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Longitudinal clinical evaluation of antibiotic use among patients with infecton

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Abstract

The present study aimed to evaluate clinical outcomes of used antibiotic among patients with infection and to compare sociodemographics with the type of infection and used antibiotic. A 6-week prospective longitudinal analysis was performed among patient who receive antibiotic in general ward HUSM. Patients were selected on the basis of used antibiotic and diagnosis of infection. Patient follow-ups were made on daily basis until discharge from hospital. All laboratory data were recorded to determine clinical outcome. Statistical analysis was undertaken using SPSS 17®. The total of sample was 44 patients (100%). Among them, 23 patients were males (52.3%) and 21 patients were females (47.7%). Majority 42 (95.45%) were derived from the Malay race and 2(4.55%) were Chinese. A 6 (13.64%) patients were identified as smoker. The age of patients in treatment was mean±SD (57.18±17.84) years and length of stay was mean±SD (7±4.57) days of treatment. Empirical theraphy was considered among 86.36% patient as it was not verified infection by culture and sensitivity test and only 6 (13.63%) as definitive therapy, 4 (66.67%) of them with mixture of gram (+) cocci and MRSA. Clinical outcomes showed 30 patients (68.18%) discharged without complication, 13 patients (29.55%) discharged with complication, and 1 patient (2.27%) transferred to other ward. There is no significant association between antibiotic with sociodemographics ($p>0.05$). No significant variance in betwen antibiotics with diagnosis type of infection and clinical outcomes ($p>0.05$) while in contrast there is a significant relationship between antibiotics with comorbidity ($p< 0.05$). Majority of antibiotics treatment were given based on empirical therapy not definitive therapy. There were no association among antibiotic use with sociodemographics and clinical outcomes.

Key-Words: Antibiotic, Infectious diseases, Clinical outcome

Introduction

Infections are commonly found both in comunity and hospital setting (1). World Health Organization (WHO) in 2002, reported 100.000 deaths due to various including lower respiratory infections (LRTIs), HIV/ AIDS, diarrhea, tuberculosis (TB), malaria, measles, pertussis, tetanus, meningitis, syphilis, Hepatitis B, and other tropical diseases (1, 2, 3). WHO reported (2011) several cases of infections both in Malaysia and Indonesia. In Malaysia (2009), it was reported that about 17.341 cases of TB, 19 cases for tetanus, 5 cases for pertussis and while in 2010 resources identified 153 cases of measles. However in Indonesia (2009) reported 292.754 cases of TB, 231 cases of tetanus, 209 cases of rubella, 20.818 cases of measles, 544.470 cases of malaria, and 17.260 cases of Leprosy (4).

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The rational use of antibiotics is still quenstionable in hospital protocole. In developed countries 13-37% of all patients admitted to hospital with infections and take antibiotics either single or combination therapy, whereas 30-80% patients in hospital of developing countries are treated with antibiotics (5). Thawani *et.al* (2006) reported that high prevalence of infection cause a quarter increase in cost of hospital annual budget with antibiotic (6, 7).

The appropriate dosing of antibiotics needed to achieve optimum therapeutic concentration (7). Pathogen resistance is one of leading cause of irrational antibiotic prescribing practices. If antibiotics are not used appropriately and effectively, the goal of therapy is not achieved and problem of resistance pathogens to antibiotics is emerged raised (8). As a result of this resistance, new antibiotics are needed to treat the old manerred infection. Unfortunately clinical discovery of new antibiotics is time dependent and costly procedure (10). To optimize rational use of antibiotics, a strategic

need of monitoring is required to evaluate the use of antibiotics (11, 12).

Monitoring parameter of the antibiotics treatment can be achieved by assessing the associated Drug Related Problems (DRPs) during antibiotic administration (12). DRPs defines are inappropriate clinical practices of antibiotics (11). In theoritically DRPs are defined as unexpected adverse event experienced by patients. It is also defined as the problems be caused by drug therapy and are actually or potentially interfere the outcome of management (13).

Few studies aimed to address problems that have associated with DRPs (13, 14). However theoritical gap have been found among the existing guidelines for the use of antibiotics in respective hospitals and literature also identified non-adherent clinical practices with antibiotics as mentioned per guidelines. Finding of teaching hospital in Australia showed that less than 50% practices adhere to guidelines for antibiotic use. In the United States, only 20-25% of antibiotic use based on line assesment of culture and sensitivity results. Similarly Italy only 2%, while India is 1% with hospital facilities is available in much smaller amounts (6).

Sociodemographics assesment (gender, ras, length of stay/LOS, smoking, etc) as vital role in appropiate selection and dosing design of antibiotics in general population (9,11,13). Sosiodemographics differences affect frequency of infections. It is dependent on different degree of pathogen exposure, immunity status, pathogenesis and differences in the severity of certain diseases associated with community (15).

The study aimed at evaluation the clinical outcomes for the antibiotics administration among patients with infection and to describe the influence of sociodemographic on the different types of infections.

Methodology

Type of Research

A longitudinal prospective study design was selected for this reserach. The data collection will be analyze descriptively and statistically with SPSS 17®.

Data Collection

Duration periode of data collecton was 6 weeks. It was from April 1st to May 15th, 2012. Data collection included: doses of antibiotics, physical examination and laboratory values, patients related information, completeness of therapy included demographic data (gender, age, race, LOS, smoking, etc), history of patient illness, drug regimen, causative organism, diagnosis, and clinical outcomes of treatment. After the data have taken. It transferred to the data collection sheet and followed by statistical analysis.

Selection of Patients

The inclusion of data samples were hospitalized infected patients who use antibiotics, either as treatment or prophylaxis of disease in the general ward HUSM Kelantan. The exclusion data were Inpatients who are not taken antibiotics in general ward and another ward who received antibiotic therapy in HUSM Kelantan.

Sources of Data

The sources of data included medical records of all patients who received antibiotic therapy for infections, laboratory test values, direct observation to the patient or family of patients treated in the general ward. The other sources for collect data were nursing record and observation directly to the patient or family of patients who treated in the general ward.

Analysis of Data

The data for patients receiving antibiotic therapy are presented in both tabulated and graphical forms. Sociodemographic data (gender, race, LOS, smoking), diagnosis, comorbidities, use of antibiotics, other drugs used along with antibiotics, and clinical outcome were presented in descriptive form. Variable are entered into both categorical and continous form.

Statistical analysis using Chi-square and one-way ANOVA were conducted to know the association of antibiotics with sociodemographics, diagnosis, comorbidities, and clinical outcomes. Statistical Package for Social Sciences (SPSS 17®) used to perform inferential statistic of this study.

Ethical Clearence: this research have approved by the Directur of Hospital Universiti Sains Malaysia Kelantan

Study Flowchart

Hypothesis of The Study is antibiotics used in HUSM Kelantan are not in accordance with treatment guidelines.

Results

The total of sample was 44 patients (100%). Among them, 23 patients were males (52.3%) and 21 patients were females (47.7%). Majority 42 (95.45%) were derived from the Malay race and 2(4.55%) were Chinese. A 6 (13.64%) patients were identified as smoker. The age of patients in treatment was mean±SD (57.18±17.84) years and length of stay was mean±SD (7±4.57) days of treatment (Table 1).

Table 1: Frequency of sociodemography distribution among patient

Characteristic	N (%)	Mean+SD
Gender		
Male	23 (52.3)	
Female	21 (47.7)	
Race		
Malay	42 (95.5)	
Chines	2 (4.5)	
Smoking		
Yes	6 (13.64)	
No	38 (85.36)	
Age		57.18±17.84
Length of Stay		7.27±4.57

The majority of diagnose were 22(50%) patients for CAP, followed by ACS 3(6.8%). Table 2 showed frequency of diagnosis of admission (Table 2).

Table 2: Frequency diagnose among patient

Characteristic	N (%)
CAP*	22 (50)
COPD**	2 (4.5)
ALLERGIC OF DRUG	2 (4.5)
tro infection	1 (2.3)
Urosepsis	2 (4.5)
ACS***	3 (6.8)
Limfadenitis	1 (2.3)
CCF******	1 (2.3)
Tuberculosis	1 (2.3)
DM*******	1 (2.3)
HAP********	1 (2.3)
Prolonged Fever	2 (4.5)
Lung Cancer	1 (2.3)
Hypotention	1 (2.3)
Sepsis	2 (4.5)
fluid overload	1 (2.3)
CKD********	

* CAP: Community Acquired Pneumonia
** COPD: Chronic Obstructive Pulmonary Diseases
***ACS: Acute Coronary Sydnrome
****CCF: Congestive Cardiac Failure
*****DM: Diabetes Mellitus
******HAP: Hospital Acquired Pneumonia
*******CKD: Chronic Kidney Diseases

Table 3 showed the frequency distribution of clinical characteristics between patients. A total 44 patients, 38 (86.36%) of them use antibiotics for empirical treatment and 6 (13.63%) patients used antibiotics for definitive treatment. The culture and sensitivity test result of showed no bacterial growth (so far not growth within 48 hours), there was a mixture of cultures between Gram (+) cocci + MRSA in Blood C & S inspection and ufeme. Culture and sensitivity tests also found 4 cases of MRSA in the sample ufeme at 3 patients and 1 case of the blood sample.

Table 3: Frequency of clinical characteristic distribution among patient

Characteristic	N (%)
AB.Prophylaxis*	
YES	38 (86.36)
NO	6 (13.63)
AB. Treatment	
YES	6 (13.63)
NO	36 (86.36)
Blood C&S*	
None	34 (77.3)
SFNG*	8 (18.2)
GRAM (+)	1 (2.3)
COCCI +MRSA	1 (2.3)
Pseudomonas	
Aeuruginosa MRSA	36 (81.8)
Ufeme C&S	4 (9.1)
None	3 (6.8)
SFNG	1 (2.3)
GRAM (+)	
COCCI +MRSA	37 (84.1)
Pseudomonas	5 (11.4)
Aeuruginosa MRSA	2 (4.5)
Sputum C&S	
None	39 (88.6)
SFNG	3 (6.8)
Specimen rejected	2 (4.5)
Nasal C&S	
None	43 (97.7)
SFNG	1 (2.3)
No. MRSA	
Trachea Swab C&S	42 (95.5)
None	2 (4.5)
SFNG	
Pleural C&S	
None	
SFNG	

*AB: Antibiotic
**C&S: Culture & Sensitivity
***SFNG: So Far Not Grow

There were about 12 types of used antibiotics among study population. The most widely used antibiotic was azithromycin. it were used by 29 patients (65.91%) followed by a cephalosporin antibiotic used 27 patients (61.36%), augmentin (amoxicillin + clavulanate) 8 patient (18.18%), erythromycin as many as 6 patients (13.64%), anti-tuberculosis, tazosin

(piperacillin+tazobactam) and metronidazole respectively by 4 patients (9.09%), ciprofloxacin for 3 patients (6.82%), imipenem and vancomycin respectively as many as 2 (4.55%), meropenem, amoxicillin, doxycycline, and cloxacillin each of 1 patients (2.27%) (Table 4).

Table 4: Frequency distribution of used antibiotics among patients

	Characteristic	N (%)
1.	**Cephalosporine[1]**	36 (81.82)
	IV.Cefotaxime	20 (45.45)
	IV.Ceftriaxone	3 (6.82)
	IV.Cefepime	1 (2.27)
	IV.Ceftazidine	6 (13.64)
	IV/T. Cefuroxime	6 (13.64)
2.	**IV/T.Azithromycin[2]**	29 (65.91)
3.	**Anti Tuberculosis[3]**	4 (9.09)
	T.INH	3 (75)
	T.Rifampicin	4 (100)
	T.Pyrazinamide	3 (75)
	T.Ethambutol	3 (75)
	IM. Streptomycin	1(2.27)
4.	**IV/T.Augmentin (Amoxicillin + Clavulanate)[4]**	8 (18.18)
5.	**T. Erythromycin 400 mg BD**	6 (13.64)
6.	**IV.Tazosin (Piperacillin +Tazobactam)[5]**	4 (9.09)
7.	**IV. Metronidazole 500 mg TDS**	4 (9.09)
8.	**IV/C. Cyprofloxacin[6]**	3 (6.82)
9.	**IV.Imipenem 1 G start then QID**	2 (4.55)
10.	**IV.Vancomycin[7]**	2 (4.55)
11.	**IV.Meropenem 2 G start then 50 mg TDS**	1 (2.27)
12.	**IV/C. Cloxacillin[8]**	1 (2.27)
13.	**IV. Amoxicillin 1 G start then 500 mg**	1 (2.27)
14.	**C.Doxycyclin 100 mg start then BD**	1 (2.27)

1. Cephalosporine: IV. Cefotaxime 2g start then 1 g BD, IV. Cefotaxime 1.5 g start then 750 mg TDS; IV Ceftriaxone 2 g start then 1 g BD, IV. Ceftriaxone 0.25 g OD; IV.Cefepime HCl 1 g start then 500 mg BD; IV.Ceftazidime 2 g start then 1 g BD ; IV. Cefuroxime 1.5 g start then 750 mg TDS; T.Cefuroxime 500 mg BD.
2. IV.Azythromycin 500 mg OD ; T. Azyhtromycin 500 mg OD.
3. Anti Tuberculosis: T.Isoniazid (INH) 300 mg OD; T.Rifampisin 450 mg, 600 mg OD ; T.Pyrazinamide 1000, 1500 mg OD; T. Ethambutol 800. 1000. 1200 mg; IM. Streptomycin 0.75 g OD.
4. IV augmentin (sodium amoxcicilin dan potassium clavulanate) 1.2 g start then TDS; T.Augmentin 625 mg BD
5. Tazosin: IV. Tazosin 2/0.25 (2 g Piperacillin & 0.25 mg Tazobactam) TDS; IV.Tazosin 4/0,5 g TDS
6. IV. Cyprofloxacin 400 mg; T. Cyprolfoxacin 500 mg BD
7. IV.Vancomycin 1 g OD; IV.Vancomycin 500 mg OD
8. IV.Cloxacillin ig QID; IV.Cloxaciliin 500 mg

Table 5 presented the distribution of frequency the other drugs among patients of study population. There were 9 non-antibiotic drug classes, namely: cardiovascular drug was 19 (43.18%), gastrointestinal drugs was 16 (36.36%), anti diabetic was 14 (31.82 %), asthma medications were 13 (29.55%), diuretic drugs were 11 (25%), antihypertensive was 10 (22.73%), analgesics, and antipyretics were 8 (18.18%), anticoagulation was 2 (4.55%), anti-thyroid was 1(2.27%), and the others include corticosteroid drugs were 7 (15.91%), antihistamines were 7 (15.91%), vitamins were 7 (15.91%), cough medicine was 6 (13.64 %), laxatives were 6 (13.64%), anti-anxiety was 4 (9.09%), anti-emetics were 2 (4.55%).

Tabel 5: Frequency of distribution drug non antibiotics among patients of study population

Non Antibiotics drug	N (%)
Cardiovaskular	19 (43.18)
T.Aspirin 150 mg OD	12 (63.16)
T.Clopidogrel 75 mg OD	6 (31.58)
T.ISDN 10 mg TDS	3 (15.79)
T.Atorvastatin 40 mg OD	13 (68.42)
SL. Fondaparinux 2.5 mg OD	3 (15.79)
T.Lovastatin	1 (5.26)
T.Fenofibrate	1(5.26)

Gastrointestinal Drug	16 (36.36)
IV.Ranitidine 50 mg	3 (18.75)
T.Pantoprazole 40 mg OD	7 (43.75)
T.Omeprazole 20 mg OD	3 (18.75)
T.Esomeprazole 40 mg OD	3 (18.75)
Antidiabetic Drug	14 (40.91)
Insulin	13 (92.86)
T.Metformine 850 mg BD	4 (28.57)
T.Glicazide 10 mg BD	1 (7.14)
Asthma Drug	
Neb Combivent every 6 H	13 (29.55)
Diuretic	11 (25)
HCT 16/25 OD	1 (9.09)
IV/T.Furosemide	11(100)
Antihypertensi	10 (22.73)
T. Propanolol 40 mg TDS	2 (20)
T.Felodipine 15 mg OD	5 (50)
T.Ramipril	2 (20)
T.Bisoprolol	2 (20)
T.Atenolol 100 mg OD	1 (10)
T.Valsartan	1 (10)
T.Diltiazem 30 mg TDS	1(10)
T.Enalapril	1(10)
T.Atenolol	1(10)
T.Perindopril	1(10)
Analgetic antipiretic	
T.PCM 1 g PRN	8 (18.18)
Anticoaguln	2 (4.55)
T.Warfarin 35 mg OD	1 (50)
Heparin	1 (50)
Anti Thyroid	1 (2.27)
The other drug	
Corticosteroid	7 (15.91)
Antihistamin	7 (15.91)
Vitamin	7 (15.91)
Cought drug	6 (13.64)
Lacsatif	6 (13.64)
Anti-anxiety	4 (9.09)
Anti-emetics	2 (4.55)

IV : Intravena
OD : once daily
PRN : Pro Re nata
SL : Sub Lingual
T : Tablet
HCT : Hydrochlorthiazide
PCM : Paracetamol
H : Hours

DRP were identified in 12 patients (27.27). DRPs are often associated with drug interactions and dosage regimen. Patients discharge without complications were the dominant clinical outcome occurred in 30 cases (68.2%).

Statistically, there was no significant association found in sociodemographic ($p>0.05$). it was not association betwen antibiotics with diagnosis and clinical outcome ($p>0.05$) but there was significant association among antibiotics with LOS, CrCl, and WBC ($p<0.05$).

Discussion

During the study period, total patients were 44. Based on gender 23 patients (52.35%) were male and 21 patients (47.7%) were female. Male more risk to get infection than female. Because of hormonal differences are owned by male and female (18).

Hormone testosterone, which is owned by male, may increase the effects of imunodepresan so the body fights the bacteria has decreased. Meanwhile, the hormone estrogen works vice versa so that it can trigger an immune or immunostimulatory high power (15).

Other researchers also reported that the risk of infection in postmenopausal female were almost equal to male. This corresponds to a decrease in the amount of the hormone estrogen, and found many dehydroepiandrosteron. 5α reductase enzyme can be converted dehydroepiandrosteron hormone into dehydrotestosteron lowers the body's immune system (16).

Based on race, the general patient population was Malay race. A 42 patients (95.45) originated from Malay race and the other 2 patients originated from the Chinese race.

Analysis on smoking habit, showed that patients were 6 (13.64%) as active smokers and 38 (85.36%) non-smoker. Statistically there was no clinical significant of smoking with infection or antibiotic used. All female who received antibiotics did not smoke, while some male patients have a story of active smoking. Data showed no significant association between smoking and the diagnosis. In this study there were 4 cases with a diagnosis of TB. The patients were smoker. Some studies showed an association of smoking with the infection for TB cases (17).

The result also showed mean±S.D age was 57.18±17.84. Fatimah (2006) reported the increasing age can lead to the greater the risk of infection. This was attributed to the ability of immunity to an increasingly advanced age decreases (18). In old age the body in a large number of changes, especially decreased immune function Cell Mediated Immunity (CMI) or cell-mediated immunity (19). So it can be concluded that the elderly≥ 60 years were more at risk of infection than adults. Non-significan one-way ANOVA obtained value of $p>0.05$. The results can be

interpreted. There were no significant relationship between age of the antibiotics given and between age of diagnosis. This indicates no effect on average age of diagnosis of the patient. Adults and the elderly have the same level of risk for infections at diagnosis.

Based on the length of stay, patients who received antibiotics were treated for 3-24 days. The average of length of stay was Mean±SD (7.27±17.84) days. Length of stay 5-6 days was found in 7 patients and a maximum of 24 days was found in one patient with a diagnosis of sepsis. In addition to sepsis, patients also have more than one comorbidity was end stage renal failure (ESRF), diabetes mellitus type 2, and Methicillin resistant *Staphylococcus aureus* (MRSA) which further aggravated the situation so that patients require longer treatment. Besides a longer treatment may also be due to the inappropriate use of antibiotics and the occurrence of bacterial resistance to antibiotics were given. Other studies also indicate an inappropiate the use of antibiotics can prolong the length of stay (21, 22).

Antibiotic have two purposes. They are empirical and definitive therapy. In this study, 38 patients (86.36%) use antibiotics for empirical therapy and 6 patients (13.64%) for definitive therapy. Only 6 patients used antibuotic with evidence of the existence of bacteria found in the patient's body. It was based on culture and sensitivity test. That why for definitive therapy were only 6 patients.

The samples for culture and sensitivity were blood, urine, sputum, nasal, pleural fluid, and swab of trachea. The samples depend on the diseases. On blood samples from two patients discovered the bacteria MRSA. The two patients diagnosed with sepsis, patient was initialed A get vancomycin antibiotic therapy while the patient was initialed B get antibiotics ciprofloxacin. The selection of antibiotic vancomycin in patients A was right, because vancomycin is active against bacteria Staphylococcus aureus resistant to the antibiotic methicillin and derivatives (20, 24).

Patient A was a length of stay with the longest, because usually the patients infected by MRSA bacteria are patients with chronic disease, often come and go to the hospital for treatment (24). Vancomycin is a drug with a narrow therapeutic index, so that the plasma drug levels monitoring needs to be done (25). Before get vancomycin, firstly, blood sample was taken 0-30 minutes prior to administration and 1 hour after the drug through an intravenous infusion given out. Blood was drawn by a doctor at least 1 mL was taken to the Therapeutic Drug Monitoring (TDM) for examination in drug plasma levels. Examination results will be analyzed by a pharmacist, and then set out the decision whether drug levels in the range of therapeutic or toxic levels have been passed. If the results obtained through the levels of toxic, then the pharmacist recommend a reduced dose or frequency of drug use extended or stopped for a while. Result of TDM test was reported to the physician on the ward through a computerized system, and physician will print the results of the investigation and entered into the patient's medical record (Therapeutic Drug Monitoring Unit HUSM staff).

Patients A get an initial dose of vancomycin at 500 mg once daily. Based on TDM, concentration of drug in plasma was 5.48 microg / mL. Drug levels did not reach therapeutic levels (therapeutic drug levels of 10-15 microg / mL). So that the dose was increased to 1 g on the third day treatment and results of TDM showed the drug in the plasma levels of 10.1 mg / mL. On day 13 maintainability, result of TDM showed toxic levels of drug in plasma was 20.73 mg / mL.

Drug administration was stopped with the aim of the drug concentration decreased with time in the renal elimination and drug delivery resumed as planned on day 16 shows the results of TDM in plasma drug levels 15.98 mg / mL. Toxic level of patient A was reached due to patients diagnosed with sepsis but also the ESRF patients with CrCl 11.4 mL / min. The dose should be received by the patients 15 mg/ kg Body weight (BB) (BW patient A was 60 kg patient) was 900 mg.

The doses of 100 mg of vancomycin can reach toxic levels after day 13, because the drug is a narrow therapeutic index, and t ½ value of drugs become longer in patients with impaired renal function, then the same dose as patients with normal renal function, will result in accumulation that exceeded MTC (19, 26).

After intravenous administration of vancomycin, the patient A showed clinical improvement, the temperature dropped from 38.4^0 C to 37^o C, and the WBC dropped from 12.4 to 9.24 x103/µL x103/µL. This shows the selection of appropriate antibiotics, and antibiotic was still effective against the bacteria MRSA. Vancomycin was administered in intravenous bolus infusion rather than in this case aims to maintain the steady state drug levels within the desired time and to reduce the release of histamine which can cause allergic reactions (28).

In patients B, MRSA infection by bacteria treated with ciprofloxacin. Antibiotic was also active against the bacteria MRSA, but many reported high risk of resistance in long-term use because of ability of ciprofloxacin against bacteria is limited. A related study ever conducted using ciprofloxacin, and obtained the result that within three months of the use of ciprofloxacin against MRSA bacteria, the level of

resistance to ciprofloxacin increased to 75% (26). Patient B also showed clinical improvement after the use of antibiotics, namely WBC dropped from 12.67 to 8x103/µL x103/µL. These results indicate ciprofloxacin was effective against the bacteria MRSA in this patient.

Handling of MRSA in hospital patients HUSM get special treatment. It aims to prevent cross-infection or the so-called nosocomial infections. Patients in the MRSA isolated labeled, and placed in a special room separated from other patients who were treated not as an infection. For MRSA patients, food equipment and used medical equipment such as stethoscopes, thermometers, and test equipment vital sign separately from other patients, including patients who were treated for infections caused by bacteria but not MRSA. Each will, and after conducting an examination of the patient, medical personnel must use a hand sanitizer (hand sanitizer).

Other precautions taken to prevent cross infection in HUSM for all types of infectious diseases is by means of inpatient wards designed to have two cabins, cabin next to treated patients was not due to infection and the rear cabin for patients treated for infection. Each table contained patient hand sanitizer that medical personnel can easily use it at will, and after an examination of the patient. For patients diagnosed with TB, patients should wear masks to minimize the spread of infection and should only be one accompanying family member during treatment.

Empirical use of antibiotics in this study was found in 38 patients. A total of 22 such patients diagnosed with CAP and two other patients had comorbidity CAP. Antibiotics used were based on the National Antibiotic Guidelines (2008) Malaysia. Empirical antibiotics are used as initial therapy before culture and sensitivity test results come out, but in reality there was no culture and sensitivity test done so that the antibiotics used remained as empirical therapy. When it should be for the therapeutic use of antibiotics, is necessary to culture and sensitivity test to know for certain bacteria that cause infections.

Antibiotics that used the patient with CAP were monotherapy amoxicillin + clavulanate or azithromycin combination therapy with penicillin and its derivatives group or class of third-generation cephalosporins. This was precisely the choice of antibiotics according to the National Antibiotic Guideline Malaysia (27).

Evaluation of Use of Antibiotics in geriatric patients or patients with Impaired Renal Function weres 21 of all patient geriatric had renal impairment. Antibiotics were often used in azithromycin a total of 11 patients (52.38%), cefotaxime many as 6 patients (28.57%), ceftazidime and augmentin each of the 5 patients (23.81%).

The use antibiotic of azithromycin dose adjustment was not necessary because the excretion of drugs in general along with the feces, only 6% of the drug is excreted through the kidneys (19). Antibiotic cefotaxime 46% excreted through the kidneys. It did not need dose adjustment in renal dysfunction mild to moderate, the dose should be reduced only in severe renal impairment, after a loading dose of 1 g administered, lower doses of half the usual dose given to the maintenance dose (19).

Ceftazidime dose adjustment should be done with the provisions of CrCl 31 to 50 mL / minute dose given after a loading dose of 1 g was 1 g every 12 hours, CrCl 16 to 30 mL / min was1 g every 24 hours. CrCl 6 to 15 mL/ minute was 500 mg / day. CrCl <5 mL / minute, the dose was 500 mg every 48 hours. In severe infections the dose may be increased, but may not cross the plasma concentration of 40 ug / mL. For patients peritoneal dialisi, 1 g loading dose followed by 500 mg / day. At patient with CrCl 11.3 mL / min received 1 g dose of ceftazidime TDS (three times daily), when it should patients simply get drugs 500 mg per day, in this case patients received excessive doses of antibiotics.

Augmentin is an antibiotic amoxicillin + clavulanate. This drug needs to be adjusted and must be reduced in patients with impaired renal function from moderate to severe. With the provisions of CrCl 10 to 30 mL / minute was 250-500 mg dose every 12 hours. CrCl <10 mL / minute, the dose was 250-500 mg every 24 hours. In this study, the use of augmentin was found to have the appropriate dose for CrCl> 30 mL / min, so no need for dose adjustment.

Antibiotics were evaluated on the accuracy of the selection of antibiotics according to the National Antibiotic Guidelines (2008) in Malaysia and evaluated according to the official literature (Dipiro and Martindal). Evaluation of antibiotics can also be seen from the development of the labor of data regarding patients with symptoms of infection include the number of WBC, body temperature, and hematocrit of patients. If antibiotics were given and the patient shows improvement, supported by the labor of data it can be said of antibiotics used were correct.

Result of evaluation antibiotic were 14 patients (31.82%) received appropriate antibiotics, 16 patients (31.82%) received antibiotics with incorrect dosing interval, 4 patients (9.09%) received antibiotics were not effective and each sequential 2 patients (4.55%) received antibiotics with no indication of the use of

antibiotics. In addition, there were 7 patients (18.18%) received inappropriate antibiotic combinations.

Appropriate use of antibiotics was the right type of antibiotic chosen, appropriate dosing regimen, and most importantly, the clinical improvement that occurs after antibiotic use is body temperature and WBC to normal.

The selection of antibiotics with inappropriate dosing interval in this group, the patient has received appropriate antibiotic selection, but the dose and frequency of administration not appropriate. This error occurs in patients with a diagnosis of moderate to severe CAP. According to the National Antibiotic Guideline (2008) Malaysia, and Dipiro (2009), for moderate to severe CAP who administered the drug combination azitromycin 500 mg tablets once daily with a third generation cephalosporin was 1-2 g per day. Meanwhile, patients get a third-generation cephalosporin drugs with an initial dose of 2 g after which 1 g three times a day (6, 28).

The use of inappropriate doses antibitoics can also increase the risk of bacterial resistance to antibiotics used. On the use of antibiotics was not appropriate intervals, a total of 8 patients of them did not show any symptoms of infection a patient's body temperature is 37 ^{0}C included in the normal range (36.5 to 37 ^{0}C), WBC <11x103/µL, and culture and sensitivity test results did not reveal any bacteria. In this case, although the diagnosis of CAP patients, but it showed no symptoms of infection and no evidence of bacteria causing the infection, then there was no indication was given antibiotics as a prophylactic therapy for prophylactic therapy is given only once at the time before surgery (6, 23).

Two patients with length of stay were 7 days, as long as the use of antibiotics did not show clinical improvement, the patient's WBC increased. This occurs in addition due to inappropriate dosage regimen Malaysia National Antibiotic Guidelines, (2008). It can be caused by antibiotics which have been resistant. Antibiotics that used were azithromycin 500 mg tablets once daily for three days and an intravenous injection of cefotaxime 1 g three times daily for 6 days.the other patients using azithromycin tablets 500 mg once daily for two days and intravenous injection of cefotaxime 1 g three times a day for two days while the drug should be used for one week.

Four patients in the interval other inappropriate antibiotic dose, showed clinical improvement after antibiotic use, normal body temperature of patients with WBC values decreased. This indicates that the selected antibiotics were appropriate, but the interval was not appropriate dose.

The combinations of antibiotics were inappropriate. Patients received a combination of antibiotics and even up to 3 pieces of antibiotics, while the culture and sensitivity test results do not prove the presence of bacteria. Patients got (ceftazidime + ceftriaxone), a combination of antibiotics used and the generation coming from the same drug class is the third-generation cephalosporins. This combination was inappropriate. Because the principle is the combination of antibiotic drugs should come from different groups and is active against the infecting bacteria (6, 23).

Patients with a diagnosis of urosepsis, a combination antibiotic therapy (ciprofloxacin + cloxacillin), according to the guideline for urosepsis, an antibiotic that used was one only, namely ciprofloxacin because it has broad-spectrum antibiotics. However, because of the combination was included ciprofloxacin, the patient showed clinical improvement, namely the patient's body temperature and WBC decreased (6).

Patients received a combination of antibiotics with other antibiotics were not effective against TB bacteria. Patients get antibiotics ceftriaxone and metronidazole in addition to anti-TB antibiotics. The other patients get antibiotics (cefotaxime and azithromycin) in addition to antibiotics for TB while the culture and sensitivity test results show that only bacteria are mycobacteria. In this case the use of other antibiotics were not needed because there was no indication in patients and patient also have renal deseases by CrCl 37.4 mL / min. Cefotaxime is an antibiotic that a major excretion in renal and affects the kidneys. During antibiotic therapy administered to a slight decline in kidney function of the data indicated a CrCl 34.3 mL / min.

Patients that used combination of antibiotics were doxycycline, augmentin, and cefuroxime. Use of antibiotics proved ineffective for the use of antibiotics there was no clinical improvement, the patient's temperature rose from 38.4 0C to 38.7 0C and the patient's WBC rose from 11.30 to 12.94 x103/µL x103/µL. This suggests that antibiotics were used inappropriately, but not a suitable antibiotic can be recommended, because patient was only diagnosed with prolonged fever and did not reveal any of the bacterial culture and sensitivity test results. In these patients the disease was suspected another diagnosis could not be determined.

The results can be compared with results of other researchers in the world, it was reported that a study in China in 1997 showed the use of antibiotics in acute respiratory tract infection 63% is not appropriate in terms of dose (31). In 2011, WHO also reported that 70% of antibiotic injections given to patients who do not need. Evaluation of antibiotic research conducted at

the Hospital Dr. Kariadi Semarang use of antibiotics without indication was found to be 19-76% and the RS. DR. Sutomo Surabaya for 10-80% of antibiotic use is not appropriate (29). Another study on antibiotics conducted in the department of Dr. M.Djamil Padang (2011) concluded only 43.81% of appropriate antibiotic use/ rational (30).

Evaluation of Use of Antibiotics in Patients with Impaired Liver Function was 8 patients (18.18%) who have impaired liver function. Patients at risk for liver function were patients receiving anti-TB drugs. Because of TB drugs have hepatotoxic effects. Patients who were diagnosed with TB should use the drug for 6 months to fight the TB bacteria. Drug use is continuous for a long time can increase the risk of hepatotoxic. In one patient showed rash, redness, itching, and swelling. Patients also complain of nausea and vomiting after two weeks of using anti tuberculosis (INH 300 mg + 400 mg rifampicin + pyrazinamide + ethambutol 1000 mg 800 mg). In these patients has been suspected hypersensitivity reaction to the antituberculosis was used. For reduce hypersensitivitas, patient get therap of hydrocortisone and chlorpheniramine maleate intravena. Therapeutic have been appropriate because both drugs can prevent the release of excess inflammatory mediators produced during hypersensitivity (8, 23, 33). A similar case was found in a patient hospitalized in the department of pulmonary ward. Patient showed hipersensitivity reaction after two weeks of using OAT.

Statistical analysis used in this research using Chi-square test and one-way ANOVA. Chi-square test for the observed was the relationship of antibiotic use by sex, race, smoking, diagnosis, komorbiditi, and clinical outcome. One-way ANOVA test examine the relationship of antibiotic use with age, length of day care, body temperature, hematocrit, WBC, CrCl, AST, ALT. The relationship was said to be meaningful if the number of significance or p value less than 0.05 ($p < 0.05$).

After analysis Chi-square test was the relationship of sex, race, smoking, diagnosis, and comorbidityy. There was no significant but there was a significant association between antibiotic used by diagnosis. Antibiotics given to patients with a diagnosis of infection by bacteria, in the absence of infection by bacteria then antibiotics may not be used (6, 8, 23).

Statistical results, after a one-way ANOVA test, was only given WBC before treatment, CrCl, and length of stay in the treatment of which has a significant association with antibiotic use ($p < 0.05$). This is because the WBC is a sign of infection (Dipiro, 2009), statistical results obtained show the influence of the use of antibiotics administered to the patient's WBC and antibiotics can be given effective means to improve the patient's clinical condition. Also indicated a significant influence on the value of CrCl, this was because 27 patients (61.67%) of 44 patients were geriatrics and as many as 21 patients including decreased renal function, and some antibiotics that were used to do a dose adjustment based on the value of CrCl (19).

Statistically, length of stay also had a significant association with the use of antibiotics, because antibiotics were different then the length of stay was also different, eg 3-day azithromycin used for the diagnosis of CAP and antibiotic ceftazidime should be used for one week. This relationship can also be viewed from the correct use of antibiotics, if antibiotics was used appropriately, then the patients will show improvement and length of stay will be shorter than the inappropriate use of antibiotics (32, 21).

Conclusions

Based on the evaluation of antibiotics used in the ward, it can be concluded that as many as 14 patients (31.82%) received antibiotics appropriately and as many as 30 patients (68.18%) have antibiotics inappropriately. The relationships between antibiotic use by gender, race, smoking, and age showed that the relationship were not statistically significant ($p > 0.05$). But there were significant association between antibiotic use with: length of stay, WBC, and CrCl ($p < 0.05$).

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