



**Full Length Research Article**

**RELATIONSHIP BETWEEN INTRINSIC AND EXTRINSIC FACTORS IN KLEBSIELLAPNEUMONIAE BACTERIUM NOSOCOMIAL INFECTION PATIENTS WITH CARBAPENEM RESISTANCE BY NEW DELHI METALLO-B-LACTAMASE 1 IN MEDICAL AND SURGICAL CASES**

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**ABSTRACT**

This article aimed to examine the relationship between intrinsic and extrinsic factors characteristics in the nosocomial infection case patients caused by the Klebsiella pneumoniaebacterium which is resistant to antibiotic of carbapenem type. The subjects of this study were the patients hospitalized at Dr. Hasan Sadikin General Hospital Bandung in the case of both medical and surgical experienced nosocomial infection in accordance with inclusion criteria reaching 287 cases. The study was conducted from the period of January 1 2015 to June 30 2015. The data were analyzed by using univariate test and bivariate with chi-square and comparison tests. The study revealed that the intrinsic factors relating to resistance of carbapenem were the Hb level on Cut off point  $\leq 11.35$  g/dL, the risk magnitude of resistance to Klebsiella pneumoniae bacterium was 2.38 times higher compared to Hb level  $> 11.35$  g/dl; and major medical intervention reaches 3.03 times higher (CI 95%; 1.21–7.61); the factors relating to unhealing process in the nosocomial case were medical treatment case, leukocyte  $> 16.600$ , minor medical intervention, and open skin condition, each of them had OR value of 2.89:2.09:5.05 and 1.88. There are significant differences between intrinsic (sex, age, nutritional status, and skin condition) and extrinsic factors (treatment duration, sample origin, and genera condition of the hospital) reaching  $p < 0.05$ .

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**INTRODUCTION**

Nosocomial Infection or known as Healthcare-Associated Infections (HAIs) is an infection acquired by a patient during a hospital treatment (Teresa *et al.*, 2008; Bereket *et al.*, 2012; Graves, 2004). Generally a patient is infected after undergoing several medical and laboratory examinations. The intense use of antibiotic in the world today certainly affects the life of bacterium on Earth and gives a significant opportunity of antibiotic resistance. The nosocomial infection is hardly treated due to most of the microorganism causing the infection are resistant to antibiotic (Nikaido, 2009; Raschka *et al.*, 2013).

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At the present the use of broad-spectrum antibiotic especially carbapenem increases due to high prevalence of drug resistant pathogens (U.S. Department of Health and Human Services, 2013). Meanwhile, the data regarding the prevalence of carbapenem and genecarbapenem are barely developed. Klebsiella pneumoniaeis one of the bacteria that can cause nosocomial infection by producing New Delhi Metallo- $\beta$ -lactamase 1 (NDM-1) as one the main mechanism of resistance to broad-spectrum carbapenem antibiotic (Nikaido, 2009; U.S. Department of Health and Human Services, 2013). The Klebsiellapneumoniae bacterium resistant to Carbapenem antibiotic possesses plasmid DNA profile New delhiMetallo  $\beta$  lactamase (NDM-1) with its characteristic of being able to hydrolyze carbapenem and being resistant to  $\beta$  lactamase inhibitor which is susceptible to metal ion influence. New

Delhi Metallo β lactamase is a carbapenem enzyme that can hydrolyze all βlactam antibiotics except monobactam such as aztreonam and it is resistant to other types of antibiotic such as aminoglycoside, fluoroquinolone, macrolide, and sulfonamide (Ravikant et al., 2014).

The high case of Klebsiellapneumoniae bacterium infection in the inpatients along with Carbapenem Resistant Klebsiellapneumoniae (CRKP) at the Dr. HasanSadikin General Hospital proves the need of controlling the infection and its spread. On the other hand, the hospital policy in the program of prevention and treatment must be based on the nosocomial infection case prevalence of plasmid DNA profile of NDM-1Klebsiellapneumoniae. Therefore, a research is a need to identify Klebsiella pneumoniae producing NDM-1 through direct detection of gene NDM-1 with PCR method and as a gold standard of genotype identification of plasmid DNA profile study, sequencing method is used to analyze the type in order to conduct rational limitation in using carbapenem antibiotic to prevent Klebsiella infection that produces NDM-1(Ravikant et al., 2014; Betteridge et al., 2013).

This study aimed to examine the relationship between intrinsic and extrinsic factors characteristics in the nosocomial infection case patients caused by the resistant Klebsiella pneumoniaebacterium in the medical and surgical cases at the Dr. HasanSadikin General Hospital, Bandung.

The development and multiplication of microbes' resistance to antibiotic cause the increasing of morbidity, mortality and health cost. Thus, the commitment to realize patient safety and satisfaction by applying quality and cost controls policy at hospital is a must.

## MATERIALS AND METHODS

The study involved inpatients at Dr. HasanSadikin General Hospital, Bandung who were infected by Klebsiella pneumonia. There were 287 patients diagnosed with nosocomial infection from the period of January 1 to June 30 2015. The subjects of the study were selected based on inclusion and exclusion criteria. The subjects of the inclusioncriteraincluded patients experiencing nosocomial infection, the infection could be both local and systemic, and patients with clinical infection signs and complete medical records. The subjects of exclusion criteria were the patients with less than 24 hours intervention and the patients with clinical examination showing a disease similar to nosocomial infection. The subjects who were dropped ut consisting of those who resigned, experienced errorin the laboratorium examination and lost administrative files. The object of the research was a colony of nosocomial infection bacteria. The resistance level of the bacteria colony was tested to carbapenem type antibiotic from the specimen of the inpatients of medical and surgical unit at the Dr. HasanSadikin General Hospital Bandung. The bacteria colony was reserved by putting it into Tryptic Soy Broth (TSB) Glyceroland stored in the temperature of -80°C.

The inclusion criteria of the research objects were the results of bacterial culture from the specimen of the nosocomial

infection patients caused by Klebsiella pneumonia and the colony of Klesiella pneumonia bacteria which was resistant to antibiotic of carbapenem type of the nosocomial infection patients treated at the Medical and Surgical Unit of Dr. HasanSadikin General Hospital Bandung. The exclusion criteria of the study objects were the incomplete subjects' data and missing financial record data. The data were analyzed by using univariate test and bivariate with chi-square and comparison tests. The multivariate analysis used multiple logistic regression analysis.

The study is an analytical-descriptive research revealing the prevalence number of nosocomial infection caused by Klebsiella pneumonia bacterium that is resistant to carbapenem antibiotic (CRKP) with PCR.

## RESULTS

This study involved several disciplines in medicine such as surgical study: obstetrics and gynecology, surgery, and otolaryngology along with medical study: internal medicine and pediatrics. There were 287 cases of nosocomial infections caused by Klebsiella pneumonia bacterium fulfilling the inclusion criteria with the intrinsic factors (sex, age, skin condition/wound and nutritional status, Hb level, the total of leukocytes and thrombocytes) and extrinsic factors (treatment duration, sample origin and patients' general condition.

**Table 1. The resistance prevalence of Klebsiella pneumonia to Carbapenem and the differences between surgical and medical cases**

Treatment Unit	Bacteria Resistance <i>Klebsiellapneumoniae</i>		Total
	Resistant	Sensitive	
Surgical	28 (19.2%)	118 (80.8%)	146
Medical	17 (12.1%)	124 (87.9%)	141
Total	45 (15.7%)	242 (84.3%)	287

Note :Z (dual proportion test) = 1.659; p = 0.049 (p < 0.05)

The resistance test was conducted by using Vitek 2 test to analyze 287 subjects regarding the antibiotic resistance of carbapenem type. The prevalence of Klebsiella pneumonia bacterium case that was resistant to carbapenem antibiotic reached 15.7% (45/287) and 84.3% (242/287) which were sensitive by using Vitek 2 method (Table 1). In the case of surgical treatment, it reached 19.2% (28/45), that was resistant more than the medical case reaching 12.1% (17/45) by using Z test (dualproportion test). The value was significant (p=0.049).

There were differences of intrinsic factors (sex, age, laboratory examination results, nutritional status, skin and wound condition) between the cases of surgical and medical units (Table 2). In the surgical case, there were more males than females, significant comparison test (p<0.001), the age average of the surgical unit was older than of the medical unit significantly (p=0.045), the skin/wound condition of the surgical unit was more covered than of the medical one significantly (p=0.045), the nutritional status of the surgical unit was better than of the medical unit significantly (p=0.002), the average conditions of Hb level, leukocytes and thrombocytes of surgical case were higher than of the medical one with insignificant statistics (p>0.05).

**Table 2. The differences of patients' intrinsic and extrinsic factors between surgical and medical cases**

Variables	Case Origin		p* Value
	Surgical(n=146)	Medical (n=141)	
<b>I. Intrinsic</b>			
1. Sex	108 (74.0)	76 (53.9)	<0.001**
Male	38 (26.0)	65 (46.1)	
Female			
2. Age(years)	10	28	0.045
< 15	85	78	
15-59	51	35	
≥ 60	47.6 (20.3)	41.6 (23.8)	
Mean(SD)	50.5	46.0	
Median	1 - 86	0 - 91	
<b>Range</b>			
3. Skin/Wound Condition	100 (68.5)	83 (58.9)	0.045**
Closed	46 (31.5)	58 (41.1)	
Opened	24 (16.4)	50 (35.5)	
4. Nutritional Status	69 (47.3)	52 (36.9)	0.002**
Less	48 (32.9)	32 (22.7)	
Moderate	5 (3.4)	7 (5.0)	
Well			
5. Hb level (g/dl)	11.1 (2.3)	10.8 (2.8)	
Mean(SD)	11.1	10.5	
Median	4.4 - 16.9	4.1 - 19.8	
<b>Range</b>			
6. Leukocytes (/mm <sup>3</sup> )	17526.2	22567.4	0.657
Mean(SD)	(10413.3)	(54008.5)	
Median	15900	14800	
Range	1930-88900	300-630300	
7. Thrombocytes (/mm <sup>3</sup> )	332541.1	293238.6	
Mean (SD)	(184221.8)	(172120.7)	
Median	293500	267500	
<b>Range</b>			
<b>II. Extrinsic</b>			
1. Treatment Duration :	6000-944000	12000-785000	0.041**
<5 days			
5 - 10 days			
> 10 days	9 (6.2)	20 (14.2)	
2. Sample Origin :	45 (30.8)	48 (34.0)	
Urine	92 (63.0)	73 (51.8)	
<b>Sputum</b>			
Pus	68(46.6)	46 (32.6)	<0.001**
Blood	32 (21.9)	53 (37.6)	
3. General Condition :	40 (27.4)	25 (15.7)	
Minor Illness	6 (4.1)	17 (12.1)	<0.001**
Moderat Illness			
Major Illness	71 (48.6)	35 (24.8)	
	50 (34.2)	62 (44.0)	
	25 (17.1)	44 (31.2)	

**Note:** SD= standard deviation

\*based on comparison test of Mann-Whitney, with chi-square test \*\* for sex, skin condition, nutritional status, sample origin, general condition

The differences of extrinsic factors (treatment duration, sample origin, general condition, medical intervention) referred to the condition that the treatment duration of the surgical case was longer than of the medical case significantly ( $p=0.041$ ), the sample origin of surgical case mostly came from urine while in the medical case, it came from sputum significantly ( $p<0.001$ ), the general condition of the surgical case was mostly minor illness compared to the medical case that mostly moderate and major illness in the significant comparison test ( $p<0.001$ ) (Table 3).

There were differences of the patients' intrinsic factors with resistance to carbapenem in which the average median of Hb level of the resistant patients was lower than the significantly sensitive ones ( $p=0.023$ ), and the leukocytes median in the

resistant case was higher than the significantly sensitive one ( $p=0.032$ ) (Table 3).

There were differences of the patients' extrinsic factors regarding the patients' medical intervention. There were more minor medical intervention in the resistant case significantly ( $p=0.010$ ).

**Table 3. The differences of patients intrinsic and extrinsic factors towards Carbapenem resistance**

Variables	Bacteria resistance <i>Klebsiella pneumoniae</i>		p Value	
	Resistant (n=45)	Sensitive (n=242)		
<b>I. Intrinsic</b>				
1. Sex	26	158	0.335*	
Male	19	84		
Female				
2. Age (years)	6	34	0.588*	
< 15	26	135		
15 - 59	13	73		
≥ 60	44.9 (21.5)	44.6 (22.4)		
Mean (SD)	50	48		
Median	1 - 85	0 - 91		
<b>Range</b>				
3. Skin/Wound Condition	26 (57.8)	157 (64.9)	0.363*	
Closed	19 (42.2)	85 (35.1)		
Opened				
4. Nutritional Status	14 (31.1)	60 (24.8)	0.720*	
Less	17 (37.8)	104 (43.0)		
Moderate	14 (31.1)	78 (32.2)		
Well				
5. HB Level (g/dl)	10.2 (1.9)	11.1 (2.6)		
Mean(SD)	9.7	11.0		
Median	7.0 - 14.0	4.1 - 19.8		
<b>Range</b>				
1. Leukocytes (/mm <sup>3</sup> )	19951.1	20012.5	0.023*	
Mean(SD)	(9962.6)	(41823.0)		
Median	17000	14550		
Range	6000 -	300 -		
2. Thrombocytes (/mm <sup>3</sup> )	43500	630300		
Mean(SD)				
Median	317844	312454		
Range	(190052)	(177470)		
<b>II. Extrinsic</b>				
1. Treatment Duration :	286000	275000	0.878*	
<10days	26000 -	6000 -		
≥ 10 days	944000	897000		
<b>2. Sample Origin :</b>				
Urine				
Sputum	20 (44.4)	102 (42.2)		
Pus	25 (55.6)	140 (57.9)		
<b>Blood</b>				
3. General Condition :	22 (48.9)	92 (38.0)	0.580*	
Minor Illness	12 (26.7)	73 (30.2)		
Moderate Illness	8 (17.8)	57 (23.6)		
Major Illness	3 (6.7)	20(8.3)		
<b>4. Medical Intervention :</b>				
Minor	17 (37.8)	89 (36.8)		
Moderate	14 (31.1)	98 (40.5)		
Major	14 (31.1)	55 (22.7)		
	19 (42.2)	158 (65.3)		
	17 (37.8)	61 (25.2)		
	9 (20.0)	23 (9.5)		

**Note:** SD= standard deviation

\*based on comparison test of Mann-Whitney, with chi-square test \*\* for sex, skin condition, nutritional status, sample origin, general condition, univariate test.

**Table 4. The Relationship between Hb and Leukocytes cut off values with Carbapenem Resistance**

cut off Value	Bacteria Resistance <i>Klebsiella pneumoniae</i>		Relative Risk (Confidence Interval 95%)
	Resistant (n=45)	Sensitive (n=242)	
1. Hb (g/dl) :			
≤ 11.35	34 (21%)	128 (79%)	2.38 (1.26–4.52)
> 11.35	11 (8.8%)	114 (91.2%)	
2. Leukocytes :			
> 16600	23 (19.3%)	96(89.7%)	1.48 (0.86–2.52)
≤ 16600	22 (13.1%)	146 (86.9%)	

**Table 5. Factors Related to Resistance Incidence to Carbapenem**

Variables	Koef (B)	SE (B)	p Value	Relative Risk (Confidence Interval 95%)
Hb (≤ 11.35 g/dl)*	0.919	0.376	0.015	2.51 (1.20–5.24)
Medical Intervention : **				
- Moderate	0.704	0.372	0.050	2.06 (1.0–4.28)
- Major	1.109	0.469	0.018	3.03 (1.21–7.61)

**Note:** Model Accuracy = 84.3 %; \*) based on ROC curve  
 \*\* as reference of minor medical intervention RR (CI 95%) : Relative Risk and Confidence Interval 95 %.

The Hb level < 11.35 g/dl showed higher risk of resistance reaching 2.38 times compared to the Hb level > 11.35 g/dl. (CI 95%) (Table 4). The leukocytes > 16.600 showed higher risk of resistance reaching 1.46 times compared to the leukocytes level < 16.600.

There were two apparent variables relating to resistance in the nosocomial infection patients caused by *Klebsiella pneumoniae* who were received carbapenem antibiotic, that was, Hb < 11.35 g/dl with the relative risk of resistance 2.51 times higher than Hb > 11.35 g/dl and in the moderate and major medical interventions, each of them had relative risk of resistance 2.06 and 3.03 times higher compared to the potential resistance to carbapenem of the minor medical intervention (Table 5).

## DISCUSSION

This study showed that the characteristics of the subjects referred to the intrinsic factors including more males patients compared to females, the average age of the patients was between 15 and 59 years old, most of the skin/wound condition was covered, the patients' nutritional status were varied from malnourished to well-nourished status and most of them were well-/moderate-nourished. The incidence composition of the nosocomial infection between surgical and medical units was almost comparable.

This study is similar to other study which reported that the tendency of patients experienced nosocomial infection is determined by the intrinsic and extrinsic factors (Poirel et al., 2013; Emory, 1993). The intrinsic factors influencing the nosocomial infection included age, sex, the use of immunosuppression chemotherapy, the original disease causing to be treated at the hospital, nutritional and skin disorders. Therefore in the case of nosocomial infection, the intrinsic and

extrinsic factors will be useful for prevention and treatment in order to treat the patients identified resistant to infection.

The nosocomial infection patients caused by *Klebsiella pneumoniae* bacterium treated at the Surgical and Medical Units of Dr. Hasan Sadikin General Hospital Bandung, it was revealed the antibiotic resistance of carbapenem type with its resistance prevalence of carbapenem reaching 15.7% and the sensitive reached 84.3% (242/287) (Table 1). Previous research reported 15.2% of isolate *Klebsiella pneumoniae* that was resistant to carbapenem antibiotic (Chen et al., 2012; Glasner et al., 2013). Moreover, other study revealed the examination results of 552 isolate stating 51 (9.3%) were CRKP (Parwati et al., 2013). The bacterial resistance mechanism to carbapenem happened through β lactamase enzyme production, efflux pump mechanism, the transformation of porins and penicillin binding protein functions (PBPs) (Nikaido, 2009; Madigan et al., 2012; Vyas et al., 2011). The resistance incidence of *Klebsiella pneumoniae* bacterium can be found in both surgical and medical cases. The result showed that the resistance incidence of carbapenem in the surgical case was higher than in the medical one of nosocomial infection caused by resistant *Klebsiella pneumoniae* to carbapenem.

The research revealed similar result to a research reporting that surgical patients had higher incidence level of nosocomial infection in other areas such as pneumonia and urinary tract infection (Langley et al., 2012). The urinary tract infection at several institutions was included as one of the five-highest nosocomial infections. The high development of nosocomial infection relates to the use of high risk medical tools such as ventilator, urine catheter, and central intravascular lines during and after surgery.

This research shows that there are differences between the intrinsic and extrinsic factors of the patients in surgical and medical cases, namely sex, age, skin condition and nutritional status. The development of nosocomial infection can be declined through preventing direct contact with infected patients by using protection tools such as gloves, protective eyewear, gown and mask. In addition, nurses of the patients must apply washing hand rule to prevent transmission of nosocomial infection (Emory, 1993; Duce et al., 2012).

The intrinsic factors refer to Hb level and leukocytes number that is statistically significant between the resistant and sensitive cases to carbapenem antibiotic (Table 4). In the nosocomial infection patients receiving carbapenem antibiotic with Hb level ≤ 11.35 g/dl, the risk of resistance to *Klebsiella pneumoniae* bacterium was 2.38 times higher compared to those with Hb level > 11.35 g/dl; meanwhile, for leukocytes > 16.60, the risk of resistance was 1.48 time higher compared to those with leukocytes ≤ 16600. The bacterial resistance mechanism to antibiotic occurs through two mechanism, namely gene mutation of the plasmid itself and gene from the plasmid of other resistant bacteria (Madigan et al., 2012; Martinez and Baquero, 2009). The irrational use of antibiotic can cause gene mutation in the bacterium plasmid as an adaptive form towards chemotherapeutic effects (Parwati et al., 2013; Madigan et al., 2012). A bacterium possesses adaptive ability to its neighbourhood which later makes it resistant to antibiotic (Vyas et al., 2011).

The extrinsic factors causing nosocomial infection include the use of medical tools and surgical procedures. The incidence level of nosocomial infection in the patients using medical tools is higher than those who are not exposed to medical tools. Patients requiring several medical tools to treat their diseases usually suffer from several diseases which make them vulnerable to infection. The medical tools can also become pathway for microorganism from surrounding neighbourhood to enter the body, to facilitate pathogens transfer from one part of patients' body to the other parts and can as well act as inanimate foci where the pathogens may multiply while protected from patients' immune system (Betteridge *et al.*, 2013; Poirel *et al.*, 2011; Emory, 1993). Based on the results of the study, quality and cost controls policy of antibiotic use especially carbapenem type are required so that the use of antibiotic can be appropriate, rational and controlled focusing on patient's safety and satisfaction.

### Conclusion

The prevalence of resistant *Klebsiella pneumoniae* bacterium in the patients of nosocomial infection case treated at the Surgical and Medical Units of Dr. Hasan Sadikin General Hospital Bandung reaches 15.7% (45/287 cases). Meanwhile the prevalence of resistant *Klebsiella pneumoniae* bacterium to carbapenem antibiotic from the specimen of the nosocomial infection patients in the inpatients of Surgical Unit reaches 19.2% (28/45 cases), higher than Medical case reaching 12.1% (17/45 cases).

The intrinsic factors (sex, age, nutritional status, and skin condition) and extrinsic factors (treatment duration, sample origin and general condition when admitted to hospital) in the case of nosocomial infection caused by the resistant *Klebsiella pneumoniae* are higher in the Surgical case than the medical one. Therefore, there is a relationship between the intrinsic factors (Hb level and medical intervention) and extrinsic factors of nosocomial infection case caused by *Klebsiella pneumoniae* with resistance to carbapenem in all inpatient cases (Surgical and Medical).

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