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Costs for carbapenem-resistant versus carbapenem-sensitive *acinetobacter baumannii* infections

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***Abstract*---**The emergence and spread of Gram-negative bacteria namely Acinetobacter baumannii, is a serious public health challenge worldwide due to antibiotics resistance. Infections caused by this bacterium demonstrated significantly high economic burden. Nevertheless, economic burden of carbapenem resistant-Acinetobacter

baumannii (CR-AB) and carbapenem susceptible -Acinetobacter baumannii (CS-AB) infections in Indonesia remain unknown. The aim of the study was to evaluate the cost of hospitalized patients associated with CR-AB and CS-AB infections. Methods: In a retrospective observational case control study, we evaluated the medical records of patients with CR-AB and CS-AB infections hospitalized in the Dr. Soetomo Hospital Surabaya, Indonesia between 2018-2021. Also, we retrieved the data of sex, clinical specimen, dates of admission and discharge. The study outcome was hospital costs such as antibiotic and diagnostic costs including radiology and lab investigations charges from the payer perspective. Results: The antibiotic and diagnostic costs for CR-AB infection was higher than CS-AB infection, US$ 1039.3 versus US$ 492.2 ($p < 0.001$). It showed that the CR-AB antibiotic cost was higher than CS-AB, US$ 77.2 versus US$ 19.7 ($p < 0.001$), and the CR-AB diagnostic cost was higher than CS-AB, US$ 882.1 versus US$ 463.1 ($p < 0.05$). Conclusion: The economic burden for hospitalized patients with CR-AB infection was higher compared to the hospital cost for CS-AB infections.

***Keywords*---**Acinetobacter baumannii, Carbapenem-resistance, Hospital cost, Indonesia, Infectious diseases.

Introduction

Acinetobacter baumannii is the major cause of Health care associated infections worldwide (Dijkshoorn et al., 2007) and resistant to carbapenem which is the urgent global threat (Hamidian and Nigro, 2019). *Acinetobacter baumanni* is a most frequently isolated bacterium, resistant to multiple antibiotics (El Tahawy and Khalaf, 2013) and is a core cause of infections particularly ventilator-associated *pneumonias* in hospital settings (Munoz-Price and Weinstein, 2008). Dissemination of *Acinetobacter baumannii* infections is widespread in a clonal manner with in the hospital or to the other hospitals, it is evident that it increases the length of stay and hospital cost (Peleg *et al.*, 2008). The *Acinetobacter baumannii* infections are in WHO 1st priority critical pathogen list, associated with increased clinical and economic burden and multidrug resistant specifically carbapenem which is last resort to treat it (World Heath Organization, 2017).

The increase prevalence of carbapenem resistant-*Acinetobacter baumannii* (CR-AB) is the major cause of mortality in hospital acquired infections (Rossi et al., 2019). CR-AB infections are itself is a risk factor of hospital admitted patients and put a heavy burden on total hospital cost (Zhen et al., 2017). According to China study CR-AB infection put significant burden on hospital cost and is associated with high mortality (Huang et al., 2016), another study stated that CR-AB hospitalization cost was higher than carbapenem-susceptible *Acinetobacter baumannii* (CS-AB) and have impact on hospital cost (Lemos et al., 2014).

The burden of healthcare-associated infections (HAIs) are significantly higher in low- and middle-income than in high-income countries (Maki and Zervos, 2021).

The rate of CR-AB was highest in south east Asia including Indonesia (LY et al., 2017). Indonesia is fourth most populated country worldwide (The World Bank, 2022). Although Indonesia has very limited data on CR-AB and its hospital cost. However, the Studies from indonesia reported the CR-AB highly prevalent in the hospitals (Karuniawati *et al.*, 2011; Saharman *et al.*, 2018). In this study, we estimated the antibiotics and diagnostic cost of carbapenem resistant *Acinetobacter baumannii* hospitalized patients.

Materials and Methods

Study design, setting and duration

The retrospective case control study was carried out at department of microbiology, Dr. Soetomo Hospital, Surabaya Indonesia during period March 2018 to February 2021. It is a general academic hospital with 1514 beds and 26 departments, serving the community of eastern Indonesia**.** This study was approved by the Ethics Review Committee (ERC) of Dr. Soetomo Hospital, Surabaya Indonesia vide letter No. 0188/KEPK/IV/2021 dated 29th Aprill 2021.

Selection criteria

We reviewed the medical records of all those patients who hospitalized in Dr Soetomo Hospital, Surabaya, Indonesia during the period from March 2018 to February 2021. Total 198 patients including 66 with caused by CR-AB and 132 patients caused by CS-AB, were selected. Other criteria included age ≥18 years, males and females, COVID-19 negative, admitted in surgical, medical, and ICU wards were included in the study.

Data collection

The retrospective data such as gender, clinical specimen, carbapenem status, antibiotic cost, diagnostic cost, dates of admission & discharge retrieved. Outcomes of interest were hospitalization cost such as diagnostic cost and antibiotic cost. Diagnostic cost included radiology and lab investigations charges like Clinical pathology, pathology anatomy and clinical microbiology from the payer perspective

Statistical analysis

Data were managed through IBM Statistics SPSS version 20.0. Data for gender, organism, specimen and other drugs susceptibility was described by using frequency and percentages and comparison between two groups by carbapenem resistance was performed by using Chi-square and likelihood ratio test. Data of costs for different factors were described by using median (IQR) for groups by carbapenem resistance status, and comparison between groups was made by using Mann Whitney U test. The comparison among two groups by carbapenem status using Kruskal Wallis followed by Mann Whitney for pairwise comparison. resistant and sensitive cases were made by using Mann Whitney U test. P-value ≤ 0.05 was considered significant.

Results

This study was started in January 2021 until August 2021. The data was extracted from electronic medical record since March 2018 until February 2021. Total 198 cases included in the study and of them 66 (33.3%) cases were found carbapenem-resistant. The frequency of carbapenem-resistant cases was higher in males than females. However, the difference between two genders was insignificant (51.5 % vs. 47.7 %; $P > 0.05$). Among clinical specimens, carbapenem-resistant cases were more frequent in Blood (60.6%), followed by urine (31.8%), CSF (4.5%) and pleural fluid (3.0 %). However, the frequency of carbapenem-resistant cases was not significantly different across different specimens with p>0.05. (Table 1)

Table. 1. Distribution of cases by gender and specimen as per carbapenem status

		Acinetobacter baumannii					
		Susceptible		Resistant		Total	
		Count	%	Count	%	Count	%
Specimen	Urine	66	50.0	21	31.8	87	43.9
	Blood	43	32.6	40	60.6	83	41.9
	Pleural Fluid	10	7.6	2	3.0	12	6.1
	CSF	5	3.8	3	4.5	8	4.0
	Peritoneal	5	3.8	0	0.0	5	2.5
	Pericardial	3	2.3	0	0.0	3	1.5
Sex	Female	69	52.3	32	48.5	101	51.0
	Male	63	47.7	34	51.5	97	49.0

The CR-AB total median cost was $1039.3 and CS-AB total median cost was $492.2. The CR-AB had significantly higher median cost as compared to carbapenem susceptible with *p*-values < 0.001. For CR-AB cases, the total median cost for antibiotics was $77.2 and for CS-AB cases $19.7. The CR-AB had significantly higher median cost of antibiotics as compared to carbapenem susceptible with *p*-values < 0.001. For CR-AB cases, the diagnostic total median cost was $882.1 and for CS-AB cases the diagnostic total median cost was $463.1. The CR-AB had significantly higher diagnostic median cost as compared to carbapenem susceptible with *p*-values < 0.001 (Table.2)

Table 2. Comparison of various kind of costs between carbapenem susceptible and resistant cases (in 2021 US$)

Hospital cost	*Acinetobacter baumannii*		P-value
	Susceptible Median (IQR)	Resistant Median (IQR)	
Antibiotic	19.7 (6.5 – 47.3)	77.2 (27.5 – 253.0)	< 0.001
Diagnostic	463.1 (335.9 – 786.4)	882.1 (564.7 – 1343.4)	< 0.001
Total	492.2(362.5 – 925.2)	1039.3 (615.7 – 1562.1)	< 0.001

Statistically significant, p <0.05

Discussion

In 1911 the *Acinetobacter* was first defined by Micrococcus calco-aceticus, in 1950 becomes *Acinetobacter* (Silvia Munoz-Price and Weinstein, 2008). This bacterium becomes difficult to control because of its airborne transmission and survive in very depraved environment (Bernards et al., no date; Wagenvoort and Joosten, 2002; Falagas et al., 2008). The Carbapenems are the most effective antibiotics for the treatment of *Acinetobacter baumannii* (Qureshi et al., 2015; Ozsurekci et al., 2017). Carbapenem resistance has increasingly worldwide (Nordmann and Poirel, 2019). However, in Indonesia, very little is known about costs associated with CR-AB versus CS-AB. We found that compared with CS-AB with CR-AB were associated with significantly increased hospital costs, as Zhen et al. reported that the carbapenem-resistant *Acinetobacter baumannii* hospital cost was higher than the carbapenem susceptible (Zhen et al., 2020).Similar to this study CRAB hospital charges increases after culture due to prolong stay (Lautenbach et al., 2009).The present study showed higher diagnostic and antibiotics cost of CRAB than CSAB likewise Zhen et al. calculated higher laboratory cost, antibiotics cost and may have contributed to higher total medical cost (Zhen et al., 2017). In the same way Yang *et al.* found that miss use of antibiotics could increases cost of the hospital (Yang *et al.*, 2010). Without confirmation by antibiotics sensitivity test the prescription of antibiotics in hospital in patients not only increases the burden on hospital cost (Bimba *et al.*, 2020), also increases the resistance (Ayukekbong *et al.*, 2017). The continues same findings were found from last ten years previous studies that the carbapenem resistance was linked with increase economic costs for infections caused by gram-negative bacteria, specifically *Acinetobacter baumannii, Klebsiella pneumoniae* and *Pseudomonas aeruginosa* (Lautenbach *et al.*, 2009; Tian *et al.*, 2016; Ayukekbong *et al.*, 2017; Bimba *et al.*, 2020). Our results showed the diagnostic and antibiotics cost of CRAB higher than CSAB as in some studies shows that inpatients with serious illness probably have multiple diagnosis, treat with different kind of antibiotics compare with outdoor patients (Jiao *et al.*, 2015; Judd *et al.*, 2016),all these lead to spread of carbapenem resistance and ultimately increase the cost of the hospital. Our study some limitations are worth noting, it's a single centre study and total hospital cost such as bed, pharmacy and administration cost was not included in this study. To provide complete view related to infections cost of the hospital should include all kind of cost expenditure use during stay in hospital and expand this study to multicentre in different areas.

Conclusions

Our study concluded that the CRAB antibiotics and diagnostic cost were higher than the CSAB. Further studies are needed to explore and regulate to early diagnosis and identification of infectious organisms. Early treatment ultimately reduces the extra burden on hospital cost.

Author Contributions

Conceptualization, Y.L., A.K.R.P. and K.K.; methodology, Y.L., M.R., H.B.N., A.K.R.P. and K.K; software, Y.L; validation, M.R., H.B.N., A.K.R.P., R.S. and K.K;

formal analysis, Y.L., H.B.N., A.K.R.P. and K.K; investigation, Y.L., M.R., H.B.N., A.K.R.P., R.S. and K.K; resources, Y.L., M.R., A.K.R.P. and K.K.; data curation, Y.L., R.S. and K.K; writing—original draft preparation, Y.L., M.R., A.K.R.P. and K.K.; writing—review and editing, Y.L., M.R., A.K.R.P. and K.K.; visualization, Y.L., M.R. and K.K.; supervision, M.R. and K.K; project administration, Y.L. and R.S.; funding acquisition, Y.L., M.R. and K.K. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was approved by the Research ethical committee Dr. Soetomo Hospital, Surabaya, (No. 0188/KEPK/IV/2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study

Data Availability Statement:.The data will be provided upon resonable request from the coreesponding auther.

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Conflicts of Interest: The authors declare that there is no conflict of interest to disclose

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