Original article

Prescribing medication in patients with impaired renal function

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Abstract

Introduction: Renal failure has been emerging as a major public health problem in Nepal in recent years. Chronic renal failure affects renal drug elimination and other pharmacokinetic processes. Drug dosing errors are common in patients with renal impairment and can cause adverse effects and poor outcomes. Medications with toxic metabolites should be avoided, and alternative medications should be used if potential nephrotoxicity exist. Dosages of drugs cleared renally were adjusted according to creatinine clearance and glomerular filtration rate.

Methods: A Descriptive, cross-sectional study was conducted in TUTH. Data were collected from all the renal failure patients admitted at TUTH from 2009 February to April 2009. Parameters studied included age group, gender, duration of hospital stay, causes of renal failure, any associated co-morbidity, serum creatinine (Scr) at admission and at discharge, blood urea nitrogen (BUN) and different drugs prescribed. Creatinine clearance (Clcr) in ml/min/1.73 m^2 was calculated by using Cockroft-Gault equation.

Results: Majority of patient (98.1%) had raised urea level. Renal function at the time of presentation showed that 39.5 % patients had End stage renal failure and 39.5%, 19.7% and 1.3% patients had severe impairment, moderate impairment and mild impairment respectively. Average number of drugs prescribed was 5 to 6. In the list of prescribed medicine, 23% were antibiotic. Of the total antibiotic prescribed, dose adjustment was done for 27.3% and 1.5% drugs were prescribed which are supposed to be avoided in renal failure patients. Similarly in non-antibiotic group, 62.9% drug don't required dose adjustment (they are safer in renal failure), dose adjustment was done in 22.9 %. The mortality rate of the renal failure at TUTH was found to be 15.3%. Kidney diseases, diabetes and hypertension were found to be the common causes of renal failure accounting for 29.5 %, 24.8% and 22.9% respectively.

Conclusions: Most of the patients with renal failure had end stage renal disease at presentation. Though they were prescribed multiple drugs, only few had dose adjustment done and some were even prescribed nephrotoxic drugs.

Key words: Acute renal failure, chronic renal failure, creatinine clearance, end stage renal diseases

Introduction

Renal failure is a serious medical condition affecting the kidneys. In renal failure the kidneys undergo cellular death and are unable to filter wastes and to maintain fluid balances. This dysfunction causes a build up of toxins in the body which can affect functioning of body organ as well as leads to other complications. Renal failure is very serious and even deadly if left untreated.

Biochemically; it is typically detected by an elevated serum creatinine. In the science of physiology, renal failure is

described as a decrease in the glomerular filtration rate. Long-term kidney problems have significant repercussions on other diseases, such as cardiovascular disease.[1] Renal failure can broadly be divided into two categories: Acute renal failure (ARF) and chronic renal failure (CRF). The type of renal failure is determined by the trend in the serum creatinine. Other factors which may help differentiate acute and chronic renal failure include the presence of anemia and the kidney size on ultrasound. Chronic renal failure generally leads to anemia and small kidney size.[1]

Kidney related health problem has been emerging as a major public health problem in Nepal in recent years. Exact incidence and prevalence of CRF in a community is difficult to know due to asymptomatic nature of early stages of CRF. In fact CRF patients are increasing in number day by day. According to National Kidney Center (NKC) of Nepal, around 10, 000 people are suffering from kidney failure in Nepal. The number goes up by 2,500 to 3,000 every year.[2]

In CRF the normal doses of the drug that are cleared renally may prove toxic dose due to accumulation in the body. So the dose of renally cleared drug must be reduced in order to prevent its accumulation in body. In this regard, aminoglycosides are an important cause of renal insufficiency.[3] As kidney is the major regulator of the internal fluids environment, physiology changes associated with renal diseases have pronounced effects on the pharmacology of many drugs. So, renal function should be considered when choosing medications and dosages. An accurate estimation of renal function is calculated Glomerular filtration rate (GFR). Once renal impairment has been detected and Crcl estimated, the need of dose alteration of renally cleared drugs can be determined. Adjustment can be achieved by a reduction in dose or an extension of the interval or both. There are several methods for estimating renal function. The Cockcroft and Gault formula is one method which is commonly recommended.

Methods

A descriptive, cross-sectional study was conducted in Medical Department of the Tribhuwan University Teaching Hospital, Kathmandu, Nepal from Februry 2009 to April 2009. Data was collected from all the renal failure patients admitted during this time period. This center is a Teritiary hospital with various sub-specialties, and receives patients from all parts of Nepal. A total of 105 renal failure patients were seen during the study period, and constituted the study group. Data were collected by using a questionnaire that included age, gender, duration of hospital stay, causes of renal failure, any associated co-morbidity, serum creatinine (Scr) at admission and at discharge, blood urea nitrogen (BUN), diagnosis, as well as prescribed drug .

Creatinine values were extracted from the laboratory system of the hospital. Renal function was estimated by calculating the average creatinine clearance based on the average serum creatinine levels during admission. Creatinine clearance (Clcr) in ml/min/1.73 m^2 was calculated by using Cockroft-Gault equation

a. For men: CrCl = [(140 - Age) x Weight (kg)]/SCr x 72

b. For women: CrCl = ([(140 - Age) x Weight (kg)]/SCr x 72) x 0.85

Dosage adjustments are usually recommended when the creatinine clearance decreases to 50 mL/min. To assess the need for dosage adjustment, ASHF drug 2007 (American Society of Health System Pharmacist) and BNF (British National Formulary) were referred. Firstly the GFR of the patient was calculated and drugs that required adjustment at particular GFR were identified. Then the dose of the prescribed drugs was compared with dosage adjustment done according to their renal function in these references. As in references, the doses of the various drugs were calculated according to the excretion capacity of the kidney.

Results

The mean age of patients was found to be 48.55 ± 20.49 and the median as found to be 47 years. The age range varied from minimum 17 to maximum 84. Among the total 105 patients studied, 54 were male and 51 were female accounting for 51.5% and 48.5% respectively. Renal failure was most common in age group above 60 years and it account for 31.4 % of the total cases. The cases of renal failure are least in the age group of 46-60, accounting for 20% (Fig. 1, 2).

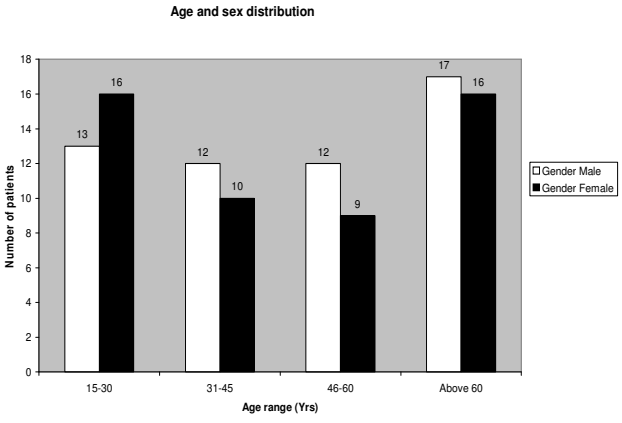


Fig.1: Age Distribution

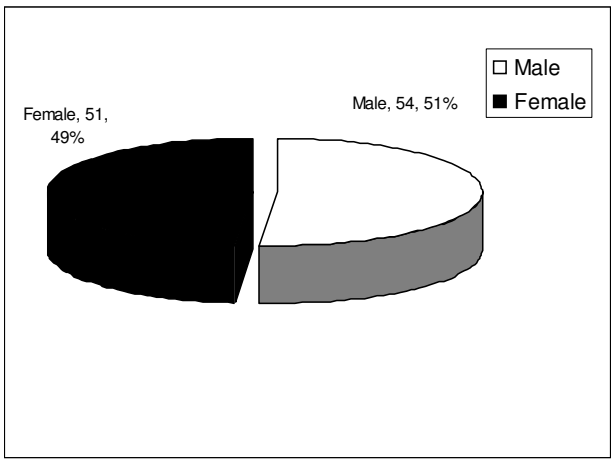


Fig. 2: Sex Distribution

Failure to excrete urea and uric acid adequately, manifested as progressive elevation of blood urea nitrogen (BUN) and serum creatinine, results in uremia. Study showed majority of patients to have increased level of BUN. Of the total 105 patients studied, 103 (98.1%) had raised urea level. Similarly 72% patients had raised uric acid level. Retention of urea and uric acid level is due to reduced GFR and its excretion.

Common causes of renal failure were glomerulonephritis, nephrotic syndrome, pyelonephritis etc accounting for 29.5%. Others were diabetes and hypertension accounting for 24.8% and 22.9% respectively. Diabetes and hypertension were more common cause of chronic than acute renal failure. Others include heart failure, nonsteroidal anti-inflammatory drugs, malignancy, obstructive uropathy and calculi etc.

Table 1: Renal function of CRF patients at the time of presentation.

S.N.	GFR	Renal Function	Frequency	%
1	>90 ml/min	Normal GFR	0	0
2	60-89 ml/min	Mild impairment	1	1.3
3	30-59 ml/min	Moderate impairment	15	19.7
4	15-29 ml/min	Severe impairment	30	39.5
5	<15 ml/min	ESRD	30	39.5

Chronic kidney failure can affect almost every part of the body and result complications. There are many complications associated with renal failure, especially over the long-term. Some complications are more common while others are less. Study showed anemia as most common complication followed by dyselectrolytemia. Others complications include cardiovascular, skeletal, abnormal hemostasis, and neuromuscular abnormalities (Fig. 3).

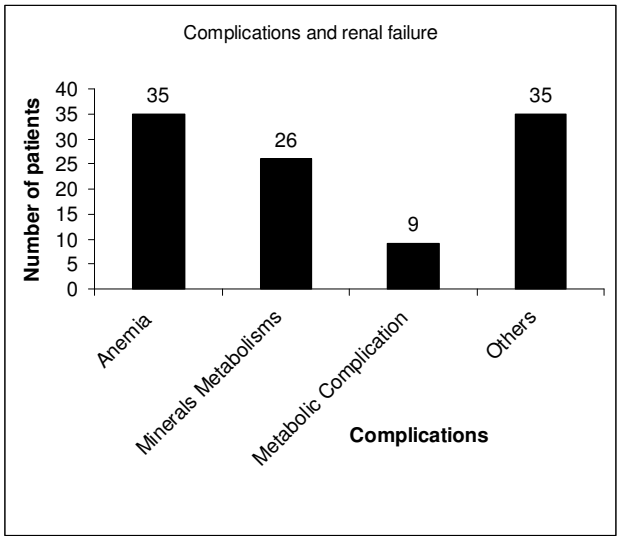


Fig. 3: Complications and renal failure

Duration of hospital stay ranged from minimum 2 days to maximum of 23 days(Table 2).

Table 2: Duration of Stay

S.N.	Diagnosis	Frequency	Mean Duration	Std. Deviation
1.	Acute	29 (27.6 %)	8.31	4.986
2.	Chronic	76 (72.4 %)	9.24	4.360
3.	Total	105 (100 %)		

Among the total studied patients, 53.3 % patients improved with medication, 27.6 % patients required dialysis, 3.8% patients required kidney transplanted and finally 15.3% patient died (Table 3).

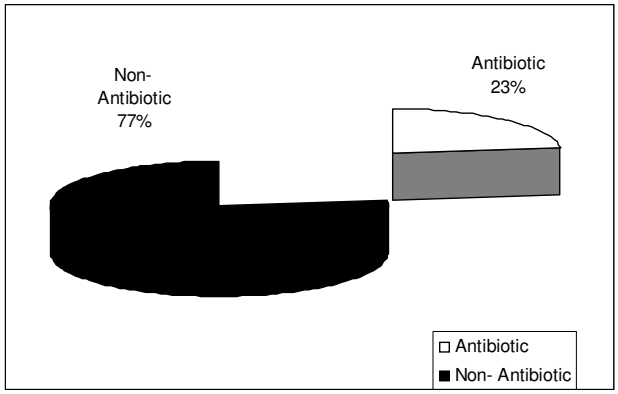
Table 3: Outcome and Renal failure.

S.N.	Outcome	Total
1.	Improvement	56 (53.3%)
2.	Dialysis	29 (27.6%)
3.	Transplantation	4 (3.8%)
4.	Died	16 (15.3%)
5.	Total	105 (100%)

Various medicines were prescribed for the patients with renal failure to control complication, to treat the cause, comorbidity and other infectious and non infectious diseases associated with renal failure. The most commonly prescribed medicines includes hypotensive agents, loop diuretic, proton pump inhibitor and in antibiotic cephalosporin. The total no of medicines per patient were either 5 or 6.

The study showed that most of the drugs prescribed were not antibiotic. 77% of the total prescribed drugs were not antibiotic and remaining were antibiotics (Fig. 4).

Fig. 4: Antibiotic and Non-antibiotic category



Renal insufficiency can markedly alter one or more of the pharmacokinetic parameters of a drug including oral bioavailability, volume of distribution, drug binding to plasma proteins, and most importantly the rates of metabolism and excretion, i.e., drug clearance. To minimize drug toxicity and maximize therapeutic benefits, it is often necessary to adjust drug dosage in proportion to the degree of renal insufficiency (Table 4).

Table 4: Drug therapy and dose adjustment

S.N.	Adjustment	Antibiotic		
Non-Antibiotic		**Total**		
1.	Required and done	36(27.3%)	101 (22.9%)	137 (23.9%)
2.	Not required	44(33.3%)	278 (62.9 %)	322 (56.1%)
3.	Required and not done	50(37.9%)	58 (13.1%)	108 (18.8%)
4.	To be avoided	2(1.5%)	5 (1.1%)	7 (1.2%)
5.	Total	132(100%)	442 (100%)	574 (100%)

Discussions

Renal failure is strongly associated with older age because the renal function decreases with the ages.[4] Another study conducted at NMC teaching hospital has also reported similar result. Of the total patients studied, 57% were male and 43% were female and average age was 46.9±17.9 years. In the same study, 80% of patients were between the ages of 20-60 years.[5] Other studies also have similar results, the study conducted in the Nephrology Department at the Mostafa Khomeini Hospital in Tehran, Iran from March 2001 to March 2005, showed that of the 1200 patients, 61% were males and 39% females. The most frequent age group was 61-75 years (38.3%) and the mean age of the study patients was 51.6 ± 17 years.[6] The present studies showed that majority of patients with renal failure were not smokers and consume alcohol more. Out of total 105 patients taken 47(44.76%) were smoker, 58(55.24%) were non-smoker. 50(47.6%) patients were alcohol.

The high level of blood urea affects the kidney. If the uric acid content becomes high it can cause pains in your joints. More raised level of uric acid in the body leads to the formation of kidney stone and finally deteriorate kidney function. Higher level of the blood urea gets converted to uric acid. When excess of urea and uric acid deposited in the body, indicates the failure or less functioning of the kidneys.

Renal parenchymal diseases (glomerulonephritis, nephrotic syndrome and pyelonephritis), diabetes, hypertension have long been known to be linked with an increased risk of renal failure. Present studies showed that kidney disease was the most common causes of renal failure followed by hypertension and diabetes. Study at USA reported that, diabetes mellitus was the major cause of renal failure accounting for 44.4% of the cases while hypertension was the cause in 26.6%, kidney diseases cause renal failure in 21.4% and miscellaneous causes in 9% of the patients.[7] Similarly, a study in Nepal showed that chronic glomerular disease was most common cause of chronic renal failure accounting for 36.0% of cases while HTN caused CRF in 29.0%, diabetes mellitus in 9.0%, obstructive uropathy in 11.0% and others 2.0%.[8] Similar result was obtained in another study**.** The various causes of renal failure in study patients included: diabetes mellitus in 26.8%, hypertension in 13.5%, kidney diseases 32.8% and unknown causes in 29.5% of the patients.[6] Observational studies involving in patients with established renal insufficiency have also demonstrated that lowering blood pressure preserves renal function.[9]

Decreased kidney function is associated with many complications, such as anemia, malnutrition, bone disease, and a decreased quality of life. These complications can be treated effectively. Complications related to chronic kidney disease and the risk of severe kidney failure is highest among patients with stage 4 or 5 of the disease. Late diagnosis is associated with increased rates of morbidity and mortality.[10]

Anemia was found the most common complication in renal

failure because of insufficiency in production of erythropoietin (EPO) by the diseased kidneys and additional factors include iron deficiency, acute and chronic inflammation with impaired iron utilization and severe hyperparathyroidism. It occurred in 35 patients, accounting for 33.3% of the total population studied. The second common complication was minerals metabolisms and was found in 24.8% of the total study population. The third was metabolic complications and was found in 8.6% of the total population studied. Others complications was found in remaining patients.

Besides anemia, in renal failure bones do not get enough calcium to grow. One reason is that the production of the vitamin D hormone may be deficient. Impaired kidneys may cause high level of phosphorus in the blood and consequently, phosphorus keeps calcium from getting to the bones.

The studies showed that hospital stays range from minimum of 2 days to maximum of 23 days. The mean duration of stay at hospital was 8.92 ±4.536 days. Various studies had mentioned different duration of hospital stay for renal failure patients. Difference in duration of the stay differs mainly due to comorbid conditions associated and the stages of the diseases. The result obtained in study conducted by Shigehiko Uchino and his team was higher than our present study because it included ICU patients in the study. In the study the median length of ICU stay was 10 days and the median length of hospital stay was 22 days.[11]

Among the total studied patients, 15.3% patient died and the mortality rate of the renal failure was found to be 15.2%. Similar study at NMC showed, 20% of patients underwent kidney transplantation and 15% patients' died.[5] In study conducted by Shigehiko Uchino overall hospital mortality was 60.3%, which was very much higher than present study conducted at TUTH.[11] Study conducted by Cameron showed that mortality rates in acute renal failure range from approximately 7% among patients admitted to a hospital with prerenal azotemia to more than 80 % among patients with postoperative acute renal failure. When acute renal failure occurs in the setting of multiorgan failure, especially in patients with severe hypotension or the acute respiratory distress syndrome, the mortality rate ranges from 50 to 80 %. [12]

The dosage of many drugs must be adjusted in patients with renal impairment to avoid adverse reactions and to ensure efficacy. The level of renal function according to which the dose of a drug must be reduced depends on toxicities of the drug and whether it is eliminated entirely by renal excretion or is partly metabolized to inactive metabolites. Retention of these drugs and metabolites are problematic because are accumulated and prolong the action of the drug.

In present study, of the total antibiotic prescribed, dose adjustment was done for 27.3%, 33.3% don't required dose adjustment (safer in renal failure). Dose adjustment was required but not done in 37.9% cases and 1.5% drugs were prescribed which are to be avoided in renal failure patients. Similarly in non-antibiotic therapy, 62.9% drug didnot require dose adjustment (they are safer to renal failure), dose adjustment was done in 22.9 %. Dose adjustment was required but not done 13.1% and 1.1 % drug used are contraindicated in renal failure patients.

Similar study from Thailand by Ayuthya SK et. al. to evaluate the use to antimicrobials showed that 39 prescription out of 111 didnot have dosage adjustment in patients with renal impairment.[13] Another study showed that dosage adjustment based on renal function was necessary in 23.9% of the total prescriptions. The adjustments were performed in only 58.9% prescriptions required dose adjustment.[14] various studies have also shown inappropriate dosing with respect to renal function. A study done by Chertow et al. identified 60.3% prescriptions that needed dosage adjustment according to guidelines. Of these, 66.0% complied with guidelines; whereas 34.0% did not and in this case 14.0% contraindicated medications were found to be prescribed.[15]

Conclusion

Renal failure is a disease seen more commonly in elderly, and is associated commonly with renal parenchymal diseases, hypertension and diabetes. Anemia is the most common complications of chronic renal failure. Most of the patients with renal failure had end stage renal disease at presentation. Though they were prescribed multiple drugs, only few had dose adjustment done and some were even prescribed nephrotoxic drugs.

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