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Research Article

EVALUATION OF ANTIBIOTICS UTILIZATION AND DOSING FOR MANAGEMENT OF PATIENTS WITH CHRONIC KIDNEY DISEASE IN AN INDONESIAN HOSPITAL

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ABSTRACT

Objective: Provision of antibiotics to patients with chronic kidney disease (CKD) without dosage adjustment could result in complicated problems, including progression of kidney damage. This study analyzed utilization and dose rationality of antibiotics administered to Stage 4 and 5 CKD patients in Haji Adam Malik (HAM) Hospital, Indonesia.

Methods: This retrospective cohort study was conducted on 6-month JAMKESMAS database (n=80). Inclusion criteria were in-patients received antibiotics and glomerular filtration rate of ≤30 ml/minutes/1.73 m^2. Exclusion criteria were patients with cancer and human immunodeficiency virus and below 18 years old. Characteristics of the study population were descriptively analyzed. Antibiotics utilization was determined by assessing unit numbers of the provided antibiotics. Dose rationality of the antibiotics was analyzed by referring to the dose recommended in literatures based on the patients' creatinine clearance. Proportion of the patients received irrational doses were analyzed applying frequency analysis. All statistical analyses were performed using SPSS program version 19.

Results: Mean age of the CKD patients was 47.08 (standard deviation=13.80) years. There were more male patients (66%) compared with female, p=0.003. There were more patients with CKD Stage 5 (83%) compared with CKD Stage 4, p≤0.001. 11 classes of antibiotics were provided to CKD patients of which nine had irrational doses received by 34% of the patients. Ceftriaxone, ciprofloxacin, ceftazidime, cefadroxyl, and amoxicillin had the highest irrational dose incidence.

Conclusion: Incidence of irrational antibiotics dosage provided to the CKD patients was still high.

Keywords: Chronic kidney disease, Infection, Antibiotics dosing.

INTRODUCTION

Incidence of infection among patients with chronic kidney disease (CKD) remains high in developing countries such as Indonesia as a consequence of the high incidence of glomerulonephritis and interstitial nephritis [1,2]. It is also a common complication and the second leading cause of death of patients with CKD, especially those in Stage 4 and 5 [3]. Few studies proved that CKD patients always experienced neutrophil dysfunction as a result of many complicated problems which placed the patients to high risk for infection. Epidemiological studies showed that patients with end-state renal disease are likely to experience infectious complications mainly urinary tract infection, pneumonia, and sepsis [4]. Furthermore, a study reported that mortality rate of hemodialysis patients was about 100-300 fold compared with that of patients without hemodialysis [5]. Previous study also confirmed that infection is a common event in patients with regular hemodialysis and associated with cardiovascular disease, morbidity, and mortality. Thus, to avoid from further negative clinical outcomes, approaches to anticipate and resolve these complications must always be sought including administration of antibiotics [6].

However, provision of antibiotics to treat infection in patients with CKD without proper dose adjustment could result in accumulation of the parent compounds and their metabolites in the body and toxic effects on organs, including kidneys. Furthermore, progression of kidney damage could also be induced by the nephrotoxicity of few antibiotics. The ultimate negative outcome is death. Therefore, appropriate dosing of antibiotics therapy for patients with CKD is crucial to avoid adverse drug reaction, to prevent additional renal injury, and to optimize clinical outcomes [7-9]. Hence, medication reviews in the management of CKD is the key point that should always be performed by clinical pharmacists through a structured examination of patients' medications including evaluation and analysis of antibiotic dosing to avoid adverse drug reaction, to prevent additional renal injury, to improve CKD management and to achieve optimal outcomes [10].

In response to these facts, the objective of this study was to analyze the utilization and dose rationality of systemic antibiotics for management of infection in patients with CKD Stage 4 and 5 in Haji Adam Malik (HAM) Hospital, Indonesia.

METHODS

Study design

This retrospective cohort study was conducted on 80 patients with CKD based on 6-month JAMKESMAS database (middle of September 2009 through middle of March 2010) in HAM hospital, Indonesia. HAM hospital is a teaching and the only class A hospital in the Northern part of Sumatera Island (a Class A hospital means it has broad facilities and capability of specialist and subspecialist healthcares) and included into the pilot project for the case mix system by Indonesian Drug Related Group. JAMKESMAS is an Indonesian government social insurance covering 76.4 million people (~one-third of the Indonesian population). The insurance aims to protect the poor and near poor population from the catastrophic payment due to sickness [11]. All patients received antibiotics and glomerular filtration rate of ≤30 ml/minutes/1.73 m^2 (0.5 ml/seconds/1.73 m^2) were included into this study. Patients below 18 years old due to immaturity of their organs, patients with cancer, and patient with human immunodeficiency virus were excluded from the study [12,13].

Data collection

Permission to collect data from the patients' medical record was provided by the Director of HAM hospital. Using a predetermined

data collection form, data recorded were medical record number, date of admission, age, gender, body weight, smoking history, alcohol drink history, stage of the patients, histories of previous diseases and medications, patient condition at the end of treatment, administered antibiotics, and related laboratory tests.

Data analysis

Characteristics of the study population were grouped and analyzed according to gender, age, and stage of the disease. Grouping of the patients on the basis of severity was performed applying the Modified of Diet and Renal Disease study equation before antibiotic therapy [14]. Mean age of the patients was descriptively analyzed and proportions by gender and stage were analyzed applying chi-square analysis at 95% level of confidence ($p<0.05$ is considered as significant) using Statistical Package for the Social Sciences (SPSS version 19, Chicago, IL, USA).

To determine the antibiotics utilized for the management of infection, all of the antibiotics and their number of units administered to the patients with CKD Stage 4 and 5 were recorded, organized, and inputted into Microsoft Excel 2007 (Microsoft Corporation, Redmond, Washington) for further analysis.

Dose rationality analysis of the systemic antibiotics provided to the CKD patients was undertaken based on the recommended dose in literature according to the magnitude of creatinine clearance (Cl_{cr}) of the patient with CKD. The creatinine clearance of each patient was calculated prior to the provision of antibiotics by applying the following formula:

$$Cl_{cr}\ (ml/minutes) = ([140-age]\ body\ weight)/72 \times S_{cr} \times 0.85\ (if\ female)$$

in which: Scr, serum creatinine concentration of the patient with CKD.

In this approach, dose rationality of the antibiotics administered to CKD patients was analyzed by comparing the provided dose to dose recommended in the literature [15,16]. The choice of the approach was limited by lengthy culture and sensitivity test completion (about 1 week) and urgency for immediate antibiotics treatment for the safety of advanced stages of CKD patients as usually executed by physicians. Subsequently, frequency of irrational dose occurrence was analyzed by applying Friedman test and its mean value was statistically analyzed at 95% confidence level by applying t-test in the SPSS program version 19 ($p<0.05$ is considered significant).

RESULTS

The total number of admission of patients with CKD Stage 4 and 5 during the study period was 297 of which 80 patients fulfilled the inclusion criteria and were included into this study. Mean age of the CKD patients was 47.08 (standard deviation [SD]=13.80) years. In this study, it was found that there were more male (66%) compared with female (34%), $p=0.004$. There were more patients' admission on Stage 5 (83%) compared with Stage 4 (17%), $p\leq0.001$.

Overall antibiotics utilized for the 80 patients with CKD Stage 4 and 5 are shown in Fig. 1. This study found that there were 11 classes of antibiotics with different number of units commonly provided to CKD patients obtained from the 6-month database. As also shown in Fig. 1, the six largest utilized antibiotics for the treatment of infection in patients with CKD Stage 4 and 5 in decreasing order were ceftriaxone injection, ciprofloxacin infusion, metronidazole tablet, erythromycin capsule, ceftazidime injection, and ciprofloxacin tablet. While, the least utilized antibiotics were amoxicillin capsule, cefadroxil capsule, clindamycin capsule, cefotaxime injection, metronidazole infusion, and chloramphenicol injection.

Irrational dosages of antibiotics provided to the CKD patients were observed. Mean value of irrational doses was 0.54 (SD=0.75). Listed in Table 1 is the summary of overall irrational dosing of the administered antibiotics. Five of the major occurred irrational doses provided to the CKD patients were ceftriaxone injection, ciprofloxacin tablet, ceftazidime injection, cefadroxil capsule, and amoxicillin capsule. The least frequent occurred irrational doses of the provided antibiotics were cefotaxime injection, metronidazole infuses, ciprofloxacin infuse, and meropenem injection. Based on frequency analysis performed, it was found that 27 (34%) of the patients' population received irrational doses of antibiotics.

In term of the incidence of irrational dose of antibiotics experienced by each of the individual CKD patients varies from 1 to 3 as demonstrated in Fig. 2. Of the 34% of CKD patients whom received irrational dosages, 26.3% received one irrational dose, 6.3% received two irrational doses, and 1.3% received three irrational doses of the antibiotics.

Friedman test indicated that there were statistically significant difference in the true mean of the irrational dose of the nine provided antibiotics, $\chi^2_{(8)} = 26.38 > \chi^2_{(8)\,calc} = 15.51$, $p=0.001$.

DISCUSSIONS

Rational antibiotics provision is important to optimize the treatment outcomes. Assessment of antibiotics provided to CKD patients and analysis of their rationality are the key points that should always be performed by clinical pharmacists to improve the treatment and to achieve optimal outcomes.

This study found that the six most utilized antibiotics for the treatment of CKD patients in decreasing order were ceftriaxone injection, ciprofloxacin infuse, metronidazole tablet, erythromycin capsule, ceftazidime injection, and ciprofloxacin tablet. These differences resulted from many possible reasons including the wide range of complications suffered by the patients, appropriateness of

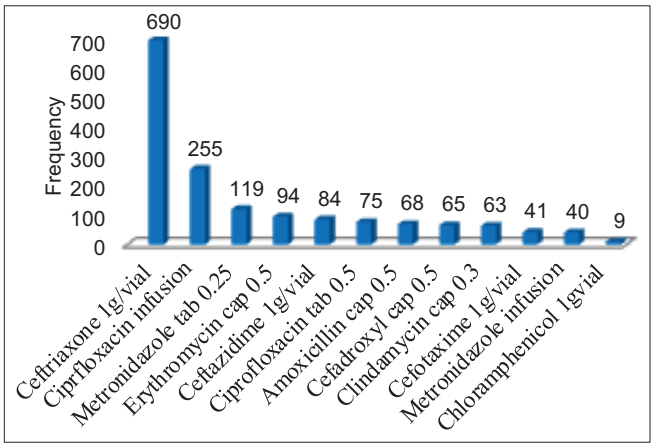

Fig. 1: Overall antibiotics utilization in patients with chronic kidney disease Stage 4 and 5

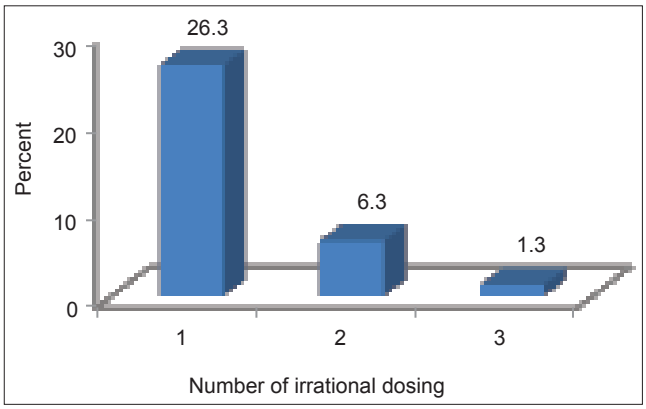

Fig. 2: Proportion of the chronic kidney disease patients received irrational dosing by number

Table 1: Summary of overall irrational dosing of the administered antibiotics

Drug	OID	Dose administered	Cl_{cr} of the patient (ml/min)	Recommended dose
Ceftriaxone inj	11	2 g q 12 hrs	2.6-23.7	Maximum 2 g/day (hepatic disorder)
Ciprofloxacin tab	10	500 mg q 8-12 hrs	4-10	Cl_{cr}<30 ml/minutes: Reduce dose by 50%
Ceftazidime inj	1	2 g q 12 hrs	9.5	Cl_{cr}<15 ml/minutes: 0.5 g q 24-48 hrs
	1	2 g q 12 hrs	13.2	Cl_{cr} 15-30 ml/minutes: Maximum 1 g q 24 hrs
	1	2 g q 8 hrs	10.7	
	1	1 g q 8 hrs	10.1	
	1	1g q 12 hrs	9.5	
	1	1 g q 12 hrs	23.4	
	1	1 g q 8 hrs	23.7	
	1	1 g q 12 hrs	23.5	
Cefadroxyl cap	1	500 mg q 12 hrs	<15	Cl_{cr} 10-25 ml/minutes: 1 g, then 500 mg q 24 hrs
	1	500 mg q 12 hrs	6.9<30	Cl_{cr}<10 ml/minutes: 1 g, then 500 mg q 36 hrs
	1	500 mg q 12 hrs	2	
	1	500 mg q 12 hrs	5.2	
	1	0.5 g q 12 hrs		
Ciprofloxacin inf	1	0.4 g q 12 hrs	9.5	Cl_{cr}<30 ml/minutes: Reduce dose by 50% or double τ;Iv, 0. 2-0.4 g q 18-24 hrs
Amoxicillin cap	3	1 g q 12 hrs	<20	Cl_{cr} 10-20 ml/minutes: 0.25-0.5 bid
	1	500 mg q 8 hrs	6.9	Cl_{cr}, 10 ml/minutes: 250-500 mg q 24 hrs
Cefotaxime inj	1	2 g q 12 hrs	3.7 (GFR)	Cl_{cr}<20 ml/minutes: 50% of usual dosage; maximum
	1	1 g q 6 hrs	7.1	2 g/day
Metronidazole inf	2	500 mg q 8 hrs	5.2	Reduce dose or change interval to once or twice daily
Meropenem inj	1	0.5 q 8 hrs	23.7	Maximum 1 g/day

OID: Occurrence of irrational dose, Tab: Tablet, Inf: Infuse, Cap: Capsule, Inj: Injection, q: quaque (every), τ: Interval, GFR: Glomerular filtration rate, Cl_{cr}: Creatinine clearance

therapy, and difference in severity of infection suffered by the CKD patients [17,18]. Other determinant of the choice of antibiotics was their susceptibility based on assessment of 6-month culture and sensitivity test performed in this hospital.

As identified by this present study, 34% of the study population received irrational antibiotics dosing with ceftriaxone being the highest occurrence. As shown in Table 1, creatinine clearance values vary from one patient to another. These values represent the ability of kidneys to eliminate drugs from the body. Metabolism of many compounds takes place in the liver through different pathways. Most of these metabolites are excreted by the kidneys. These processes are interfered in patients with hepatic and kidney diseases causing accumulation of drugs as well as their metabolites and toxic effects to organs unless dose adjustment is performed [19,20].

There were 11 CKD patients with hepatic disorder (13%) diagnosed based on laboratory tests performed immediately after admission. Each of these patients received ceftriaxone with 4 g daily dose. Without monitoring of serum concentration, the recommended MDD of ceftriaxone for these patients is 2 g [16]. Ceftriaxone is highly bound to plasma protein and not significantly removed by hemodialysis. In addition, hypoalbuminemia always experienced by CKD patients can also result in elevated unbound ceftriaxone concentration in blood, which subsequently could increase toxicity. Thus, to administer ceftriaxone over 2 g daily dose, its plasma concentration should be monitored to decide if dose adjustment is required to avoid from its toxic effect [19,21].

Provision of 500 mg ciprofloxacin tablet twice to 3 times daily was also noticed in 10 (12.5%) of the CKD patients. Dose reduction of ciprofloxacin by 50% is recommended for patients with creatinine clearance of <30 ml/minutes. Provision of ceftazidime injection ranging from 3 to 4 g daily was observed in 8 (10%) of CKD patients. While, maximum recommended daily doses of ceftazidime to treat infection in Stage 4 and 5 CKD patients are only 1 g and 500 mg, respectively. Cefadroxil capsule with 1 g daily dose was also observed in 5 (6%) of CKD patients. Dose reduction of Cefadroxil is required for Stage 4 and 5 CKD patients. Depending on the kidney function, dose should be reduced to 500 mg every 24-36 hrs. Amoxicillin capsule with 1.5-2 g daily doses were provided to four patients. The MDDs of this antibiotic should not exceed 1 g and 500 mg for patients with creatinine clearance 10-20 ml/minutes and ≤10 ml/minutes, respectively. The rest of occurred irrational antibiotics doses were also related to overdose including cefotaxime injection, metronidazole infuse, ciprofloxacin infuse, and meropenem injection. All of the irrational antibiotics dosing were higher than those recommended in literatures [15]. In the future, healthcare providers should pay attention on similar problems and resolve them to avoid from toxic effects of these antibiotics.

Friedman analysis proved that there were statistically significant differences in the true mean of the irrational dose of the nine provided antibiotics. Nevertheless, all of these antibiotics need the same attention and their doses should be corrected to improve outcomes. In addition, active role of clinical pharmacists involved in the multidisciplinary healthcare team is crucial to achieve this goal.

Currently, there are few barriers to effective management of CKD in HAM hospital i.e. selection of antibiotics to treat infection in CKD patients is based on empirical approach, previous 6-month culture and sensitivity test results, trusty literatures, and available antibiotics covered by JAMKESMAS. These conditions contributed to the problems faced for the management of CKD in the hospital. Firstly, even though culture and sensitivity tests are performed on the patients' specimen, but, due to lengthy culture and sensitivity test completion (about 1 week), consequently, physicians are lack of asses to rapid test for prompt antibiotics selection. Secondly, infectious patients need immediate treatment and hemodialysis for the patients' safety [22]. The third problem deals with budget constraint allocated by JAMKESMAS to the patients. The choice of drug as well as service provided to the CKD patients must also be in accordance with JAMKESMAS tariff due to constraint budget allocation. Treatment of each specific disease has a fixed budget allocation [23]. Fourth, advanced planning and procurement of drugs including antibiotics is another constraint that limits to assess and select the best antibiotic. Lastly, even though HAM Hospital review inhibition capability of the administered antibiotics every 6-month period based on culture and sensitivity test, the best selection of antibiotics is almost impossible. Facts indicate that rapid spreading of bacterial resistance to antimicrobial agents occurs over time [24].

The Pharmacy and Therapeutic Committee (PTC) in HAM Hospital regularly review and update the formulary addressing the use of drugs including antibiotics based on scientific clinical evidence to optimize outcomes. According to WHO, antibiotic utilization and infection controls are the topics of the action programs that can be the focus for the PTC activities [25]. Thus, consistent assessment of antimicrobial resistance trend across geographical area should also be continued and taken into account in drug selection development of standard treatment guidelines. Additionally, a great attention of policy maker on development of programs focused on improvement of hygiene and sanitation to avoid and minimize nosocomial infection as well as reduce the need for antibiotics use is also important [26]. Lastly, continuous efforts to minimize drug related problems (DRPs) and improve outcomes should be done by improving collaboration of all healthcare providers including pharmacists are now in the process of moving from product-oriented toward patient-oriented.

Few studies on identification of dosing errors and recommendation to resolve them have been reported in literatures. Manley *et al.*, in a pooled analysis, found that dosing error accounted for 20.4% of medication-related problems in ambulatory hemodialysis patients [9]. An intervention study performed in Swiss community pharmacy indicated that wrong dosage was the main DRP occurred and accounted to 31.7% of the intervention [27]. Subsequently, Kumar, *et al.* proved that appropriateness of initial antibiotics therapy was the determinant of the patients' outcomes. The survival rates after appropriate and inappropriate initial antibiotics therapy were 52.0% (with OR of 9.5) and 10.3% (with OR of 11.5), respectively. It was also indicated by other study that appropriate empiric antimicrobial therapy reduced death of septic patients with bacteremia [18,22]. Degrees of DRPs resolved were affected by acceptance of the prescribers [28,29]. However, resource limitations may also prevent physicians to provide the best choice of antibiotics [30]. Selection of antibiotics to treat infection in patients with CKD in the hospital is limited by many factors as previously described. Additionally, the best selection of antibiotics is almost impossible due to the facts that rapid spreading of bacterial resistance to antimicrobial agents continue to emerge [24]. Nevertheless antibiotics dose in CKD patients should always be adjusted to improve outcomes.

CONCLUSIONS

Various classes of antibiotics were utilized to patients with CKD Stage 4 and 5. The three most widely provided were ceftriaxone injection, ciprofloxacin infusion, and metronidazole tablet. Ceftriaxone injection, ciprofloxacin tablet, and ceftazidime injection had the highest incidence of irrational dosage of the systemic antibiotics provided to patients with CKD Stage 4 and 5 in HAM hospital. Occurrence of irrational antibiotics dosing was still high in HAM hospital. This study finding, even with limitations, is an important consideration for healthcare providers in rationalizing antibiotics provision to patients with CKD in order to improve outcomes. Understanding and implementation of dose adjustment in CKD patients are important to avoid drug toxicity.

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