CKD

The result showed that the majority (n=7) (64%) of drug items were adjusted appropriately in age



> 59 and (n=8) 50% of drug items were adjusted inappropriately in the same age group (Figure 3).

Table 4 shows the frequency of inappropriately adjusted drugs. Majority (n=18) (41.9%) of drug inappropriately adjusted were from an antibiotic group (ciprofloxacin, levofloxacin, meropenem, nitrofurantoin). Among these antibiotics, nitrofurantoin (n=6) (14%) was the most commonly prescribed inappropriate drug.

Figure 3: Appropriateness of drug across various age group

Table 5 shows the frequency of appropriately adjusted drugs. The majority (n=11) (24.4%) of drugs piperacillin+tazobactum were appropriately adjusted while nebivolol only (n=1) (2.2%) were adjusted appropriately which was very less than other remaining drugs.

Table 6 shows an association between stages of chronic kidney disease and socio-demographic characteristics. In this study, age was found to be significantly associated with the stages of CKD but other socio-demographic variables were not found associated with stages of CKD.

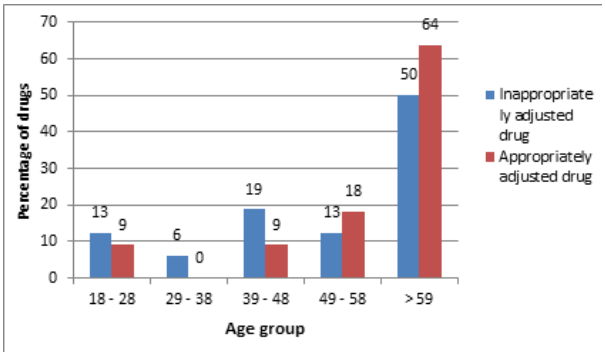


Table 4: Frequency of inappropriately adjusted drugs

Inappropriately adjusted drugs	N	%
Acetaminophen+Tramadol	2	4.7
Ciprofloxacin	3	7.0
Fenofibrate	1	2.3
Fexofenadine Hydrochloride	5	11.6
Hydrochlorthiazide + Losartan potassium	3	7.0
Ketorolac tromethamine	1	2.3
Levofloxacin	5	11.6
Losartan potassium	2	4.7
Meropenem	4	9.3
Metformine Hydrochloride	1	2.3
Metoprolol tartrate	4	9.3
Nitrofurantoin	6	14.0
Pregabalin	1	2.3
Rosuvastatin	1	2.3
Sitagliptin	3	7.0
Spironolactone	1	2.3

Table 7 shows an association between stages of chronic kidney disease and the number of prescribed drugs. In this study, the number of prescribed drugs was found to be significantly associated with the various stages of CKD.

Table 8 shows an association between a number of prescribed drugs and comorbidity of CKD. In this study, the number of prescribed drugs was found to be significantly associated with the various comorbidities of CKD.

Table 5: Frequency of appropriately adjusted drugs

Appropriately adjusted drugs	N	%
Acetaminophen	6	13.3
Clonazepam	5	11.1
Insulin	8	17.8
Levocetirizine	4	8.9
Nebivolol	1	2.2
Piperacillin+Tazobactum	11	24.4
Potassium chloride	3	6.7
Tramadol	4	8.9
Phenobarbitone	2	4.4
Sodium valproate	1	2.2

DISCUSSION

The present study has shown that, of the total study population, 66.3% had stage V, 25% had stage IV, 5% had stage III and 3.8% had stage II CKD. This result is consistent with other studies conducted in India in which 76% had stage V, 18% had stage IV and 6% had stage III CKD.[18] The patient with stage V, CKD is higher in this study which may be due to the absence of symptoms in stages I and II, while minimal and common symptoms are observed in stages III, IV and V respectively. This finding contradicts the study done by Kuznik A et al., 2013, which found a higher prevalence (49.1%) in stage III and very low (3.7%) in stage IV CKD.[19]

The present study has shown that the mean age of the CKD patients was 58.90 while the age group of >59 years comprises the highest percent (48.8%). This showed the prevalence of CKD is seen in older age groups however the study from Nepal, National Kidney Center, Banasthali, Kathmandu, the mean age of the CKD patients was 47 years while the age group between 41-60 years comprises the highest percent.[20]

In this study, 58.8% of patients were normal in BMI, 30% were underweight and only 6.3% were overweight. This finding contradicts the study

Table 6: Association between stages of chronic kidney disease and socio-demographic characteristics

Characteristics	Stages of CKD				Chi-square	p-value
Age	**II**	**III**	**IV**	**V**		
18 – 28	4(100)	0	0	0	26.6	0.009*
29 – 38	4(80)	0	0	1(20)		
39 – 48	12(66.7)	3(16.7)	1(5.6)	2(11.1)		
49 – 58	14(0)	0	0	0		
> 59	19(48.7)	17(43.6)	3(7.7)	0		
Gender						
Male	21(65.6)	9(28.1)	1(3.1)	1(3.1)	6.2	0.88
Female	32(66.7)	11(22.9)	3(6.3)	2(4.2)		
BMI						
Under weight	18(75)	4(16.7)	1(4.2)	1(4.2)	2.2	0.9
Normal weight	32(62.7)	14(27.5)	3(5.9)	2(3.9)		
Over weight	3(60)	2(40)	0	0		
Source of income						
Agriculture/Farming	21(70)	7(23.3)	2(6.7)	0	9.67	0.84
Family Business	15(68.2)	5(22.7)	1(4.5)	1(4.5)		
Remittance	8(66.7)	3(25)	0	1(8.3)		
Private/Government Job	4(66.7)	1(16.7)	0	1(16.7)		
Labor/Daily wages	2(50)	2(50)	0	0		
Pension	3(50)	2(33.3)	1(16.7)	0		
Marital status						
Married	45(71.4)	13(20.6)	2(3.2)	3(4.8)	11.26	0.25
Unmarried	1(100)	0	0	0		
Divorced	2(100)	0	0	0		
Widow/Widower	5(35.7)	7(50)	2(14.3)	0		
Religion						
Hinduism	37(63.8)	15(25.9)	4(6.9)	2(3.4)	7.69	0.56
Mushilm	2(50)	1(25)	0	1(25)		
Buddhism	11(78.6)	3(21.4)	0	0		
Christianity	3(75)	1(25)	0	0		
Type of family						
Nuclear	14(82.4)	3(17.6)	0	0	9.08	0.16
Joint	31(63.3)	13(26.5)	4(8.2)	1(2)		
Extended	8(57.1)	4(28.6)	0	2(14.3)		
Monthly Income						
Rs. 5000- Rs. 10,000	2(5.9)	1(2.9)	7(2.6)	24(70.6)	2.759	0.838
Rs.15,000-Rs. 30,000	1(2.8)	2(5.6)	11(30.6)	22(61.1)		
Rs.35,000- Rs. 60,000	0	1(10)	2(20)	7(70)		
Education status						
Illiterate	30(65.2)	14(30.4)	2(4.3)	0	13.05	0.16
School Level/SLC	21(72.4)	3(10.3)	2(6.9)	3(10.3)		
Intermediate	2(50)	2(50)	0	0		
Numbers of cigarette smoked per day						
1-5 cigarette/day	9(69.2)	3(23.1)	1(7.7)	0	11.94	0.063
6-15 cigarette/day	14(51.9)	12(44.4)	0	1(3.7)		
Whole packet	7(77.8)	0	2(22.2)	0		
Ever consumed alcohol product						
Yes	24(75)	6(18.8)	1(3.1)	1(3.1)	1.88	0.59
No	29(60.4)	14(29.2)	3(6.3)	2(4.2)		
If consumed alcohol, frequency of drinking alcohol						
Low (<1 glass/week)	37(92.5)	3(7.5)	0	0	19.21	0.084
Moderate (1-3 glass/week)	5(62.5)	1(12.5)	1(12.5)	1(12.5)		
High (> 3 glass/week)	6(66.7)	3(33.3)	0	0		
Heavy Drinker	3(100)	0	0	0		

Table 7: Association between stages of chronic kidney disease and the number of prescribed drug

	Stages				Chi-square	p-value
Number of drugs	**II**	**III**	**IV**	**V**		
4	1(100)	0	0	0	45.018	0.016*
5	0	1(16.7)	3(50.0)	2(33.3)		
6	1(7.1)	2(14.3)	0	11(78.6)		
7	0	1(5.9)	7(41.2)	9(52.9)		
8	1(6.2)	0	4(25)	11(68.8)		
9	0	0	4(28)	10(72)		
10	0	0	0	3(100)		
11	0	0	1(20)	4(80)		
12	0	0	1(33)	2(67)		
13	0	0	0	1(100)		

Table 8: Association between the number of prescribed drug and comorbidity of CKD

Number of drugs	Comorbidity			Chi-square	p-value
	Single	**Double**	**Multiple**		
4	1(100)	0	0	63.492	0.000*
5	5(83.3)	0	1(16.7)		
6	13(92.9)	1(7.1)	0		
7	12(70.6)	5(29.5)	0		
8	12(75.0)	4(25.0)	0		
9	4(28.6)	10(71.4)	0		
10	2(66.7)	1(33.3)	0		
11	0	4(80.0)	1(20)		
12	0	3(100)	0		
13	0	0	1(100)		

done in Japan by Iseki K et al., 2003 which found cumulative incidences of ESRD per 1000 screens were, from the lowest to highest BMI quartile 2.48, 3.79, 3.86 and 5.81.[21] The study showed that normal and underweight patients might be due to the patient on a normal diet under hemodialysis.

Mean hospital stay in this study was found to be more than six days. This was inconsistent with the result of Kshirsagar et.al, 2000, the study was done in North Carolina in which the length of hospital stay for admissions to the nephrology service was 6.3 days.[22] The length of hospital stay in this study was found to higher which might be due to the presence of multiple comorbidities.

In the present study, the prevalence of hypertension is higher (31.25%) and this result is slightly higher

to the finding made by Dasari et al., 2014 in India in which 23.3% were found to be hypertensive patients.[18] The higher prevalence of hypertension in a patient with CKD the reason behind this might be due to hypertension is the cause and complication of CKD and it is also difficult to control.[23]

In the present study, out of 135 antihypertensive drugs, most commonly prescribed 65 (48.14%) were from diuretics. This finding is similar to 144 (46.1%) to the study conducted in the North-Eastern part of Malaysia by Khan et al., 2016.[24] The patient with moderate to the last stage of CKD has the problem of fluid overload, which is also associated with hypertension, congestive heart failure, left ventricular hypertrophy as well as edema, for this case diuretics are most commonly prescribed to control blood pressure and symptomatic relief.[25]

In this study, 19.75% of the drugs required dose adjustments were inappropriately prescribed and this result is similar to the study carried out at Tribhuvan University Teaching Hospital (TUTH), Kathmandu by Sah et al., 2015 which revealed 20% of inappropriate drugs for CKD patients.[15] The medication dosing errors in the present study were much lower than the studies reported from Palestine, India and South Africa, whereby the percentages of unadjusted drugs were nearly 73.6%, 81.1%, and 59.0% respectively.[26-28] The medication error was found to be decreased in this study as compared to other underdeveloped countries which could be due to proper dosage by the skilled, trained nephrologist to the CKD patients.

In this study, it was found that dosing error was gradually increased as the staging of CKD was advancing e.g., with lesser CrCl. Of the total 27 medications, the majority of drugs 13 (48.14%) were inappropriately and only 4 (14.81%) were adjusted appropriately in stage V CKD patients. These results are similar to another study conducted in Ethiopia by Getachew et al., 2015[29] Out of the 10 number of prescription-only 2 (20%) were found to be appropriately prescribed in the patient with stage V CKD, which has a higher chance of dose inappropriateness due to multiple drugs prescribed to manage multiple disease condition.

The highest proportion of inappropriateness 8 (50%) in age >59 was observed in the study which was followed by the age group 39-48 (18.75%). The proportion of inappropriateness was higher in the older age group which might be due to the higher number of those age group patients who were admitted to the Nephrology ward. This result is supported by the result of Getachew et al., 2015, who showed that a greater proportion of inappropriate dose adjustment in prescription entries was observed in the elderly (≥60 age group).[29]

The frequencies of inappropriately prescribed drugs for CKD patients were observed. In a total of 16 inappropriately adjusted drugs, antibiotic groups (Ciprofloxacin, levofloxacin, meropenem, nitrofurantoin) were frequently prescribed drugs (41.9%). And among these antibiotics, nitrofurantoin (14%) was the most commonly prescribed inappropriate drug because the dosage prescribed is not in conformity to the patient's CrCl as per the recommendation of The Renal Drug Handbook.[30] These findings are in line with previous studies done by [15,28]. But this finding contradicts the study done by Getachew H et al., 2015, which found a high frequency of diuretics (spironolactone) as inappropriate drugs.[29]

Limitation of The Study

The data collection time was limited so it is also the limitation of the study. The sample size was less in number i.e. 80 which could not represent the whole scenario of CKD in Nepal was another limitation of this study.

Recommendations

Further research should be conducted to assess the impact of more variables such as the specific drug classes and the specific comorbidities on the medication dosing errors in chronic kidney disease patients. For the avoidance of harmful DDIs, interaction should be checked.[31,32] Awareness creation programs should be conducted for healthcare professionals to minimize the risk associated with potentially harmful drug combinations.[33] The multicenter study should be done for assessment of drug dose adjustment as well as drug-drug interaction in that site. Drug information via drug information center of the hospital can be provided to the CKD patients regarding DDI and ADR.[34] Further study should be conducted to find out the pharmacological management system of CKD in a hospital that either follows the standard guidelines of treatments or not in any tertiary care hospital.

CONCLUSION

This study concluded that proper dose monitoring and adjustment was not done by the health care practitioners to the patient with CKD. The finding of this study specified the need for providing various guidelines and important information regarding dosage adjustment appropriateness to the health care provider to prevent dosage related toxicity in a patient with CKD. The present study indicated the need and role of health care provider for identifying and reducing dosage related medication error, which could be possible by providing sufficient updated clinical guidelines and health-related information to the prescriber. Therefore, a collaboration of physicians with a pharmacist or a clinical pharmacist is necessary for the early detection and prevention of dose-related medication error which will help to improve the therapeutic outcome and reduces the consequences associated with adverse events in the patients with CKD.

Abbreviations

GFR: Glomerular filtration rate;
CKD: Chronic kidney disease;
CrCl: Creatinine clearance;
SCr: Serum creatinine;
eGFR: Estimated glomerular filtration rate;
MDRD: Modification of diet in renal disease study:
ESRD: End-Stage Renal Disease;
HD: Hemodialysis;
IDWG: Interdialytic Weight Gain;
KDOQI: Kidney Disease Outcomes Quality Initiatives;
LDL: Low-Density Lipoprotein;
LVH: Left Ventricular Hypertrophy;
NKF: National Kidney Foundation;
PD: Peritoneal Haemodialysis;
QOL: Quality Of Life;
WHO: World Health Organization

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