Factors Causing *Acinetobacter Baumannii* Resistance to Carbapenem Antibiotics in Patients with *Healthcare Associated Infection* (HCAI) at Dr. Moewardi Hospital, Surakarta

Widana Primaningtyas[1)], Eti Poncorini Pamungkasari[2)], Sugiarto[2)]

[1)]Master Program in Public Health Sciences, SebelasMaret University
[2)]Faculty of Medicine, SebelasMaret University Surakarta

ABSTRACT

Background: *Acinetobacterbaumannii* is a negative gram opportunistic bacteriumhaving high survival ability in the environment. Carbapenem is a drug of choice for infections caused by *Acinetobacterbaumannii*, which in the last decade prevalence of *Carbapenem Resistant Acinetobacterbaumannii* (CRAB) has increased. CRAB is commonly found in a nosocomial infection case and even into disease outbreak and epidemics in various hospitals. However, CRAB in community-associated infection data is still limited primarily in Indonesia. Therefore the researchers intend to do study factors causing CRAB in hospital and community setting in patients with Healthcare Associated Infection (HCAI).
Subjects and Method: This study was an observational analytic study, with *case control* design. The study was conducted in RS Dr. Moewardi Surakarta in March-August 2017. Taking subject used *fixed disease sampling* method with the number of samples were 104 subjects. The dependent variable was the incidence of *Acinetobacterbaumannii* resistance to carbapenem antibiotics in HCAI patients. Independent variables were history of antibiotic use, patient functional status, intensive *unit* maintenance and comorbid conditions. Dependent and independent variables were measured by using a questionnaire*checklist* and then analyzed by using multiple logistic regression analysis.
Results: Previous antibiotic conformity history (OR = 0.12; 95% CI = 0.03 to 0.45; p = 0.002) and the patient functional status (OR = 6.72; 95% CI = 2.08 to 21.68; p = 0.001) increased risk of resistance of *Acinetobacterbaumannii* to carbapenem (CRAB) in *Healthcare-Associated Infections* (HCAI) patients and was statistically significant. Treatment at *intensive unit* (OR = 0.76; 95% CI = 0.26 to 2.23; p = 0.613) and comorbid conditions (OR = 0.38; 95% CI = 0.12 to 1.23; p = 0.106) increased risk of *Acinetobacterbaumannii* resistance to carbapenem (CRAB) in *Healthcare Associated Infections* (HCAI) patients although it was statistically insignificant.
Conclusion: Previous antibiotic conformity history and functional status of patients are a factor affecting *Acinetobacterbaumannii* resistance to carbapenem (CRAB) in *Healthcare-Associated Infections* (HCAI) patients.

Keyword: *Acinetobacterbaumannii*, carbapenem, healthcare associated infection.

Correspondence:
Widana Primaningtyas. Master Program in Public Health, Sebelas Maret University, Jl. Ir. Sutami 36 A, Surakarta 57126, Central Java. Email: widanadoctor@gmail.com Mobile: +6285229035800.

BACKGROUND

Antibiotic Resistance (AMR) is one of the greatest health threats that develop from clinical health problems into a global public health problem (Schechner *et al*., 2013; WHO, 2016a). A bacterium is said to be resistant to antibiotics when it has changed its response to an antibiotic type (WHO, 2016a), so the expected response of death or cessation of bacterial growth does not occur. The antibiotic resistance appearance is almost identical to the time of antibiotic discovery itself, for example when penicillin was mass-produced in 1944, three years

later an England doctor reported that there had been resistance to *Staphylococcus pyogens* bacteria against penicillin (Schechner *et al*. 2013).

AMR can occur if it begins with irrational use of antibiotics, both in the therapy terms (doctor) and in the consumer distribution (pharmacy) and when received by the patient (Moeloek, 2015; WHO, 2016b). AMR cases in the United States resulted in death at least 23,000 people and in Europe at least 25,000 people per year (Lim *et al*., 2016). According to WHO data, Southeast Asian holds the highest number of AMR cases in the world. Indonesia as a member of the Southeast Asian country also takes the AMR case seriously, but *surveillance* data related to AMR mortality and morbidity in the field are still very limited (Moeloek, 2015).

One of the bacteria that cause AMR is *Acinetobacterbaumannii*. These bacteria are gram-negative bacteria that can be found in many places, such as on soil, water, human skin surfaces, equipment and hospital floor (Tjoa*et al*., 2013). A. *baumannii* is also an opportunistic bacterium whose pathogenicity is low, but over the time, these bacteria have high pathogenic capability because they have become resistant bacteria not only on one type of antibiotics but also on several types of antibiotics (Multi Drugs Resistance/ MDR) Adibhesami*et al*., 2016; Garnacho Montero *et al*., 2016) and has been reported to have both *Panresistance* and *Extremely Drug Resistance Acinetobacterbaumannii* (XDRAB).

MDR A. *Baumannii* is a cause of increasing patient mortality and morbidity as well as length of hospitalization, the increase in patient mortality due to A. *Baumannii* is 17-46% (Tjoa *et al*., 2103). Some of the diseases often caused by A. *Baumannii* are ventilator associated pneumonia, urinary tract infections and surgical wounds, meningitis and endocarditis (Lei *et al*., 2016). The existence of infection due to MDR A. *baumannii* makes the therapy choice narrower, increases mortality and morbidity, as well as increases cost and length of hospitalization, and makes it one of the important public health issues to be solved immediately (Chang *et al*. 2015; Tjoa et al., 2013).

Healthcare Associated Infections (HCAI) is an infection acquired in hospitalized patients over 48 hours with a history of previous hospital care (within 90 days) or receiving treatment (open wound, intravenous injection or intravenous therapy) by health workers or their families at home (within 30 days) or routinely for intravenous therapy such as hemodialysis or chemotherapy (within 30 days) (Cardoso *et al*., 2014). Patients are exposed to HCAI if the first day of hospitalization does not get an infection, then the patient gets an infection after 72 hours of hospitalization (Taylor *et al*., 2016). A. *baumannii* is one of the causes of HCAI and usually these bacteria have become MDR bacteria. Data reported from the results of the 20 provincial studies in Thailand MDR A. *baumanni* this caused the *community acquired bacteremia* by 28%, *healthcare associated with bacteremia* 50% and 75% *hospital acquired bacterimia* (p <0.001) (Lim *et al*., 2016).

Carbapenem (meropenem, doripenem, imipenem, and ertapenem) is one of the recommended antibiotic groups to address the MDR A. *baumannii* (Lei *et al*., 2016). However, the resistance rate of A. *baumannii* to carbapenem continues to increase. Data from the study conducted at neonatal unit of RS Dr. Cipto Mangunkusumo Jakarta, obtained only 16% of A. *baumanni* (n = 24) isolates which were still sensitive to carbapenem antibiotics, where

the isolates from 100% blood were MDR A. *baumannii* and isolates originating from the environment around the patient in care 82 % was MDR A. *baumannii* (Tjoa*et al*., 2013).

Preliminary study conducted in RS Dr. Moewardi Surakarta on the existence of *Carbapenem Resistant Acinetobacter-baumannii* (CRAB) had been done by researchers. Data from the results of the antibiotic resistance test of carbapenem at *A. baumannii*, during September-October 2016, obtained 58.8% isolates were still sensitive to carbapenem and 41.1% of isolates had been resistant to carbapenem (n = 102). This required comprehensive study and follow-up because of the high resistance rate of *A.baumanni*, almost 50%, which made the therapeutic choice narrower and could increase mortality and morbidity.

Patients hospitalized for more than 48 hours and located in *intensive care unit* (ICU) care facilities or other similar intensive care have been generally exposed to some previousantibiotics. The patient, treated with one or more pre-existing comorbid conditions, has a low functional status, can not undergo daily activities well and often needs other's help. The patient's *performance* or functional status as measured by the *Karnofsky Scale* (*Karnofsky Index*) can provide a clinical picture of the patient's condition and the prognosis of the patient associated with the illness, when the patient has a karnofsky score <70 means that the patient is unable to perform normal activities, the lower the score, the worse the prognosis and higher mortality (Cardoso *et al*., 2012; Peus*et al*., 2013; Kelly and Shahrokni, 2016)

Procurement of antibiotic susceptibility tests against specimens from patients suspected of having HCAI with comorbid conditions and low patient functional status should be a routine agenda at a hospital. Based on the above exposure, the researchers are interested in conducting study on the factors causing *Acinetobacter-baumannii* resistance to carbapenem antibiotics in patients with HCAI in RS Dr. Moewardi Surakarta.

SUBJECTS AND METHOD

1. Study Design

Study method was observational analytic study, with *case control* design approach. The time of the study was from March to August 2017 at Dr. Moewardi, Surakarta.

2.Population and Sample

The study population was patients with *Healthcare-Associated Infections* (HCAI) who had an infection due to *Carbapenem Resistant Acinetobacterbaumannii* (CRAB) in Surakarta. The study subjects were patients with *Healthcare-Associated Infections* (HCAI) who had an infection due to *Carbapenem Resistant Acinetobacter-baumannii* (CRAB) at RS Dr. Moewardi, Surakarta. Subjects of 104 patients were selected by means of *fixed disease sampling*.

3. Operational Definition of Variables

Acinetobacterbaumannii resistance to carbapenem (CRAB) in patients with *Healthcare-Associated Infections* (HCAI) was defined as hospitalized patients over 48 hours with a history of previous hospital care (within 90 days) or received treatment (within 30 days) or got routine for intravenous therapy such as hemodialysis or chemotherapy (within 30 days) (Friedman et al in Cardoso *et al*, 2014). And the results of sensitivity test antibiotic carbapenem with Vitek 2 (bioMe'rieux, Hazelwood, MO, USA) showed that there was CRAB.

History of previous antibiotic use was defined as a history of antibiotic use by HCAI patients when the patient received

empirical antibiotics for the infection as initial therapy. The patient's functional status was defined as the condition of HCAI patients at the time of hospitalization assessed from physical activity and patient's dependence on the surrounding. Treatment in an *Intensive Care Unit* (ICU) or similar intensive care was defined as a patient with HCAI treated at an ICU facility or intensive care unit (*High Intensive Care Unit, Pediatric Intensive Care Unit, Neonatal Intensive Care Unit*) for more of 48 hours.

4. Study instrument

Data collection instrument in this study was *check list* questionnaire, Charlson Comorbidity Index and Karnofsky Performance Index. Data collection was done directly by researcher through direct interview, observation and medical record data.

5. Data analysis

Data analysis techniques used univariate, bivariate and multivariate analyzes. Univariate analysis aimed to explain each data characteristic. Bivariate analysis aimed to analyze the relationship of two variables using *chi square*test. Multivariate analysis was multiple logistic regression analysis which aimed to measure influence between more than one variable in the study. Researchers used SPSS version 22 to analyze study data.

RESULTS

A. Univariate Analysis

Study subject characteristic included gender, age, treatment room and specimen type shown in Table 1 and Table 2. Based on both tables it was found that from 104 major study subjects were male (54%). More than half of the study subjects were in the range age of 46-65 years (50.9%) and the rate age was 47 years. Subject majority treated in the care ward at Dr. Moewardi Hospital, were in the Orchid 1 ward (26.9%) and the least was from the NICU ward (0.9%).

When viewed from the specimen type, the majority of specimens came from sputum (68.2%) and the least were *bronchial aspirate* and pleural specimens respectively of only 0.9%. Based on the functional status score of the patient as measured by PPP, the study subjects had a minimum value of 10 and a maximum of 60 with an average of 38.75 and a median of 40.

While patient comorbid conditions were measured by CCI, the study subjects had a minimum score of 0 and a maximum of 10 with an average of 2.03.

Table 1. Study subject characteristic by sex and age

Subject Characteristic	Criteria	Frequency (n=104)	(%)
Gender	Man	58	55.8
	Woman	46	43
Age	Infant (0-5 years)	8	7.7
	Children (5-11 years)	3	2.9
	Young (12-25 years)	8	7.7
	Adult (26-45 years)	16	15.4
	Elderly (46-65 years)	53	50.9
	Elderly (more than 65 years)	16	15.4

Table 2. Study subject characteristic by patient care ward and specimen type

Subject Characteristic	Ward	Frequency (n=104)	(%)
Patient Care Place	ICU*	10	9.6
	HCU Melati 1*	16	15.3
	Jasmine 1	9	8.6
	Jasmine 2	10	9.6
	Orchid 1	28	26.9
	PICU*	5	4.8
	NICU*	1	0.9
	Wing Jasmine 3	2	1.9
	Jasmine 2	4	3.8
	Jasmine 3	13	12.5
	Rose 1	4	3.8
	ROI-IGD*	2	1.9
Gender	Sputum	71	68.2
	Pus	13	13.5
	Blood	10	8.6
	Urine	6	5.8
	Tracheal aspirate	2	1.9
	Bronchial aspirate	1	0.9
	Pleura Liquid	1	0.9

*intensive care place

B. Bivariate Analysis

Table 3 showed an odds ratio of 6.76 meaning that patients with a history of inadequately empirical antibiotic therapy had a 6.76 times greater possibility of triggering CRAB in patients with HCAI. Chi-Square test results showed that there was an influence of previous history of antibiotic use with CRAB in patients with HCAI and statistically significant (p = 0.001).

Table 3. Chi Square tests between previous antibiotic usage history, patient functional status, intensive care and comorbid conditions against *Acinetobacter-baumannii* resistance to Carbapenem (CRAB) in patients with *Healthcare-Associated Infections* (HCAI)

Variable	CRAB				Total		OR	95% CI	p
	Yes		No						
	n	%	n	%	n	%			
Antibiotic User History									
Unsuitable	43	55.1	35	44.9	78	100	6.76	2.13 to 21.45	0.001
Suitable	4	15.4	22	84.6	26	100			
Patient Functional Status									
<40	27	73	10	27	37	100	0.16	0.07 to 0.40	<0.001
≥40	20	30	47	70	67	100			
Care at intensive unit									
No	21	32.8	43	67.2	64	100	3.80	1.65 to 8.75	0.002
Yes	26	65	14	35	40	100			
Comorbid Condition									
<2	6	26.1	17	73.9	23	100	2.90	1.04 to 8.11	0.042
≥2	41	50.6	40	49.4	81	100			

The odds ratio of 0.16 meant that patients with low functional status had an 0.16 times greater possibility of triggering CRAB in patients with HCAI. Chi-Square test results showed that there was functional status influence of patients with CRAB in patients with HCAI and statistically significant (p<0.001).

Patients treated in intensive units had a 3.80 times greater possibility of triggering CRAB in patients with HCAI (OR= 3.80; p= 0.002). Patients with high comorbid conditions were 2.90 times greater possibility of triggering CRAB in patients with HCAI (OR= 2.90; p= 0.042).

C. Multivariate Analysis

Based on the above table, multiple logistic regression results of previous antibiotic conformity history (OR = 0.12; 95% CI = 0.03 to 0.45; p= 0.002) increased risk of *Acinetobacterbaumannii* resistance to carbapenem (CRAB) in patients with *Healthcare-Associated Infections* (HCAI) statistically significant. The patient functional status (OR = 6.72; 95% CI = 2.08 to 21.68; p = 0.001) increased the risk of the incidence of *Acinetobacterbaumannii* resistance to carbapenem (CRAB) in patients with statistically significant *Healthcare-Associated Infections* (HCAI). Treatment at intensive units (OR = 0.76; 95% CI = 0.26 to 2.23; p = 0.613) increased the risk of *Acinetobacterbaumannii* resistance to carbapenem (CRAB) in patients with *Healthcare-Associated Infections* (HCAI) although it was not statistically significant. Comorbid conditions (OR= 0.38, 95% CI= 0.12 to 1.23, p= 0.106) increased the risk of *Acinetobacterbaumannii* resistance to carbapenem (CRAB) in patients with *Healthcare-Associated Infections* (HCAI) although it was not statistically significant.

Table 4. Multiple Logistic Regression Test between Previous Antibiotic History, Patient Functional Status, *Intensive Care* Treatment and Comorbid Conditions against *Acinetobacterbaumannii* Resistance to Carbapenem (CRAB) in Patients with *Healthcare-Associated Infections* (HCAI)

Variable	B	S.E.	Wald	OR	95% CI		p
					Lower	Upper	
Constant	-0.048	0.519	0.009	0.95		0.926	
Suitable antibiotic	-2.133	0.679	9.884	0.12	0.03	0.002	0.45
Low functional status	1.905	0.598	10.166	6.72	2.08	0.001	21.68
Patientcared unintensively	-0.279	0.552	0.255	0.76	0.26	0.613	2.23
Low commodity score	-0.975	0.604	2.611	0.38	0.12	0.106	1.23
N observational	104						
-2log likelihood	107.33						
Nagelkerke R Square	39%						

DISCUSSION

1. Effect of Previous Antibiotics History on *Acinetobacterbaumannii* Resistance to Carbapenem (CRAB) in Patients with *Healthcare-Associated Infections* (HCAI)

There was an influence of previous history of antibiotic use against *Acinetobacterbaumannii* resistance to carbapenem (CRAB) in patients with *Healthcare-Associated Infections* (HCAI), got a significant result (p<0.001). Lin and Lan's (2014) study also mentioned the same that previous antibiotic use was an independent risk factor for resistance to *Acinetobacterbaumannii*.

Kim *et al*., (2012) suggested that a previous history of high antibiotic use along with several other factors was an independent risk factor for CRAB. It had also

been reported by Camp and Tatum (2010) in theirstudy, which the study mentioned that one of the factors that influenced the formation of *Acinetobacterbaumannii* resistance was due to the use of various antibiotics before. Use of antibiotics as an extensive therapy regimen is also a cause of *Acinetobacterbaumannii* resistance to carbapenem and other antibiotics (Bialvaei et al., 2017).

A study conducted by Peleq *et al.* (2008) showed that antibiotic treatment for infection therapy caused by *Acinetobacter-baumannii* incorrectly triggered both enzymatic and non enzymatic activity of the bacteria to resist, so that bacteria had innate resistance to be resistant to certain antibiotics. Many other studies also suggest that *Acinetobacterbaumannii* has a complex intrinsic ability to withstand the effects of antibiotics and eventually become resistant (Peleq *et al.*, 2008; Camp *et al.*, 2010; Giedraitiene *et al.*, 2011; Khaldi *et al.*, 2017 ; Bialvaei *et al.*, 2017).

Use of antibiotics suitable for the treatment of bacterial infections empirically and definitively is absolutely necessary to control the existence of resistance and maintain antibiotic sustainability as a therapeutic regimen, as we know that the process of making and antibiotic modification for therapy requires a considerable cost and a long time. Yoon *et al.*, (2104) conducted a study of the carbapenem antibioticuse against infections caused by *Acinetobacterbaumannii*, the study conducted with an *Acinetobacterbaumannii* infection control program with the regulation of the administration of the main empirical antibiotic (*drug of choice*) group 1 carbapenem (ertapenem) and group 2 (imipenem and meropenem) was divided into three phases of therapy. The study proved that the appropriate use of empirical or definitive antibiotics will be able to control the spread of *Acinetobacter-baumannii* infection and prevent its resistance to carbapenem as a *drug of choice*.

Carbapenem-resistant *acinetobacter-baumannii* is generally also resistant to two or more other antibiotics, especially beta-lactam antibiotics, and the researchers also found a similar phenomenon in this study (Peleq*et al.*, 2008; Camp *et al.*, 2010; Lin and Lan, 2014; Khaldi*et al.*, 2017; Bialvaei *et al.*, 2017). Therefore *Acinetobacter-baumannii* is also a *multi drug resistant* (MDR) or even *excessively drug resistant Acinetobacterbaumannii* (XDRAB) due to its resistance to colistin in addition to its resistance to other antibiotics in the list of *Acinetobacterbaumannii* (Lin and Lan, 2014) MDR, but in this study it did not find any XDRAB.

Antimicrobial stewardship program is really important to do not only in hospital environment but also in the society because the development and spread of CRAB is high enough in various parts of the world which resulted in increasing morbidity and mortality rate as well as the increase of health cost which becomes society and state burden (Yoon *et al.*, 2104; Zowawi et al., 2015).

2. Functional Status affected Patients on *Acinetobacterbaumannii* Resistance to Carbapenem (CRAB) in Patients with *Healthcare-Associated Infections* (HCAI)

The study results showed a significant effect ($p<0.001$) between the patient's functional status against *Acinetobacter-baumannii* resistance to carbapenem (CRAB) in patients with *Healthcare-Associated Infections* (HCAI). This is based on Cardoso's *et al.*, (2012) study which stated that the functional status of patients assessed with *Karnofsky Performance Status* (KPS) is one of the risk factors for

infection caused by MDR bacteria in HCAI. One of the findings in this study was that all carbapenem-resistant *Acinetobacterbaumannii* were MDR bacteria.

The *cohort* study conducted by Chang *et al*. (2015) in Taiwan also supported the results of this study. The study was conducted on patients treated in long term care facilities (LTCFs) who suffered from bacterial infection, and one conclusion from the study that lower functional status (measured by PPP) was a significant predictive factor in all infections leading to death in LTCFs. The most common cases of LTCFs were urinary tract infection (41.7%), lower respiratory tract infection (32.1%) and infection of skin or soft tissue (27.6%), whereas in the study most cases were lower respiratory tract infection (68.2%), skin and soft tissue infections (13.5%) and bacteremia and/ or sepsis (8.6%). Other studies also suggested that *functional disability* is a risk factor for the occurrence of MDC *Acinetobacterbaumannii* colonization in patients (Mody*et al*., 2015).

Measuring the patient's functional status is important to determine the patient's condition regarding the prognosis and survival of the patient including knowing the severity of the disease and patient'snext disease end consequence (Lee *et al*., 2006; Carey *et al*., 2008). The lower the functional status of the patient, the worse the condition and the prognosis of the patient, in this study it is evident that the lower functional status of the patient has a significant effect on the occurrence of *Acinetobacterbaumannii* resistance to carbapenem antibiotics. *Acinetobacterbaumannii* is a bacterium that has the ability to survive high hospital environments and has intrinsic ability to resist the antibiotics exposed to it, so when the patient has a low functional condition, it becomes easier for *Acinetobacterbaumannii* to cause resistance and worsen the patient's prognosis.

In this study, it was also found cases which the patient first examined for bacterial culture and antibiotic sensitivity test showed the results of *Acinetobacterbaumanni* that was not resistant to carbapenem, but on the next test a few days later, *Acinetobacterbaumannii* had become resistant to carbapenem, the case occurred in patients with the PPP score in Category III. The average PPP score in this study was 38.75%, and the patients in category III in the KPS not being able to care for themselves required hospital care and the disease could experience rapid development (high disease progression). The findings of this study are consistent with previous studies where low PPPs contribute significantly to bacterial infection leading to higher patient mortality and a poorer prognosis and lower survival (Looney *et al*., 2003; Lee *et al*. , 2006; Carey *et al*., 2008; Chang *et al*., 2015).

3. Effect of Treatment on Intensive Units against *Acinetobacterbaumannii* Resistance to Carbapenem (CRAB) in Patients with *Healthcare-Associated Infections* (HCAI)

This study showed that treatment at the *Intensive Unit* increased the *Acinetobacterbaumannii* resistance to carbapenem (CRAB) in patients with *Healthcare-Associated Infections* (HCAI) although it was statistically insignificant. A study supporting the results of this study was a study conducted by Liu *et al*. (2015), one of the independent risk factors for the occurrence of bacteremia caused by MDR *Acinetobacterbaumannii* was the patient's care ward in ICU. A study conducted by Uwingabiye, *et al* (2015) also explained that the number of patients admitted to the ICU infected with CRAB MDR was higher than that treated in the ward (non ICU) with a

significant difference (p<0.001). The results of an international study conducted in 2007 on infections in 1265 ICUs from 75 different countries concluded that patients treated in ICU for a long time may have increased the risk of bacterial infections especially those resistant to antibiotics, one of which was *Acinetobacter* bacteria (Radji *et al*., 2011).

The use of invasive respiratory aids such as ventilators is high enough in *intensive units*, *Acinetobacterbaumannii*is commonly found in various ventilator surfaces causing patients to have *ventilator associated pneumonia* (VAP), the majority of isolates from *intensive units* in this study were sputum, and the final diagnostic conclusion is VAP -*Pneumonia bacterial etcausaAcinetobacterbaumannii*.

Study Tsakiridou *et al*. (2014) concluded that *Acinetobacterbaumannii* infection in patients treated in ICU is an independent risk factor for VAP events. Patients treated with long-term ICU ventilators are important risk factors for the occurrence of *Acinetobacterbaumannii* MDR (Arvaniti *et al*., 2012).

Most of bacterial infection outbreaks occurs in many ICUs and may trigger the occurrence of bacterial resistance epidemics (Vlek *et al*., 2013; Cheon*et al*., 2016). ICU generally contains patients with critical conditions requiring extended intensive and invasive treatment periods, putting patients at risk of infection. Existing bacteria in the ICU environment are opportunistic bacteria, causing no infection in healthy humans only colonization, but for these bacterial patients to be highly pathogenic causing therapeutic difficulty and longer treatment periods and high cost increases (Dijkshoorn *et al*. 2007).

Duijn and Bonten (2014) mentioned that ICU is the center of the birth of *antibiotic-resistant Gram-negative bacteria* (ARGNB) resistance to antibiotic-resistant bacteria (ARGNB) due to high antibiotic usage, immunological factors of patients in acute periods appropriate for bacterial infection and close contact by health workers with patients who facilitate cross-bacterial transmission. One of the gram-negative bacteria that is opportunistic then becomes *highly pathogenic* is *Acinetobacterbaumannii*, which triggers the infection outbreak in the hospital because the ability of colonization on the human body and the environment is very high (Dijkshoorn *et al*., 2007; Mamminа*et al*., 2012; Duijn and Bonten, 2014; Uwingabiye *et al*., 2015; Taggart *et al*., 2015).

4. Influence of Comorbid Conditions on *Acinetobacterbaumannii* Resistance to Carbapenem (CRAB) in Patients with *Healthcare-Associated Infections* (HCAI)

This study showed that patients with high comorbid conditions increased the risk of *Acinetobacterbaumannii* resistance to carbapenem (CRAB) in patients with *Healthcare-Associated Infections* (HCAI) although it was not statistically significant. Study conducted by Lee, *et al*. (2004) suggested that the comorbid condition of patients is a risk factor for the occurrence of carbapenem-resistant *Acinetobacterbaumannii* (imipenem). A similar study was also conducted by Ye *et al*., (2010) which stated that the comorbid condition of patients is a risk factor for the occurrence of MDR *Acinetobacterbaumannii*, specifically resistant to immune receptor (*Imipenem Resistant* MDR *Acinetobacterbaumannii* (IR-MDRAB). Comorbid condition was concluded as one of the predictors for the risk of bacteremia caused by *Acinetobacterbaumannii* in patients treated in ICU, which CRAB in the same study was also a strong predictor factor for high mortality in patients (Shorr *et al*., 2014).

According to study Chopra *et al.* (2013) comorbid conditions in patients also affect the occurrence of *carbapenem and ampicillinsulbactam resistant* (CASR) *Acinetobacterbaumannii*. Other studies have suggested that comorbid conditions are also independent risk factors for bacteremia caused by *Acinetobacter-baumannii* (Chopra *et al.*, 2014). Conclusions from the study of Verseles*et al.* (2013), among others, patients with high comorbidity based on the *Charlson Comorbidity Index* and accompanied by colonization of MDR bacteria may increase the risk of patients being admitted to *intensive units*. Other studies also suggest that the patient's condition with high comorbidities also increases the patient death risk (low survival) infected by *Acinetobacterbaumannii* (Ballouz *et al.*, 2017).

Most of patients hospitalized in Dr. Moewardi hospital have more than one comorbid condition, especially if the patient is in the elderly age range, so at the time of this study, many patients had high comorbid conditions but were not infected by CRAB. This does not rule out that patients with high comorbid conditions will be infected with CRAB, because researchers found cases of patients who was initially infected by*Acinetobacterbaumannii* and still sensitive to carbapenem but on checking patient's culture it had been infected by CRAB. Patients who experience bacteremia caused by CRAB are generally in a chronic condition of a disease, high *severity illness*, high comorbidity and high mortality (Estherly*et al.*, 2011).

This study is the first CRAB study in Surakarta in HCAI patients and similar data in Indonesia is very limited, although this study also has limitations. The sample size in this study was 104 whereas the multivariate analysis chosen was multiple logistic regression analysis requiring large samples. Researchers only make suffice of 104 samples because the study duration has exceeded the time period of study (5 months to collect samples) and time constraints possessed by researchers during the study.

Acinetobacterbaumannii colonization in patients can be misinterpreted as patients in the control group, in this study the researchers can not distinguish these two things. To overcome this, a *surveillance* of prospective and periodic *Acinetobacterbaumannii* infection in the hospital areneeded.

Based on the results of the above study it can be concluded that the history of previous antibiotic conformity and functional status of patients is a factor that affects the occurrence of *Acinetobacter-baumannii* resistance to carbapenem (CRAB) in patients with *Healthcare-Associated Infections* (HCAI).

REFERENCE

Abernethy AP, Shelby-James T, Fazekas BS, Woods D, dan Currow DC (2005). The Australia-modified Karnofsky Performance Status (AKPS) Scale: a Revised Scale for Contemporary Palliative Care Clinical Practice [ISRCTN81117481]. BMC Palliative Care, 4(7).

AdibhesamiH, Masoumeh D, Hojjat Z, Fariba B, Mohammad R, Mohammad RP, Mahboobeh ST, Aliramezani A, dan Ghourchian S (2016). Carbapenem-Resistant Acinetobacter baumannii Recovered from Burn Patients. Journal of Pharmacy and Pharmaceutical Sciences, 19(3): 339 – 348.

Apostolopoulou E, Raftopoulos V, Terzis K, Elefsiniotis I (2010).Infection Probability Score, APACHE II and KARNOFSKY Scoring Systems as

Predictors of Bloodstream Infection Onset in Hematology-Oncology Patients. BMC Infectious Disease, 10: 135-143.

Arvaniti K, Lathyris D, Ruimy R, Haidich AB, Koulourida V, Nikolaidis P, Matamis D dan Miyakis S (2012). The Importance of Colonization Pressure in Multiresistant Acinetobacter baumannii Acquisition in a Greek Intensive Care Unit. Critical Care, 16 (R102): 1-11.

Ballouz T, Aridi J, Afif C, Irani J, Lakis C, Nasreddine R, dan Azar E (2017). Risk Factors, Clinical Presentation, and Outcome of Acinetobacter baumannii Bacteremia. Frontiers in Cellular and Infection Microbiology, 7(156): 1-8.

Bialvaei ZA, Kouhsari E, Salehi-Abargouei A, Amirmozafari N, Ramazanzadeh R, Ghadimi-Daresajini A, dan Sedighi M (2017). Epidemiology of multidrug-resistant Acinetobacter baumannii strains in Iran: a systematic review and meta-analysis. Journal of Chemotherapy, 1-11.

Camp C, dan Tatum OL (2010). A Review of Acinetobacter baumannii as a highly successful pathogen in times of war. Lab Medicine, 41(11): 649-657.

Cardoso T, Almeida M, Friedman D, Aragao I, Costa-Pereira A, Sarmento AE, dan Azevedp L (2014). Classification of Healthcare-Associated Infection: a Systematic Review 10 Years After The First Proposal. Biomed Central Medicine, 12(40): 1-13.

CardosoT, Ribeiro O, Araga IC, Costa-Pereira A, dan Sarmento AE (2012). Additional Risk Factors for Infection by Multidrug-Resistant Pathogens in Healthcare Associated Infection: a Large Cohort Study. BMC Infectious Diseases, 12(375).

Carey EC, Covinsky KE, Lui LY, Eng C, Sands LP, and Walter LC (2008). Prediction of Mortality in Community-Living Frail Elderly People with Long-Term Care Needs. Journal of the American Geriatrics Society, 56 (1): 68-75.

Chang HH, Cohen T, Grad YH, Hanage WP, O'Brien TF, dan Lipsitch M (2015). Origin and Proliferation of Multiple-Drug Resistance in Bacterial Pathogens. Microbiology and Molecular Biology Reviews, 79(1): 101-116.

Cheon S, Kim MJ, Yun SJ, Moon JY dan Kim YS (2016). Controlling endemic multidrug-resistant Acinetobacter-baumannii in Intensive Care Units using antimicrobial stewardship and infection control. Korean Journal International Medicine, 31: 367-374.

Chopra T, Marchaim D, Awali RA, Krishna A, Johnson P, Tansek R, Chaudary K, Lephart P, et al. (2013). Epidemiology of Bloodstream Infections Caused by Acinetobacter baumannii and Impact of Drug Resistance to both Carbapenems and Ampicillin-Sulbactam on Clinical Outcomes. Antimicrobial Agents and Chemotherapy, 57(12):. 6270-6275.

Chopra T, Marchaim D, Johnson PC, Awali RA, Doshi H, Chalana I, Davis N, Zhao JJ, et al. (2014). Risk Factors and Outcomes for Patients with Bloodstream Infection Due to Acinetobacter baumannii-calcoaceticus Complex. Antimicrobial Agents and Chemotherapy, 58(8): 4630-4635.

Dijkshoorn L, Nemec A, Seifert H (2007). An increasing threat in hospitals: multidrug-resistant Acinetobacter baumannii. Nature Reviews Microbiology, 5: 939-951.

Duijn PJV dan Bonten MJM (2014). Antibiotic rotation strategies to

reduceantimicrobial resistance in Gram-negative bacteria in European intensive care units: study protocol for a cluster-randomized crossover controlled trial. Trials, 15: 277-285.

Esterly JS, Griffith M, Qi C, Malczynski M, Postelnick MJ, dan Scheetz MH (2011). Impact of Carbapenem Resistance and Receipt of Active Antimicrobial Therapy on Clinical Outcomes of Acinetobacter baumannii Bloodstream Infections, Antimicrobial Agents and Chemotherapy, 55(10): 4844-4849.

Garnacho-Montero, Guiterrez-Pizayarra A, Díaz-Martín A, Cisneros-Herreros JM, Canoe ME, Gatoe E, Fernández-Cuencaf CRAF, Vilag J, Martínez-Martíneze L, Tomás-Carmonah, Álvaro Pascualc MM, Bouh G, Pachón-Diazb G, dan Rodríguez-Ba˜noc J (2016). Infecciosas Clonalidad Mortalidad Acinetobacter baumannii en Pacientes Críticos: Epidemiología Molecular, Características Clínicas y Predictores de Mortalidadr. Enfermedades Infecciosas y Microbiología Clínica, 1460: 1-8.

Giedraitiene A, Vitkauskienė A, Naginienė R, dan Pavilonis A (2011). Antibiotic Resistance Mechanisms of Clinically Important Bacteria. Medicina (Kaunas), 47(3): 137-146.

Kelly CM, Shahroni A (2016). Moving beyond Karnofsky and ECOG Performance Status Assessments with New Technologies. Journal of Oncology: 1-13.

Khaldi H, Maoualainine MF, Younous S, dan Soraa N (2017). Epidemiology of Acinetobacter baumannii Infection in a University Hospital. Journal of Pathology and Microbiology, 2(1): 1012-1018.

Kim SY, Jung JY, Kang YA, Lim JE, Kim EY, Lee SK, Park SC, Chung KS, et al. (2012). Risk Factors for Occurrence and 30-Day Mortality for Carbapenem-Resistant Acinetobacter baumannii Bacteremia in an Intensive Care Unit. Journal of Korean Medical Science, 27: 939-947.

Lee SJ, Lindquist K, Segal MR, and Covinsky K E (2006). Development and validation of a prognostic index for 4-year mortality in older adults. Journal of the American Medical Association, 295(7): 801-808.

Lee SO, Kim NJ, Choi SH, Kim TH, Chung JW, Woo JW, Ryu J dan Kim JS (2004). Risk Factors for Acquisition of Imipenem-Resistant Acinetobacter baumannii: a Case-Control Study. Antimicrobial Agents and Chemotherapy, 48(1): 224-228.

Lei J, Han S, Wu W, dan Wang X, Xu J (2016). Extensively Drug-Resistant Acinetobacter baumannii Outbreak Cross-Transmitted in an Intensive Care Unit and Respiratory Intensive Care Unit. American Journal of Infection Control, 44: 1283-1287.

Lim C, Takahashi E, Hongsuwan M, Wuthiekanun V, Thamlikitkul V, Hinjoy S, Day NPJ, Peacock SJ, dan Limmathurotsakul D (2016). Epidemiology and Burden of Multidrug-Resistant Bacterial Infection in a Developing Country. Elife Science, 5: 1-18.

Lin M, dan Lan C (2014). Antimicrobial Resistance in Acinetobacter baumannii: From Bench to Bedside. World Journal of Clinical Cases, 2(12): 787-814.

Liu Q, Li W, Du X, Li W, Zhong T, Tang Y, Feng Y, Tao C, et al (2015). Risk and Prognostic Factors for Multidrug-Resistant Acinetobacter Baumannii

Complex Bacteremia: A Retrospective Study in a Tertiary Hospital of West China. PLoS ONE, 10(6): e0130701.

Mammina C, Palma DM, Bonura C, Aleo A, Fasciana T, Sodano C, Saporito MA, Verde MS, et al., (2012). Epidemiology and clonality of carbapenem-resistant Acinetobacter baumannii from an intensive care unit in Palermo, Italy. BMC Research Notes, 5: 365-373.

Mody L, Gibson KE, HorcherA, Prenovost K, McNamara SE, Foxman B, Kaye KS, Bradley S. (2015). Prevalence of and Risk Factors for Multidrug-Resistant Acinetobacter baumannii Colonization Among High-Risk Nursing Home Residents. Infection Control Hospital Epidemiology, 36(10): 1155–1162.

Moeloek NF Penggunaan Antibiotik Bijak dan Rasional Kurangi Beban Penyakit Infeksi. Kementerian Kesehatan Republik Indonesia. (2015). http://-www.depkes.go.id/article/print/15081100001/penggunaan-antibiotik-bijak-dan-rasional-kurangi-beban-penyakit-infeksi.html (diakses 10 Oktober 2106).

Peleg AY, Seifert H, dan Paterson DL (2008). Acinetobacter baumannii: Emergence of a Successful Pathogen. Cinical Microbiology Reviews, 21(3): 538–582.

Peus D, Newcomb N, dan Hofer S (2013). Appraisal of the Karnofsky Performance Status and Proposal of a Simple Algorithmic System for its Evaluation. BMC Medical Informatics and Decision Making, 13: 72-79.

Radji M, Fauziah S, Aribinuko N (2011). Antibiotic Sensitivity Pattern of Bacterial Pathogens in The Intensive Care Unit of Fatmawati Hospital, Indonesia. Asian Pacific Journal of Tropical Biomedicine, 1(1): 39-42.

Schechner V, Temkin E, Harbarth S, Carmeli Y, dan Schwaber MJ (2013). Epidemiological Interpretation of Studies Examining the Effect of Antibiotic Usage on Resistance. Clinical Microbiology Reviews, 26(2): 289–307.

Shorr AF, Zilberberg MD, Micek ST dan Kollef MH (2014). Predictors of hospital mortality among septic ICU patients with Acinetobacter spp. Bacteremia: a cohort study. BMC Infectious Diseases, 14: 572-579.

Taylor G, Garvel D, Matlow A, Embree J, LeSaux N, Johnston L, Suh K, John M, Embil E, Henderson E, Roth V, Wong A, dan the Canadian Nosocomial Infection Surveillance Program (2016). Assessing the Magnitude and Trends in Hospital Acquired Infections in Canadian Hospitals through Sequential Point Prevalence Surveys. Antimicrobial Resistance and Infection Control, 5(19): 1-7.

Tjoa E, Moeharjo LH, Rukmana A, dan Rohsiswatmo R (2013). Acinetobacter baumannii: Role in Blood Stream Infection in Neonatal Unit, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia. International Journal of Microbiology, 1-6.

Uwingabiye J, Frikh M, Lemnouer A, Bssaibis F, Belefquih B, Maleb A, Dahraoui S, Belyamani L, et al (2016). Acinetobacter Infections Prevalence and Frequency of The Antibiotics Resistance: Comparative Study of Intensive Care Units Versus Other Hospital Units. Pan African Medical Journal, 23: 191-201.

Verceles AC, Lechner EJ, Halpin D, dan Scharf SM (2013). The Association Between Comorbid Illness, Coloniza-

tion Status, and Acute Hospitalization in Patients Receiving Prolonged Mechanical Ventilation. Respiration Care, 58(2): 250-256.

Vlek ALM, Cooper BS, Kypraios T, Cox A, Edgeworth JD dan Auguet OT (2013). Clustering of Antimicrobial Resistance Outbreaks Across Bacterial Species in the Intensive Care Unit. Clinical Infectious Diseases, 57(1): 65–76.

WHO (2016a). Antibiotics Resistance. http://www.who.int/entity/mediacentre/factsheets/en/ (diakses 23 November 2016).

_____ (2016b). Antimicrobial Resistance. http://www.who.int/antimicrobial-resistance/ (diakses 30 November 2016).

Yang Y, Lee Y, Tsai W, Kuo S, Sun J, Yang C, Chen T, Lin J, et al (2013). Comparison between Bacteremia Caused by Carbapenem Resistant Acinetobacter baumannii and Acinetobacter nosocomialis. BMC Infectious Disease, 13: 311-318.

Ye JJ, Huang CT, Shie SS, Huang PY, Su LH, Chiu CH, Leu HS, Chiang PC (2010). Multidrug Resistant Acinetobacter baumannii: Risk Factors for Appearance of Imipenem Resistant Strains on Patients Formerly with Susceptible Strains. Plos One, 5(4): e9947.

Yoon YK, Yang KS, Lee SE, Kim HJ, Sohn JW, Kim MJ (2014). Effects of Group 1 versus Group 2 Carbapenems on the Susceptibility of Acinetobacter baumannii to Carbapenems: A Before and After Intervention Study of Carbapenem-Use Stewardship. PLoS ONE, 9(6): e99101.

Zowawi HM, Sartor AL, Sidjabat HE, Balkhy HH, Walsh TR, Al Johani SM, AlJindan RY, Alfaresi M, et al (2015). Molecular epidemiology of Carbapenem-Resistant Acinetobacter baumannii isolates in the gulf cooperation council states: dominance of OXA-23-type producers. Journal of Clinical Microbiology, 53: 896-903.