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Correlation Between the Suitability of Empirical and Definitive Therapies According to Culture Results with the Clinical Outcomes of Patients with Bacteremia Due to Carbapenem-Resistant *Acinetobacter baumannii* (CRAB) at Dr. Soetomo Tertiary Referral Hospital

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ABSTRACT

Carbapenem administration is an important therapy for nosocomial infections due to MDRO, especially *Acinetobacter baumannii*. The global increase in carbapenem-resistant *A. baumannii* (CRAB) that causes this pathogen has significantly threatened public health due to the lack of adequate treatment options due to the very few currently available antimicrobial agents that actively fight CRAB. Antimicrobial resistance is a major negative impact of inappropriate antimicrobial prescribing. Ineffective empiric treatment (initial antibiotic regimen not sensitive to identified pathogens based on *in vitro* sensitivity test results) is associated with a higher rate of deaths compared to effective empiric treatment. In this study, we analyzed the correlation between the suitability of empiric and definitive antibiotics and the clinical outcomes of patients with bacteremia due to CRAB treated in the inpatient ward of Dr. Soetomo Tertiary Referral Hospital, Surabaya. There were 227 isolates of bacteremia due to CRAB, consisting of 156 carbapenem-resistant *A. baumanni* and 71 carbapenem-sensitive *A. baumannii*. There were 88 isolates that met the inclusion and exclusion criteria, and all of them were resistant to ceftriaxone, cefepime, and ciprofloxacin. A total of 29.5% of the isolates were sensitive to cotrimoxazole, 3.4% of the isolates were sensitive to tigecycline, and 2.3% of the isolates were sensitive to amikacin, levofloxacin, and cefoperazone sulbactam. Adequate empirical antibiotics and definitive antibiotics (sensitive based on culture sensitivity test) amounted to 12.5% and 27.3%, respectively. There is no significant correlation between the suitability of empiric and definitive therapies with the patients' clinical outcomes (death and length of stay).

Key words: Carbapenem-resistant, *Acinetobacter baumannii*, Bacteremia, Empirical antibiotics, Definitive antibiotics, Clinical outcomes.

INTRODUCTION

Carbapenem-resistant *Acinetobacter baumannii* (CRAB) has been widely reported globally, with a worldwide prevalence reaching 30%[1] and is a major cause of nosocomial infections,[2] including bacteremia, and is associated with a high case fatality rate.[3,4] Carbapenem-resistant *A. baumannii* is included in the first priority critical pathogen based on the global priority list of antibiotic-resistant bacteria according to WHO.[5] CRAB is responsible for hospital-acquired infections[4] because it can survive for a long time on dry surfaces,[6] can be transmitted through the hands of health workers and contaminated equipment,[7] and resistant to disinfectants, which causes intractable outbreaks and affects the most vulnerable and critically-ill patients.[8] CRAB has been shown to be significantly associated with increased mortality,[2] prolonged hospital stays,[9,10] and increased costs of care.

Data reported by many countries in the global antimicrobial resistance and use surveillance system report (GLASS) from WHO shows that the highest pathogen is *Acinetobacter spp.* and *Escherichia coli*, reaching a percentage of 97%, obtained from bloodstream infections in 68 countries, urinary tract infections in 47 countries, gastrointestinal infections in 37 countries, and gonorrhea infections in 27 countries. Meanwhile, in bloodstream infections due to *A. baumannii*, the highest resistance was obtained due to carbapenem class antibiotics, including imipenem, meropenem, and doripenem, with a resistance level of 64.3%, 64%, and 54.7%, respectively.[11] Sixteen hospitals in Indonesia that provided GLASS data to the WHO reported that the most common pathogen was *Acinetobacter spp.* found in 70-100% of blood specimens, and most importantly, the emergence of carbapenem-resistant organisms.[11]

Regional surveillance programs for resistance to extended-spectrum beta-lactamase (ESBL) and CARB-R (carbapenem resistance) conducted in 12 Asia Pacific countries, including India and Taiwan, show that the level of antimicrobial resistance in Indonesia is higher than that in other Asia Pacific countries, such as Australia and New Zealand. Surveillance of antibiotic resistance in class A and B hospitals in Indonesia in 2020 found that CRAB ranks third in WHO's top priority pathogen

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distribution from all specimens.[12] In addition to increasing the severity of patients' underlying conditions,[2] inappropriate use of antibiotics can also increase patients' antibiotic resistance, clinical therapy failure, and medical costs.

Carbapenem administration is an important therapy for nosocomial infections due to Multi-Drug Resistance Organisms (MDRO), especially *A. baumannii*. Carbapenem belongs to the β-lactam antibiotics, has a wider spectrum of activity than other β-lactam antibiotics, is most effective against gram-positive and gram-negative bacteria, and is safe to use.[13] The global increase in carbapenem-resistant *A. baumannii* that causes this pathogen has significantly threatened public health[14] due to the lack of adequate treatment options due to the very few currently available antimicrobial agents that actively fight CRAB.[15]

MATERIALS AND METHODS

This analytic observational study applied a retrospective cross-sectional approach. The study population was medical record data of inpatients at Dr. Soetomo Tertiary Referral Hospital from January 2021 to October 2022 who sent blood cultures to the clinical microbiology laboratory with results of carbapenem-resistant *A. baumannii*. The inclusion criteria in this study included the culture data of inpatients at Dr. Soetomo Tertiary Referral Hospital who previously had blood culture results of CRAB with a complete medical record of antibiotic administration. The exclusion criteria included inpatients at Dr. Soetomo Tertiary Referral Hospital who had not received empiric therapy and died or were discharged from the hospital before receiving antibiotic therapy when they obtained blood culture results of CRAB for the first time. Ethical clearance for this study was issued by the Health Research Committee of Dr. Soetomo Tertiary Referral Hospital, Surabaya, number 0964/LOE/301.4.2/VII/2022.

The results of the descriptive analysis are presented in tables and figures containing frequency and percentage data. The analysis was performed using SPSS with a 95% confidence interval. The data were first analyzed univariately to obtain descriptive results regarding patients' characteristics, disease severity, comorbid history, previous length of stay, and the profile of their empirical and definitive therapies. In addition, the resistance percentage of bacteremia isolates due to CRAB was measured to obtain an overview of the empirical antibiotic resistance values used in bacteremia due to CRAB. The bivariate analysis was carried out to determine the correlation between empirical and definitive therapies, based on antibiotic sensitivity tests resulting from the culture of bacteremia isolates due to CRAB, with the clinical outcomes of inpatients at Dr. Soetomo Tertiary Referral Hospital from January 2021 to October 2022. The statistical analysis was conducted using the chi-square test for the independence test. Confounding variables were analyzed statistically with multivariate analysis using the logistic regression method.

RESULTS

Resistance rate of bacteremia isolates due to CRAB

From blood specimens collected from inpatients at Dr. Soetomo Tertiary Referral Hospital, Surabaya, from January 1, 2021, to October 31, 2022, a total of 227 *A. baumannii* data were obtained, consisting of 156 (68.72%) CRAB and 71 (31.28%) carbapenem-susceptible Acinetobacter baumanni (CSAB). Table 1 presents the data on the distribution of the study samples, consisting of patients with bacteremia due to CRAB.

Profiles of the antibiotic-resistance patterns of CRAB isolates in the inpatients' blood specimens

The results of the antibiotic resistance test of carbapenem-resistant *A. baumannii* isolates in this study indicated that all isolates were resistant

Table 1: Characteristics of patients with bacteremia due to CRAB in the inpatient ward of Dr. Soetomo Tertiary Referral Hospital.

Characteristics of patients with bacteremia due to CRAB	N	%
Sex		
Male	53	60.2
Female	35	39.8
Age	0 (0-78)**	
Neonatal state (< 28 days of age)	21	23.9
0-5 years	6	6.8
6-11 years	2	2.3
12-25 years	12	13.6
26-45 years	20	22.7
46-65 years	18	20.5
> 65 years	9	10.2
Ward Categories		
Emergency ward	3	3.4
Intensive care ward	46	52.3
Surgical ward	20	22.7
Child care ward	9	10.2
Medical treatment ward	4	4.5
Non-ICU COVID isolation ward	6	6.8
Used invasive medical devices		
Peripheral venous catheter	88	100
Urinary catheter	71	80.7
CVC	59	67
ETT	71	80.7
NGT/OGT	75	85.2
Comorbid score (Charlson comorbidity Index)		
0	63	71.6
1-3	20	22.8
≥ 4	5	5.5
Types of comorbidities based on CCI		
Myocardial infarction	0	0
Coronary heart disease	2	2.3
Peripheral artery disease	0	0
Dementia	0	0
Cerebrovascular disease	5	5.7
Chronic lung disease	2	2.3
Connective tissue disease	0	0
Diabetes without complications	8	9.1
Ulcer	7	8
Chronic liver disease	0	0
Hemiplegia	3	3.4
Moderate-severe kidney disease	8	9.1
Diabetes with complications	4	4.5
Tumor	4	4.5
Leukemia	0	0
Lymphoma	0	0
Moderate-severe liver disease	0	0
Malignant disease with metastases	0	0
AIDS	0	0
Length of stay before the collection of CRAB specimens	14,83 ± 9,7 *	
Disease severity (Pitt bacteremia score)		
0	19	21.6
1-3	29	33
≥ 4	40	46.5
COVID-19 patient	28	31.6
Clinical Outcomes		
Mortality Rate	50	56.8
Length of stay	18,98 ± 14,78 *	

Note: *: mean; **: mode

to ceftriaxone, cefepime, and ciprofloxacin. Most of the isolates were found sensitive to cotrimoxazole, amounting to 26 of 88 isolates (29.5%), followed by those sensitive to tigecycline, amounting to 3 of 88 isolates (3.4%), those sensitive to amikacin, amounting to 2 of 88 isolates (2.3%), those sensitive to levofloxacin, amounting to 2 of 88 isolates (2.3%), and those sensitive to cefoperazone sulbactam, amounting to 2 of 88 isolates (2.3%) as presented in table 2. The isolates were the first collected from inpatients with bacteremia due to carbapenem-resistant *A. baumannii*.

Risk factors affecting the clinical outcomes (Mortality Rate and Length of Stay) in patients with bacteremia due to CRAB in the inpatient ward of Dr. Soetomo Tertiary Referral Hospital

The risk factors examined in this study that affect the clinical outcomes of patients with bacteremia due to CRAB in the inpatient room of Dr. Soetomo Tertiary Referral Hospital included adequate empirical therapy and definitive therapy according to culture results. The confounding factors examined in this study that affect the clinical outcomes of patients with bacteremia due to CRAB in the inpatient ward of Dr. Soetomo Tertiary Referral Hospital included treatment in the ICU, COVID-19 patients, patients' comorbidities as indicated by the CCI (Charlson Comorbidity Index) score, and disease severity as indicated by PBS (Pitt Bacteremia Score). Table 3 depicts the risk and confounding factors that affect the clinical outcomes of the patients.

Multivariate analysis of the correlation between adequate empirical therapy to the sensitivity test of culture results with the clinical outcomes of patients with bacteremia due to Carbapenem-Resistant *Acinetobacter Baumannii* (CRAB) in the inpatient ward of Dr. Soetomo Tertiary Referral Hospital

The multivariate analysis indicated the significance of treatment in the ICU with a p of < 0.013 and an adjusted odds ratio of 3.048. It implies

Table 2: Antibiotic resistance test profile of CRAB (carbapenem-resistant A. *baumannii*) isolates in the inpatients' blood specimens.

Antibiotics	Resistant n (%)	Intermediate n (%)	Sensitive n (%)
Piperacillin	87 (98.9)	0 (0)	1 (1.1)
Ampicillin sulbactam	72 (81.8)	15 (17)	1 (1.2)
Cefoperazone sulbactam	60 (68.2)	26 (29.5)	2 (2.3)
Piperacillin tazobactam	87 (98.9)	0 (0)	1 (1.1)
Cefotaxim	87 (98.9)	0 (0)	1 (1.1)
Ceftazidime	87 (98.9)	0 (0)	1 (1.1)
Ceftriaxone	88 (100)	0 (0)	0 (0)
Cefepime	88 (100)	0 (0)	0 (0)
Amikacin	84 (95.5)	2 (2.3)	2 (2.3)
Gentamycin	87 (98.9)	0 (0)	1 (1.1)
Ciprofloxacin	88 (100)	0 (0)	0 (0)
Levofloxacin	85 (96.6)	1 (1.1)	2 (2.3)
Imipenem	87 (98.9)	0 (0)	1 (1.1)
Meropenem	87 (98.9)	0 (0)	1 (1.1)
Cotrimoxazole	62 (70.5)	0 (0)	26 (29.5)
Tigecycline	63 (71.6)	22 (25)	3 (3.4)

Table 3: Risk and confounding factors that affect the clinical outcomes of patients with bacteremia due to CRAB in the inpatient ward of Dr. Soetomo Tertiary Referral Hospital.

Risk Factors	Mortality Rate (+)/(%)	Mortality Rate (-)/(%)	OR	P-value	95% CI	Length of stay	OR	P-value
Empiric antibiotics			0.239	0.034	0.059-0.974		-	0.955
Adequate	3 (3.4)	8 (9.1)				16.09±9.45		
Inadequate	47 (53.4)	30 (34.1)				19.39±15.39		
Definitive antibiotics			-	0.079	-		-	0.576
Adequate	10 (11.4)	14 (15.9)				19.46±13.87		
Inadequate	40 (45.5)	24 (27.3)				18.80±15.21		
ICU care			3.048	0.012	1.269-7.320		-	0.675
ICU	32 (36.4)	14 (15.9)				18.76±15.54		
Non-ICU	18 (20.5)	24 (27.3)				19.21±14.08		
COVID-19 patient			-	0.891	-		-	0.284
Yes	16 (19.5)	12 (14>6)				16.93±15.17		
No	30 (36.6)	24 (29.3)				20.30±15>11		
CCI scores			-	0.544	-		-	0.081
0	32 (36.4)	31 (35.2)				19.83±13>61		
1-3	13 (14.8)	7 (8)				19.10±18.95		
≥ 4	5 (5.7)	0 (0)				7.8±2.45		
PBS scores			-	0.074	-		-	0.944
0	7 (8)	12 (13.6)				20.05±14.17		
1-3	15 (17)	13 (14.8)				18.32±17.15		
≥ 4	28 (31.8)	13 (14.8)				19.10±13.74		

Description: Scores below 0.05 indicate significant results

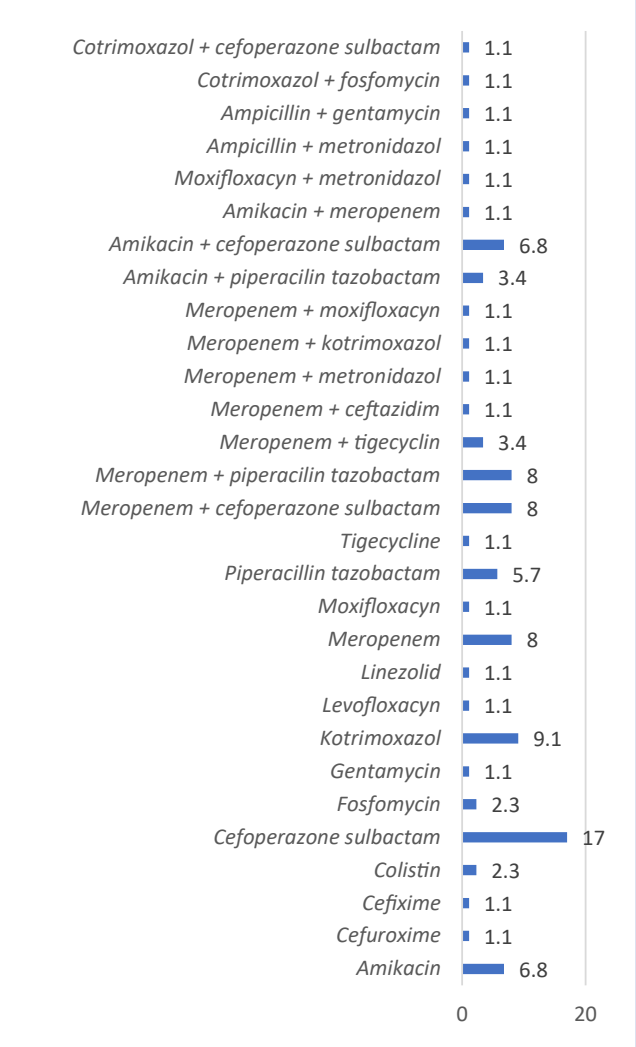

Figure 1: Percentage of definitive therapy in patients with bacteremia due to CRAB (carbapenem resistant *Acinetobacter baumannii*).

Table 4: Multivariate analysis.

Variables	aOR	95% CI	P-value
Treatment in ICU	3.048	1.269-7.320	0.013
Adequate empirical therapy to the sensitivity test of culture results	0.235	0.055-1.005	0.051

aOR: adjusted odds ratio
CI: confidence interval

that patients who receive treatment in the ICU have a mortality rate of three times that of patients who do not receive treatment in the ICU. Adequate empirical therapy to the sensitivity test of culture results does not significantly influence the mortality rate of patients with bacteremia due to CRAB with a p-value of 0.051, as presented in table 5.

DISCUSSION

The resistance rate of carbapenem-resistant *A. baumannii* in this study, which was conducted on inpatients with bacteremia at a tertiary referral hospital, reached 68.72%, obtained from 156 carbapenem-resistant *A. baumanni* (CRAB) and 71 carbapenem-susceptible *A. baumanni* (CSAB) data. It is lower than that in a study by[16] conducted at the same hospital from March 2018 to February 2021, reaching 93% with negative Covid-19 patients aged ≥ 18 years. Lashari *et al.*'s study on all specimens obtained a CRAB incidence rate of 50%.[16] It suggests that the intervention to reduce the carbapenem resistance rate in inpatients with bacteremia due to carbapenem-resistant *A. baumannii* has been successful.

The highest percentage of patients with bacteremia due to CRAB was found in neonates, accounting for 23.9% of the samples, 61.9% of whom were treated in the NICU ward, and 38.1% of whom were treated in the intermediate/neonate ward. The neonatal state is considered a risk factor because the defense system of neonates' bodies is still immature, and the frequency of invasive procedures is high.[17] This study showed that 90.5% of neonatal patients were administered with endotracheal intubation, which is an invasive procedure. Another study by Nakwan *et al.*[18] revealed that the mortality rate of patients with bacteremia due to CRAB and CSAB in the neonatal state reached 54% and 11%, respectively.[18] It is not significantly different from this study, which found that 52.4% of deaths were among neonates, and 12.5% of deaths were highest in neonates compared to other age groups.

The most common distribution of bacteremia due to CRAB was found in patients treated in the intensive care unit (ICU, PICU, NICU), accounting for 52.3% of the samples. It is lower than a multicenter study conducted in seven hospitals in Indonesia which showed that the highest prevalence of non-susceptible *A. baumannii* was found in patients treated in the ICU, accounting for 68% of the samples.[19] A study by Baran *et al.*[20] revealed that patients treated in the ICU had a three times greater risk of being infected with carbapenem-resistant *A. baumannii*.[20] Univariate analysis suggested that hospitalization in the ICU was associated with a risk of developing bacteremia due to the non-susceptible carbapenem *A. baumanii*.[22] Patients in the ICU were at risk for infection due to delayed immune responses, reduced host defense systems, and the use of invasive devices such as central venous catheterization, mechanical ventilation, and urinary tract catheterization.[21] It is consistent with this study which found that the use of invasive medical devices was most common in patients treated in the ICU, namely peripheral venous catheters (52.3%), mechanical ventilation (50.7%), and nasogastric tubes/orogastric tubes (54.7%). These percentages were higher than those in other wards.

The use of invasive medical devices was very high in this study sample. All patients in this study used peripheral venous catheters, 80.7% of whom used urinary catheters, 67% of whom used CVC, 80.7% of whom used mechanical ventilation, and 85.2% of whom used NGT/OGT. The use of a central venous catheter is an independent risk factor for bacteremia due to carbapenem non-susceptible *A. baumannii,* and the use of mechanical ventilation is associated with a risk of bacteremia due to carbapenem non-susceptible *A. baumannii*.[22] A multicenter study in China stated that the use of a urinary catheter was associated with the occurrence of infection due to MDR *A. baumannii*.[23] Other studies also revealed that the use of urinary catheters or central venous catheters was a risk factor for infection with carbapenem-resistant *A. baumannii*.

The combination antibiotics that have been widely studied include carbapenems, sulbactam, rifampin, and tigecycline. It is consistent with one of the definitive antibiotics used as a combination antibiotic in this study, namely cefoperazone sulbactam and meropenem. Cefoperazone sulbactam is the most commonly used antibiotic for definitive therapy (Figure 1). The results of a study in China conducted for five years in patients with bloodstream infection due to carbapenem-resistant *A. baumannii* showed that the combination of cefoperazone sulbactam and imipenem resulted in a lower mortality rate compared to the use of cefoperazone sulbactam alone.[24] Another study stated that the combination of cefoperazone sulbactam and tigecycline or rifampicin resulted in the highest synergy against multidrug-resistant *A. baumannii*.[25]

Many studies have identified all the risk factors that cause death in patients with carbapenem-resistant *A. baumannii*. A high Pitt Bacteremia score,[2,21,26,27] inadequate antibiotic therapies, treatment in

the ICU, and a high Charlson comorbidity index have been associated with a high mortality rate.[2,21,26]

This study suggests that giving appropriate empiric therapy does not influence the mortality rate because early mortality (0-5 days after blood sampling of patients with CRAB) were excluded from this study because there was no definitive antibiotic considering this study analyzed patients who received empirical and definitive antibiotics. A study conducted on patients treated in the ICU of a hospital in Turkey revealed that the late administration of adequate empiric therapy increased the mortality rate (> 3 days).[29]

The only influencing factor among all risk factors in increasing the mortality rate of patients with bacteremia due to CRAB (carbapenem-resistant *A. baumannii*) in this study was treatment in the ICU. This result is consistent with the result of a study in Serbia by Djordjevic *et al.*,[30] which stated that treatment in the ICU for more than one month increased the risk of being infected with carbapenem-resistant *A. baumannii*.[30,31]

CONCLUSION

There is no difference between adequate empiric therapy and definitive therapy to the sensitivity test of culture results in influencing the clinical outcomes of patients with bacteremia due to CRAB (carbapenem-resistant *A. baumannii*) in the inpatient ward of Dr. Soetomo Tertiary Referral Hospital from January 2021 to October 2022, because both do not affect the mortality rate and length of stay of the patients.

SUGGESTION

More data or multicenter studies are required to increase the validity of the results of this study.

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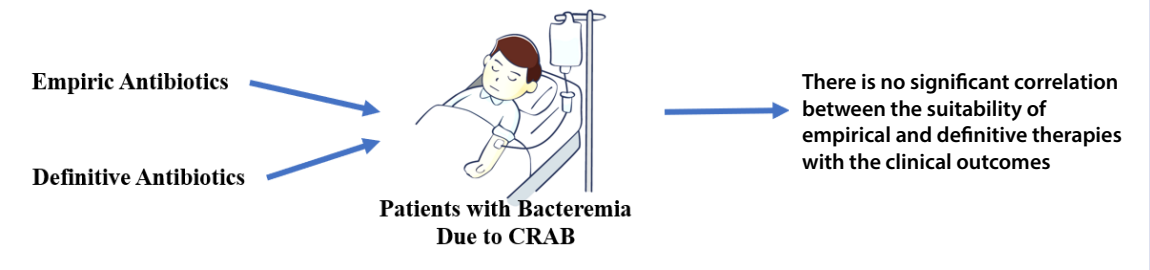
GRAPHICAL ABSTRACT



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