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A Study on Clinical Assessment of Antibiotic Used in Chronic Kidney Disease Patients

(Studi Penilaian Klinis Penggunaan Antibiotik pada Pasien Penyakit Ginjal Kronis)

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Abstract: A 6-week longitudinal prospective study was conducted to assess the effectiveness and the safety antibiotic used in chronic kidney disease (CKD) patients in internal medicine ward. We compared white blood count and glomerular filtration rate before and after antibiotic used. The CKD patients who admitted in the internal medicine ward and age ≥18 years old were included this study. Patients with incomplete laboratory data and renal replacement therapy were excluded in this study. The 25 patients who enrolled in this study were recruited. The majority gender of CKD was male (64%), the mean of age was 61.52±14.17 years old with length of stay (LOS) was 6.92±4.05 days. The highest number of patients was in CKD stage 3 (n=10, 40%) and was followed by CKD stage 2 (n=6, 24%). Most of them were diagnosed community acquired pneumonia. Tablet azithromycin (n=16, 64%) then Cefotaxime intra venous injection (IV) (n= 6, 24%), and Ceftazidime IV (n=5, 20%), Cloxacillin IV (n=4, 16%) were the most antibiotics prescribed. Generally patients had been prescribed appropriate dose of antibiotic and 88% of them showed improved white blood count. In contrast, the glomerular filtration rate of 44% CKD patients was getting worse. In conclusion, this study clearly indicate the CKD patients require close monitoring to maintenance of renal function even the antibiotic had been prescribed appropriately.

Keywords: chronic kidney disease, antibiotic, clinical assessment.

Abstrak: Sebuah studi prospektif longitudinal 6 minggu dilakukan untuk menilai efektivitas dan antibiotik keamanan yang digunakan pada pasien penyakit ginjal kronis (CKD) di bangsal pengobatan internal. Kami membandingkan jumlah darah putih dan tingkat filtrasi glomerulus sebelum dan sesudah antibiotik digunakan. Pasien CKD yang dirawat di bangsal penyakit dalam dan usia ≥18 tahun dimasukkan dalam penelitian ini. Pasien dengan data laboratorium yang tidak lengkap dan terapi penggantian ginjal dikeluarkan dalam penelitian ini. 25 pasien yang terdaftar dalam penelitian ini direkrut. Jenis kelamin mayoritas CKD adalah laki-laki (64%), rata-rata usia adalah 61,52 ± 14,17 tahun dengan lamanya tinggal (LOS) adalah 6,92 ± 4,05 hari. Jumlah pasien terbanyak adalah pada CKD stadium 3 (n = 10, 40%) dan diikuti oleh CKD tahap 2 (n = 6, 24%). Sebagian besar dari mereka didiagnosis menderita radang paru-paru. Tablet azitromisin (n = 16, 64%) kemudian Cefotaxime injeksi intra vena (IV) (n = 6, 24%), dan Ceftazidime IV (n = 5, 20%), Cloxacillin IV (n = 4, 16%) adalah antibiotik yang paling diresepkan. Umumnya pasien telah diberi dosis antibiotik yang tepat dan 88% dari mereka menunjukkan peningkatan jumlah darah putih. Sebaliknya, tingkat filtrasi glomerulus dari 44% pasien CKD semakin buruk. Kesimpulannya, penelitian ini jelas menunjukkan pasien CKD memerlukan pemantauan ketat terhadap pemeliharaan fungsi ginjal bahkan antibiotik telah diresepkan dengan tepat.

Kata kunci: penyakit ginjal kronis, antibiotik, penilaian klinis.

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INTRODUCTION

CHRONIC kidney disease (CKD) is defined as the presence of abnormalities of kidney structure or function or a reduction in glomerular filtration rate (GFR) for period of three months or longer[1]. Hwang *et.al* reported that the prevalence of CKD has increased in many countries, mainly in the US (13.1%), Japan (12.9-15.1%), Australia (11.2%), Norway (10%), Taiwan (9.8-11.9%), China 3.2-11.3%), Korea (7.2-13.7%), Thailand (8.45-16.3%)[2]. In West Malaysia, the prevalence of CKD was 9.07%[3].

The presence of CKD and its complication during therapy remain as unresolved problem. The CKD patients generally have co-morbidity that contributed to a decline in the renal function, such as infectious disease. Pneumonia and sepsis were found in higher rate in hospitalized CKD patients compared with non CKD patients[4]. CKD patients have major infectious complication 3 to 4 times the general population[5]. McDonald *et.al* (2014) had reviewed the various references and they found pre-dialysis kidney patients have more risk to get infection[6].

Antibiotic is one of medicine associate with infection. The majority of antibiotics are eliminated by kidney. Some of them are contraindicated with CKD's patients and need dose adjustment. Alahdal & Elberry (2011) reported that most of drug need dose adjustment was antibiotic and rarely adjust by physician[7]. Inappropriate dose are common in patients with renal problem which can cause adverse drug reaction and poor clinical improvement[8,9]. About 20.91% in CKD patients had been prescribed inappropriate dose in a Chinese tertiary teaching hospital[10]. Farag *et.al* (2014) reported that dossing error in prescribed antibiotic was found in CKD patients[11]. As reported in China, dosage errors for antibiotics prescribed for CKD patients were in the range of 38.85%-60.3%[12].

The dose adjustment in CKD patients is done based on patient's creatinine clearance and GFR[1]. The GFR also have correlation with renal function and able to determine the safety of drug utilization. There are many kinds of equation to calculate the GFR, such as CKD-EPI equation. The WBC of patients is an essential parameter in order to optimize the effectiveness of antibiotic used in CKD patients. Nowadays, there were many publications associated with drug prescribed in CKD patients. However, the research related to assess antibiotic used clinically and correlation with renal function is still limited. Therefore, the current study was carried out to clinical assessment the effectiveness and the safety the drug utilization of antibiotic according to laboratory data GFR and WBC before and after using antibiotic in CKD patients.

MATERIALS AND METHODS

MATERIALS. Subject in this study was patients with CKD who hospitalized in internal medicine ward at teaching hospital in Kelantan-Malaysia. The data was recorded by patient's medical record and nurse record. We used Pharmacist Workup of drug therapy pharmacy clinical clerkship to daily follow up the patients daily.

METHODS. Study Design and Patient Selection. A 6-week longitudinal prospective study was conducted to assess clinically drug utilization of antibiotic in CKD patients at teaching hospital. The evaluation was carried out by comparing GFR before and after using antibiotic to assess the safety of antibiotic used to renal function. Comparing WBC before and after using antibiotic to determine the correct treatment associate with infection also performed.

During the period of study, CKD patients who admitted in internal medicine ward and age ≥18 y.o were included this study. The incomplete laboratory data (GFR, WBC) before and after using antibiotic, renal replacement therapy were excluded in this study. The data collection and comparing GFR, WBC between before and after antibiotic used.

The demographic data of patients (gender, age, and length of stay), antibiotic utilization and laboratory data (serum creatinine, WBC before and after antibiotic used) were extracted from patient's medical record, nurse record, and interview directly patients. GFR was calculated by using CKD-EPI equation (2002) by National Kidney Foundation method according to Kidney Disease Outcomes Quality Initiative Guideline:

eGFR = 141* min(standardized Scr/k,1)α * max(standardized Scr/k,1)-1.209*0.993Age * 1.018 [if female] * 1.159 [if black]

Abbreviation and Units

eGFR = estimated glomerular filtration rate (mL/min/1.73m²)
Scr : serum creatinine (mg/dL)
K : 0.7 (females) or 0.9 (males)
α : -0.329 (females) or -0.411 (males)
min : indicates the minimum of Scr/k or 1
max : indicates the minimum of Scr/k or 1
Age in years

The stage of CKD were classified by GFR that refer to the National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI) (2002[1] as presented in Table 1.

Clinical Assessment. Clinical assessment was conducted by GFR and WBC. These parameters

Table 1. The Stage of CKD according to K/DOQI[1]

Stage	Description	GFR (mL/min/1.73m^2)
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with a mild decrease in GFR	60 to 89
3	Moderate decrease GFR	30 to 59
4	Severe decrease in GFR	15 to 29
5	Kidney failure	< 15 (or dialysis)

was divided into three categories improved, worse, and similar. The term of improved defined as GFR increased after using antibiotic and WBC in normal value and or decreased. The term of worsen means GFR decreased after using antibiotic and WBC became higher than before using antibiotic. Similar means GFR value similar between before and after using antibiotic.

Analysis of Data. The descriptive analysis was conducted to analyze characteristic patients associate with CKD and correlate the laboratory data (GFR and WBC) to assess the effectiveness and the safety of clinically the antibiotics used in CKD patients.

RESULTS AND DISCUSSION

Patient Characteristic. In all, during the study period, the 30 CKD patients were enrolled in this study by primary screening. Then, only 25 patients were fulfilled the inclusion and exclusion criteria. Patients were coded from P1 to P25. The majority gender of hospitalized CKD patients in internal medicine was male (64%), the mean of age was 61.52±14.17 y.o, with rank 38-85 y.o. The mean of length of stay (LOS) was 6.92±4.05 days with range (3-22 days). The highest number of patients was in CKD stage 3 (n=10, 40%) and was followed by CKD stage 2 (n=6, 24%). Patient characteristic in this study was presented in Table 2.

According to Table 2, CKD patients who get infection hospitalized 6 to 7 days generally. Patients with CKD stage 5 or end stage renal failure showed higher LOS in internal medicine ward. A possible explanation for this could be patients with the worsened renal function required more treatment and these patients were geriatric who had age more than 60 y.o. Therapy of geriatric patients was more complicated than adults due to comorbidities which need longer LOS. The incidences CKD was increased dramatically with age and linear with the stage

Table 2: Characteristics of enrolled CKD patients in internal medicine ward.

Stage of CKD (n, %)		Gender, n(%)		Age, Mean ± SD (y.o)	LOS, Mean ± SD (day)
		Male	Female		
CKD stage 1	(4, 16%)	4 (16%)	-	55.25±13.89	6.50±2.52
CKD stage 2	(6, 24%)	5 (20%)	1 (4%)	51.17±12.47	7.33±2.25
CKD stage 3	(10, 40%)	6 (24%)	4 (16%)	65.90±14.39	6.00±3.30
CKD stage 4	(1, 4 %)	-	1 (4%)	74.00±0.00	6.00±0.00
CKD stage 5	(4, 16%)	1 (4%)	3 (12%)	69.25±8.38	9.25±8.54
Total	(25, 100%)	16 (64%)	9 (36%)	61.52±14.17	6.92±4.05

Abbreviation: LOS, length of stay

of CKD. In the US, NHANES also reported that individual aged 60 and older was more prevalent to get CKD[13]. The increasing age is contributed to risk of progress CKD[14].

The Distribution of Chief Diagnose. In this study, we found eight kinds of the chief diagnose in CKD patient who admitted to hospital. The most of diagnose patients among CKD patients associated with infection was CAP (n=16, 64%) then was followed by urosepsis (n=2, 8%) and CCF (n=2, 8%) as well as, presented in Figure 1.

The CAP is one of common infectious disease that infected lower respiratory tract by *Streptococcus pneumonia*, *Haemophilus influenza*, *Moraxella catarrhalis*. CAP is pneumonia not acquired in hospital or a long-term care facility[15]. Other study that linier with this research was Santra *et.al* (2015) who found that respiratory tract infection was the most infection in CKD patients[16]. The incidence density rate of pneumonia was 65.6 per 1000 person per year in CKD patients and 28.4 per 1000 person per year in person without CKD[17]. The serious complication in CKD patients was pneumonia also was reported by Viasus *et.al* (2011)[18].

The Distribution of Co-Morbidity of Enrolled CKD Patients. Co-morbidity is the presence of one or more additional diseases co-occurring with a primary disease. Majority CKD patients had co-morbidity. 10 co-morbidities were recorded in this study. The most co-morbidity among CKD patients in was diabetes mellitus (n=10, 35%) and then followed by hypertension (n=8, 28%) and anemia (n-5, 20%). Santra *et.al* also found the similar result[16]. In addition, 68% CKD patients had one co-morbidity and 20% patients were with 2 co-morbidities, 4%

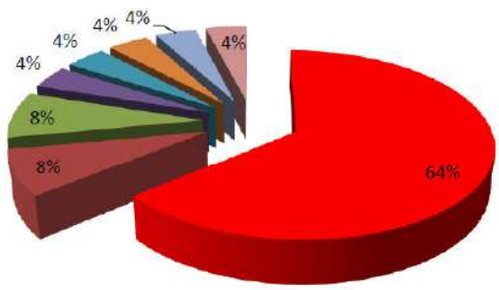


Figure 1.The distribution of Chief Diagnose in CKD patients. Abbreviation: CAP, community acquired pneumonia; CCF, congestive cardiac failure

had 3 co-morbidities and 8% of them had none co-morbidity (Figure 2). The presences of co-morbidity influenced the clinical outcome patients. Patients with the more co-morbidity had longer LOS. Other study was recorded that 23% of CKD patients suffered from diabetes[19]. More than 805 of CKD patients and diabetes have hypertension[20].

Furthermore, The 20% of CKD patients showed anemia. Most of them were patients with CKD stage 5. It was related with a decrease in renal function to product erythropoietin. Anemia in CKD reduce the quality of life, increase the risk of cardiovascular disease, hospitalization, cognitive impairment, and mortality[21,22].

The Pattern of Antibiotic Used. The prevalence infection in CKD patients is very common. Therefore most antibiotic have been prescribed among CKD patients. Figure 3 presented the utilization pattern of antimicrobials of enrolled patients with CKD. Fifteen kinds of antibiotics were recorded. The most antibiotic prescribed of enrolled CKD patients was Tab. Azithromycin (n=16, 64%) then IV. Cefotaxime (n= 6, 24%), and IV. Ceftazidime (n=5, 20%), IV. Cloxacillin (n=4, 16%), and Tablet Amoxicillin+clavulanic acid (n= 3, 12%). 53.3% antibiotic was administered by intravenous and other antibiotics were administered by orally in tablet dosage form. The use of combination of azithromycin and 3rd generation cephalosporin was predominant which comply with the National

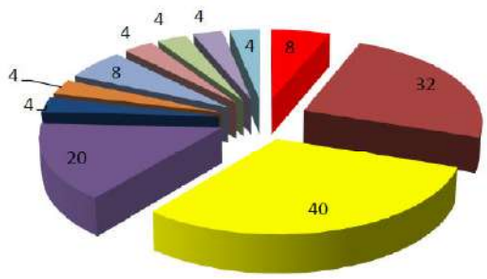
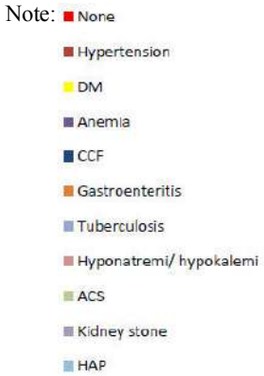


Figure 2 The Co-morbidity of Included CKD patients.
Abbreviation: DM, diabetes mellitus; CCF, congestive cardiac failure; HAP, hospital-acquired pneumonia.



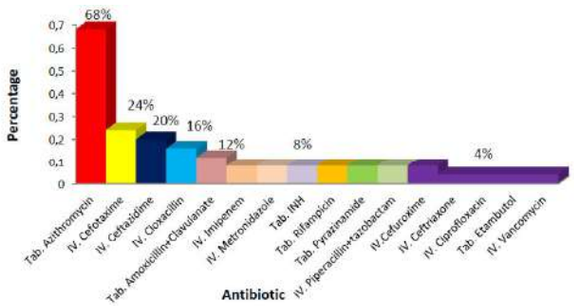


Figure 3: The utilization pattern of antimicrobials in CKD patients.

antibiotic guideline in Malaysia (2008) as the first line therapy for CAP[23].

There were two approaches in prescribing antibiotic. The first approach is an empirical antibiotic and then definitive antibiotic. An antibiotic is selected without confirmed the culture and sensitivity test of microbial in the approach of empirical therapy. On the other hand, antibiotic was selected by confirmed culture and sensitivity test of microbial in definitive therapy. In this study, 84% enrolled CKD patients prescribed antibiotic by empirical and 18% of patients prescribed with definitive therapy. Bacteria Gram (+) cocci dan Gram (-) bacil, and Methicillin-resistant *Staphylococcus aureus* (MRSA) were recorded in culture and sensitivity test. The prescription antibiotic with definitive therapy is rare and limited. Thawani *et.al* (2006) reported the selection of antibiotics in the United States based on culture and sensitivity test results, only ranges between 20-25% while in Italy about 2% and in India only 1%.

Patients who were MRSA infected in this study were hospitalized in the specific area in order to prevent nosocomial infection. Patient was given mark

Table 3: The adjusted doses utilization of antimicrobial in CKD patients.

Antimicrobial prescribed	Route of administration	Usual dosage	Dose in renal impairment (percentage of usual dosage) based on GFR (mL/min/1.73 m^2)[16,39]			Note
			>50	10 to 50	<10	
Azithromycin	Oral	500 mg q 24 h	-	-	-	No adjustment needed
Cefotaxime	IV	1 to 2 g q 6 to 12 h	q 6 h	q 6 to 12 h	q 24 h (50%)	Adjustment needed
Ceftazidime	IV	1 to 2 g q 8 h	q 8 to 12 h	q 12 to 24 h	q 24 to 48 h	Adjustment needed
Cloxacillin	IV	250-500 mg q 6 h	-	-	-	No adjustment needed
Amoxicillin+Clavulanic acid	Oral	250 to 500 mg q 8 h	q 8 h	q 8 to 12 h	q 24 h	Adjustment needed
Imipenem	IV	0.25 to 1 g q 6 h	q 6 h	q 12 h	q 24 h	Adjustment needed
Metronidazole	IV	400 mg q 6-8 h	q 6-8 h	q 6-8 h	q 12 h	Adjustment needed
INH	Oral	300 mg q 24 h	-	-	-	No adjustment needed
Rifampicin	Oral	600 mg q 24 h	-	-	-	No adjustment needed
Pyrazinamide	Oral	750 mg q 24h	-	-	-	No adjustment needed
Cefuroxime	IV	0.75 to 1.5 g q 8 h	q 8 h	q 8 to 12 h	q 12 h	Adjustment needed
Ceftriaxone	IV	1-2 g q24 h	-	-	-	No adjustment needed
Ciprofloxacin	IV	400 mg IV or 500 to 750 mg orally q12 h	q 12 h	50-75%	50%	Adjustment needed
Ethambutol	Oral	800 mg q24 h				No recomendation
Piperacillin+Tazobactam	IV	3.375 to 4.5 g q 6 to 8 h	100%	2.25 g q 6 h; q 8 h (GFR<20)	2.25 g every 8 h	Adjustment needed
Vancomycin	IV	1 g q 12 h			1 g every 12 h	Adjustment needed

Table 4: Clinical assessment of antibiotic used among stage of CKD.

Stage of CKD	Antibiotic used N(%)		Appropriate dose N(%)		GFRpre (mL/min/1.73m²)	GFRPost (mL/min/1.73m²)	WBCpre 10^3/µL	WBC post 10^3/µL	Outcome (WBC)		Outcome (GFR)		
	Empiric	Definitive	yes	no					I	W	I	W	S
CKD stage 1	4 (16%)	-	4 (16%)	-	103.00±8.98	95±7.57	8.60±1.63	7.26 ±2.01	4	-	1	3	-
CKD stage 2	5 (20%)	1 (4%)	6 (24%)	-	70.50±14.48	76.67±14.51	9.67±4.81	12.15±358	3	3	5	1	-
CKD stage 3	8 (32%)	2 (8%)	9 (36%)	1 (4%)	44.20±8.60	48.50±11.81	9.90±3.66	8.05±1.90	10	-	5	4	1
CKD stage 4	1 (4%)	-	1 (4%)	-	24.00±0.00	23±0.00	8.40±0.00	6.70±0.00	1	-	-	1	-
CKD stage 5	3 (12%)	1 (4%)	3 (12%)	1 (4%)	11.50±2.89	11.50±1.29	14.67±5.85	10.60±2.53	4	-	1	2	1
Total	21 (84%)	4 (16%0	23 (92%)	2 (8%)	53.88±30.48	55.76±29.37	10.3416±4.29	9.2584±3.04	22	3	12	11	2

I: improved; W: worse S: similar

MRSA isolated. For this patient, medical and feeding equipment were separated with other patients in the ward.

The Renal Adjusted Doses of Antimicrobial. In this study, an Antibiotic Guideline Malaysia was used to assess the appropriate antibiotic associate with diagnose. The dose in renal impairment was refer to "Use of antibacterial agents in renal failure" Livornes *et.al* (2004) and Santra *et.al* (2015)[16,25]. The dose adjustment was calculated by GFR using CKD-EPI equation. It was divided into three categories of GFR, such as, GFR>50 mL/min/1.73m²; GFR=10-50 mL/min/1.73m²; GFR<10 mL/min/1.73m².

There are antibiotic that do not need adjustment dose in CKD patients, for example, ceftriaxone, azithromycin, INH, rifampicin, Pyrazinamide and Cloxacillin. In addition, there were antibiotic that no adjustment needed in case GFR more than 50 mL/min/1.73m², such as Amoxicillin, imipenem, cefuroxime, Ciprofloxacin, piperacillin as presented in Table 3.

In this study, 17.68% of CKD patients need adjustment dose of antibiotics and remain did not adjusted (n=8.32%). Patients with GFR more than 50 mL/min/1.73m² did not need dose. Antibiotic was used in usual doses generally in patients who had GFR more than 50 mL/min/1.73m². Based on dose, the 92% CKD patients were given the appropriate dose based on their renal function. However 8% patients were prescribed inappropriate dose of antibiotic.

Tablet Azithromycin did not require dose adjustment in CKD patients because this drug is eliminated generally non renal and only 6% is excreted by renal[26]. Furthermore cefotaxime is 46% renal excreted. Hence, the prescription of this drug does not require dose adjustment in patients with mild and moderate renal impairment. In severe renal disease the doses need to decrease 50% from usual dose[25].

Clinical Assessment Antibiotic Used in CKD Patients. Clinical assessment antibiotic used was performed by analysis of GFR and WBC before and after using antibiotic. It was conducted to find out the effectiveness of antibiotic used in infection treatment and the safety of these antibiotic associate with renal function. The result of clinical assessment antibiotic used was presented in Table 4.

Serum creatinine has good correlation with renal function. An increase in serum creatinine correlate with a decrease in renal function. In this study, n=12.48% patients performed improved GFR after using antibiotic. However n=11.44% CKD patients demonstrated worse renal function after using antibiotic and n=1.4% patients had similar GFR. The 81.82% patients who had worse renal function were prescribed an appropriate dose of antibiotic used. So, even antibiotic was prescribed correctly, CKD patients require close monitoring to maintenance of renal function.

A decrease in GFR presented in patients with CKD stage 1 and stage 4. Most of them had co-morbidity more than one. An increase number of co-morbidity correlate with an increase number of drug prescribed to achieve the goal of treatment. Furthermore, an increase number of drug prescribed contributed to decline renal function.

Based on WBC, there were (n=22.88%) patients showed improvement. It defined as the antibiotic was effective to treat the infection. However as (n=3.12%) CKD patients who was found in CKD stage 2 performed increased WBC and the improvement of patient's condition did not appear. In this group, patient did not showed the decline of renal function generally.

CONCLUSION

The current study showed that predominantly CKD patients was prescribed an appropriate antibiotic used and effective to decrease WBC. Some of them showed the decline renal function. In conclusion, this study clearly indicate the CKD patients require close monitoring to maintenance of renal function even the antibiotic was prescribed appropriately.

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