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Drug Utilization Review of Antibiotics in Chronic Kidney Disease Patients and Comparison with the Standard Drug of Choice

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Abstract

The risk of morbidity and death in patients with chronic kidney disease (CKD), formerly known as chronic renal failure (CRF), is increased by a number of comorbidities, including infections, cardiovascular disease (CVD), and anaemia. The second most common reason for death in this population is infections. Antibiotics can accumulate in the body and have harmful consequences when given to CKD patients without the necessary dosage modification and in an illogical manner. The purpose of this particular study was to compare the standard treatment protocol with the reasoning and prescribing patterns of antibiotics administered for infections in CKD patients staged 3-5 in the nephrology department of a single Center in Kerala's Kottayam district. The medical records of 272 patients who met the inclusion and exclusion criteria and were admitted to the nephrology department between November 2019 and November 2020 were examined as part of single-centred retrospective research that was created to address this. Surprisingly, just 45 percent of the prescriptions were rational, while 55 percent of them were nonsensical. Additionally, we discovered that 23 percent of antibiotic selections went outside accepted therapeutic standards. Thus, we could conclude that the prescriber must use the utmost caution while prescribing to a patient with CKD to prevent future difficulties.

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INTRODUCTION

A complex, irreversible condition known as chronic renal failure (CRF) or Chronic Kidney Disease (CKD) covers all degrees of diminished kidney function, ranging from damaged-at-risk to mild, moderate, and severe chronic renal failure. It is characterized by a decrease in the glomerular filtration rate (GFR) that lasts for at least three months and may present as aberrant albumin excretion or reduced kidney function. The National Kidney Foundation (NKF) defines CKD as either kidney damage or a reduced GFR of less than 60 ml/min/1.73 m2 that persists for at least 3 months irrespective of the etiology. This definition has changed over time. The most recent version is provided by the KDOQI. Kidney diseases are most commonly identified by the presence of albuminuria which is defined as an albumin-to-creatinine ratio >30 mg/g in at least two of three spot urine specimens [1]. It should be noted that if these changes occur within less than 3 months,

it is termed acute renal failure(ARF) and if it takes place within 2-7days it is termed kidney injury [2]. The main indicator of decreased kidney function is a reduction in the GFR value which is the total amount of fluid filtered by the functioning nephrons per unit time [3]. GFR can be estimated from calibrated serum creatinine and estimating equations, such as the Modification of Diet in Renal Disease (MDRD) Study equation, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [4] equation or the Cockcroft-Gault formula. The only treatment options in advanced stages are dialysis and transplantation [1].

Several studies have shown that because of the older age of individuals at the onset of many kidney diseases, the slow rate of decline of kidney function and the high death rate due to CVD, most individuals with CKD do not develop kidney failure. However, decreased GFR is associated with a wide range of complications such as hypertension, anemia, malnutrition, bone disease, neuropathy, infections and increased hospitalizations [5]. Therapeutic interventions at earlier stages can help prevent most of the complications of kidney disease and slow the progression to end stage renal disease (ESRD). Thus, it is very important to diagnose CKD at the earliest and start proper treatment from the time of diagnosis [3]. Staging based on the progression of Kidney damage is shown in Table 1.

Various complications arise when someone is diagnosed with CKD or when one's kidney is damaged. These include Anemia, Cardiovascular diseases, CKD induced mineral and bone disorders, Cancer, Renal failure and most frequent infections. And these infections can only be managed with Antibiotics. We will be looking through the pattern in which these antibiotics are being prescribed in the selected study site.

MATERIALS AND METHODS

A Single centered, Retrospective, Observational study was conducted using the data collected from November 2020 to December 2020 on all patients admitted to the nephrology department during this period at one of the best Healthcare centers in South India, Caritas Hospital, located in Thellakom, Ettumanoor, Kottayam. Data of all in-patients and out-patients who visited the hospital during the period under study (November 2019 to November 2020) in the Nephrology Department regardless of sex and satisfied the inclusion and exclusion criteria were included in the study. Patients who withdrew treatment due to adverse events or lack of efficacy were also included.

Inclusion Criteria

1. Chronic Kidney Disease Stage: 3-5.
2. Patient must have taken at least one antibiotic treatment.
3. Patients within the age group of 18 -80 yrs age.
4. Patients who are on IV and oral forms of antibiotics only were included.

Exclusion Criteria

1. Pregnant and lactating women.
2. On immunosuppressive therapy.
3. Patients having malignancies of any form and are on therapy.
4. Patients having any Chronic Liver Disease or have undergone a transplantation.
5. Patients whose height, weight etc could not be measured.
6. Patients taking topical antibiotics.
7. Patients in the age group <18yrs and >80yrs.
8. Patients who asked for a discharge at their own risk or have not completed the therapy prescribed by the physician.

After considering the prevalence of CKD, and applying enough statistics, it was found that an estimated value of 280 samples (95% CI with a 3% Margin of Error for a condition with approximately 14-15% prevalence) were required to conduct a similar study. Though due to the current country's health scenario, though we found a little difficulty in collecting the data, we could finally include a number of 272 subjects for this particular study. Patient data for that 272 were obtained from both the patient medical chart (IP) and the electronic medical record (EMR). The collected data was then entered into the pre-prepared data collection form. A total of 324 antibiotic prescriptions were collected from the nephrology department during the study period. All these collected data were then screened for the inclusion and exclusion criteria and the data was modified further. Patient data were collected from the hospital medical records and data was collected after approval from the "Institutional Ethics Committee." The endpoint of the study will be the identification of inappropriateness in antibiotic usage in CKD patients.

Table 1: Staging of CKD based on Glomerular Filtration rate

Stages	eGFR value	Interpretation
G1	>90	Normal or high
G2	60-89	Mildly decreased
G3a	45-59	Mild to moderate decrease
G3b	30-44	Moderate to severe
G4	15-29	Severely decreased
G5	<15	Kidney failure

Table 2: Differential number of patients with their infection

Type of infection	Number (N=211)	Percentage (%)
UTI	36	17.1
RTI	66	31.27
AKI	43	20.37
CRBSI	7	3.31
Sepsis	9	4.26
AGE	14	6.63
Cellulitis	18	8.53
Vasculitis	9	4.26
Others	9	4.27

RESULTS AND DISCUSSION

Upon analysis, we could find that out of 272, only 211 took antibiotics for some sort of infection. The rest of them took antibiotics as a prophylactic approach before hemodialysis to prevent site infection or sepsis. Those 211 patients were placed into different categories based on the infection for which they received antibiotic therapy. The number of the patient population with respect to the type of infection-site infected- is given in Table 2.

It was found that 66 among 211, which contributed to 31.27% of the population were diagnosed with Respiratory tract infection; followed by infection in the excretory/urinary system.

To treat these infections, anti-microbial administrations were initiated. The chemotherapeutic agents used were analyzed in detail. The so-called chemotherapeutic agent used to either inhibit the growth (bacteriostatic) or eradicate (bactericidal) the microorganisms are called antibiotics. Based on their structure, mechanism of action and their spectrum of activity, these antibiotics are classified into many types.

The various classes of antibiotics with their major indication are found in the literature and guidelines review and are given in Table 3.

In this study, it was found that the antibiotic which was selected mainly in this population was third-generation cephalosporins with beta-lactamase inhibitor; followed by penicillins for some sort of infection.

The contributory rate for each antibiotic in the selected population is given in Table 4. 445 different compounds were given in this population in the prescribed period.

The indication or the final diagnosis as per microbiologic analysis was then compared with the antibiotic prescribed. Then the prescribed antibiotics were checked for their spectrum of activity and were compared with standard or usual therapy widely accepted.

Since Respiratory Tract Infection (RTI) was the leading type of infection in the study population, more emphasis was given to the same. Upon analyzing each RTI patient, we could find that most of them were given third-generation cephalosporins (34.66%) followed by azithromyzin (17.33%) and amoxicillin (14.66%). Other than beta-lactams, fluroquinolones (8%) were also prescribed. The number corresponding to each antibiotic is given in Table 5.

Prophylaxis for AVF installation prior to hemodialysis was the second major reason for using antibiotics in CKD patients. Amoxicillin was the drug which was widely prescribed for this indication (80%). The number corresponding to each antibiotic for this indication is given in Table 6.

Table 3: Major Antibiotic class and their primary indication

Type of Antibiotic	Major Indication
Macrolides (except Azithromycin)	Skin and soft tissue infection by Gram-positive organisms and chlamydia (Urethritis, Vaginitis)
Azithromycin	RTI, Skin and Soft tissue infection
Fosfomycin	UTI
Co-trimoxazole	UTI
Metronidazole	Intra=abdominal and Parasitic Infection
Tetracyclines	RTI, Skin and Soft Tissue Infection
Aminoglycosides	Emperical Therapy with severe illness (Sepsis, Endocarditis, Abdominal infections)
Linezolid	Gram +ve RTI (MDR)
Fluroquinolones	UTI, Intra abdominal Infections
Cephalosporins I Generation	Skin and Soft Tissue infections
Cephalosporins II Generation	RTI Gram-ve
Cephalosporins III Generation	Intra abdominal, Soft and Skin Tissue, CNS (Meningitis) infection (Gram +ve)
Cephalosporins IV Generation	Severe Gram +/- infections
Penicillins	RTI, Skin and Soft tissue, Ear/Mouth
Carbapenams	Severe RTI/UTI caused by organisms resistant to even high-end antibiotics due to beta-lactamase activity

Table 4: Selection rate of Antibiotics in CKD population

Drugs Used		Number (N=445)	Percentage
Penicillins without β-lactamase Inhibitor		55	12.4
Penicillins with β-lactamase Inhibitor		55	12.4
Cephalosporins			
First Generation	with β-lactamase Inhibitor	0	0
	without β-lactamase Inhibitor	2	0.4
Second Generation	with β-lactamase Inhibitor	1	0.2
	without β-lactamase Inhibitor	28	6.3
Third Generation	with β-lactamase Inhibitor	105	23.6
	without β-lactamase Inhibitor	46	10.3
Fourth Generation	with β-lactamase Inhibitor	1	0.2
	without β-lactamase Inhibitor	0	0
Penams		50	11.2
First Generation Fluroquinolones		4	0.9
Second Generation Fluroquinolones		37	8.3
Oxazolidiones (Linezolid)		8	1.8
Macrolides		23	5.2
Tetracycline		1	0.2
Aminoglycosides		9	2
Others	Metronidazole	14	3.1
	Cotrimoxazole	1	0.2
	Rifaximine	1	0.2
	Fosfomycin	4	0.9

Table 5: Antibiotic Utilization in RTI

Amoxycillin	Amoxycillin+ Clavulanic Acid	Cefoperazone+ Sulbactam	Cefuroxime	Levofloxacin	Ciprofloxacin	Meropenam	Azithromycin	Piperacillin Tazobactum	Ceftriaxone
1	11	26	7	4	2	3	13	5	3

Table 6: Antibiotic Utilization in Prophylactic approach before AVF

Levofloxacin	Nitrofurantoin	Cefperazone +Sulbactam	Cefpodoxime +Sulbactam	Meropenam	Amoxycillin	Cefuroxime	Cefixime	Fosfomycin	Piperacillin Tazobactum	Other
7	3	19	2	11	1	3	9	1	4	4

After respiratory tract infection, the major site of infection in CKD patients was the urinary or excretory system, which may or may not has contributed to acute reversible kidney injury. For Urinary Tract Infection also, it was the third-generation cephalosporins used more prominently (29.69%), followed by meropenam (16.9%). The number corresponding to each antibiotic for this indication is given in Table 7.

Cellulitis being more prominent in the case of CKD patients, usually, it was treated using beta-lactam antibiotics, either penicillins or cephalosporins. Most of the culture reports were suggesting the presence of beta-lactamases, and inhibitors for the same were also combined with those beta-lactam antibiotics. The number corresponding to each antibiotic for this indication is given in Table 8.

As already discussed, AKI (Acute Kidney Injury) could be seen widely in CKD patients indicated by an increase in the serum creatinine and blood urea levels. The blood counts were also elevated to an extent. Whenever an injury has occurred, electrolyte management is also impaired. To prevent further complications, antibiotics were initiated. And it was found that third-generation cephalosporins (37.78%) were the major drug of choice, followed by meropenam (24.44%). The number corresponding to each antibiotic for this indication is given in Table 9.

Sepsis was one of the major complications in CKD patients. Either the inappropriate management of infection or through the catheter used for hemodialysis can facilitate the entry of microorganisms directly to the bloodstream; which can further cause other organ damage or even be life-threatening, leading to mortality/death. Usually, high-end antibiotics are used in this scenario, considering the benefits outweighed the risk. Meropenam (41.67%) was the drug which was used more often. The number corresponding to each antibiotic for this indication is given in Table 10.

Whatever the therapy was, it might either be based on any guidelines or the prescriber's expertise. In some hospitals, antibiotic stewardship programs are there, which study major contributory microorganisms and their sensitivity/resistance; which later helps them to develop regional antibiotic selection criteria. Thus, this study never claims that those antibiotic prescriptions were wrong. This study is to analyze the antibiotic selection in the study site and use this data to compare with the standard antibiotic usage guidelines. The number of antibiotic prescriptions which followed the standard, as well as the different regimens, are given in Table 11. In most of the cases, about $1/3^{rd}$ of the regimen was not as per the standard guideline. Also, we could find that 55% of the antibiotics were not individualized based on the subject's renal clearance which may lead to drug accumulation, causing systemic toxicity.

Upon analyzing the data, it was clear that 11 types of antibiotics were prescribed for AVF installation; in which 6 out of them were in accordance with the standard treatment guideline, whereas 5 were exclusive. In the case of UTI, though antibiotic stewardship programmes suggest the use of Meropenam only in case of antibiotic resistance, here Meropenam was prescribed to a larger extent without conducting susceptibility tests. Similarly, for other indications too, various antibiotics were prescribed apart from standard guidelines (Table 11); though it can be from a physician's or nephrologist's expertise.

Misdiagnosis or Initiation with empirical therapy is the major cause of further severity progression in the case of CKD patients. In our study also, it was found that an antibiotic other than the standard was initiated without even checking the susceptibility or drug resistance. Though, prescribing an antibiotic other than the standard in the case of MDR can be appreciated.

Table 7: Antibiotic Utilization in UTI

Amoxycillin	Amoxycillin+ Clavulanic Acid	Cefperazone+ Sulbactam	Cefuroxime	Levofloxacin	Ciprofloxacin	Meropenam	Azithromycin	Piperacillin+ Tazobactum
48	2	5	1	2	0	1	0	1

Table 8: Antibiotic Utilization in Cellulitis

Piperacillin+ Tazobactum	Cefperazone+ Sulbactam	Amoxicillin+ Clavulanic Acid	Cefpodoxime+ Sulbactam	Meropenam	Others
5	4	4	3	4	10

Table 9: Antibiotic Utilization in AKI

Meropenam	Cefperazone Sulbactam	Piperacillin+ Tazobactum	Cefuroxime	Cefixime	Linezolid	Amoxicillin	Ceftriaxone	Other
11	17	2	1	2	1	5	2	4

Table 10: Antibiotic Utilization in Sepsis

Piperacillin+ Tazobactum	Meropenam	Ceftriaxone	Linezolid	Azithromycin	Tigicycline	Others
1	5	1	1	1	1	3

Table 11: Comparison Study of Prescribed versus standard therapy

	Number of antibiotics that followed	
	Standard regimen	Different regimen
AVF	6	5
UTI	16	0
AKI	18	6
RTI	18	3
Sepsis	12	4
CRBSI	6	2
AGE	8	3
Cellulitis	11	4

For instance, various antibiotic stewardship programmes have made me aware that in the case of Urinary Tract Infection, Meropenam should be administered only if the patient is resistant to multiple antibiotics. Since nitrofurantoin is contraindicated in CKD patients, fluoroquinolones would have been a better choice with dose adjustment. Here, in our study, the majority of the cases were not even tested for organism culture and drug sensitivity; but rather prescribed with conserved drugs.

A significant number of patients were administered a drug other than standard without any reason. Various studies reveal that irrational prescriptions apart from guidelines can even cause the death of the patient. The study result thus confirms that our hypothesis, which was Antibiotic prescriptions were not in accordance with standard guidelines, was true.

CONCLUSION

The final results were suggesting that the hypothesis generated-" Physicians usually prescribe antibiotics deviating from the standard guideline, continuing empirical therapy without any detailed investigation"- was true. About $1/3^{rd}$ of the antibiotic prescriptions were not as per standard guidelines for CKD patients and this can lead to further kidney damage, which can even be life-threatening.

This study concludes with advice to conduct proper microbiological and other significant tests before initiation of antibiotic therapy to ensure rationality in every aspect.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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