Original Article

Correlation of Antibiotic Resistance with Sepsis Incidence, Hospital Mortality, and Time of Sepsis Onset in Community Acquired Bacterial Pneumonia

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Abstract

Background: Community acquired pneumonia is associated with high morbidity and mortality. Treatment of multidrug-resistant organisms (MDRO) infection in pneumonia is a challenge. Antibiotic resistance is a major factor determining clinical treatment unresponsiveness and rapid progression to sepsis. Septic patients with MDRO have a higher hospital mortality. The correlation of antibiotic resistance with the incidence of sepsis and hospital mortality is yet to be known. This study analyzed the correlation of antibiotic resistance with sepsis incidence, hospital mortality, and time of sepsis onset.

Methods: Retrospective cohort study of patients with community acquired bacterial pneumonia from July-December 2019 at RSUD Dr. Moewardi. The correlation between antibiotic resistance and incidence of sepsis, hospital mortality was tested by using Chi Square and Fisher's exact test correction. Association between two variables with relative risk. Survival analysis and log rank test were used to examine the time differences of sepsis onset.

Results: There was a correlation between antibiotic resistance and incidence of sepsis in community acquired bacterial pneumonia (r = 0.417, p = 0.000) with RR = 4,294 (95% CI 2,886-6,390). The median time of sepsis onset was day 0 in the MDRO group and day 4 in non-MDRO group (p = 0.000).

Conclusion: There is a correlation between antibiotic resistance and incidence of sepsis in community acquired bacterial pneumonia with a fairly strong and significant correlation value. The presence of antibiotic resistance increases the incidence of sepsis fourfold. Antibiotic resistance also affects the time of sepsis onset.

Keywords: Hospital mortality, MDRO, Sepsis, Time of sepsis onset

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INTRODUCTION

Pneumonia is a global health issue. Community pneumonia is associated with high morbidity and mortality. Pneumonia is the leading cause of death from infectious diseases in the United States, with approximately 5–6 million cases of community pneumonia, with 1.1 million patients being treated and 45 thousand patients dying from pneumonia each year. Community pneumonia caused by bacterial infection is the leading cause of mortality in Asia and the most common cause of sepsis. The estimated incidence of community pneumonia is 0.2–1.1% in adult patients, with a mortality rate of 2–14% in developing countries and 7.3% in Asia. Basic health research data in 2013 stated that the incidence and prevalence of pneumonia were 1.8% and 4.5% in Indonesia, respectively. Pneumonia is among the top 10 diseases requiring hospitalization with a crude fatality rate of 7.6%, the highest compared to other diseases in Indonesia. The mortality rate for community pneumonia in outpatients is 2%, inpatients is 5–20%, and even higher in intensive care patients, which is >50%.[1–4]

Pathogens normally present only in the hospital setting have emerged in the community in the last twenty years, including methicillin-resistant Staphylococcus aureus (MRSA), multidrug-resistant Pseudomonas aeruginosa, or extended-spectrum β lactamase producing Enterobacteriaceae (ESBL).[2]

Antibiotic resistance is a natural phenomenon in bacteria which is unstoppable. The antibiotic resistance crisis occurs because antibiotics tend to lose their efficacy due to the spread of resistance among pathogenic bacteria. This resistance is mainly due to the overuse and inappropriate use of antibiotics and their widespread use in agriculture and the food industry. The increasing elderly population makes the use of antibiotics increase with the number of patients being hospitalized. This makes patients more prone to the hospital environment, causing an increase in the number of nosocomial pathogen infections.[2,5]

Pneumonia therapy in multi-drug resistant organism (MDRO) infection is a current challenge. Antibiotic resistance is a significant factor determining clinical unresponsiveness to treatment and the rapid sepsis and septic shock progression. Septic patients with MDRO infection had a higher risk of in-hospital mortality. Drug resistance is common in gram-negative infections. Gram-negative bacterial infection in community pneumonia often causes respiratory failure, acute respiratory distress syndrome (ARDS), sepsis, and septic shock.[2,5,6]

Zilberberg MD et al. found that MDRO infection was an important determinant of inadequate therapy associated with a threefold increase in in-hospital mortality.[7] Tores A et al. (2015) found that sepsis in MDRO infection was significantly associated with inadequate therapy. In addition, the mortality rate for sepsis with drug resistance has doubled.[8] Prina E et al stated that MDRO infection was significantly associated with increased mortality.[9]

Study addressing relationship between antibiotic resistance and sepsis and hospital mortality in community-acquired bacterial pneumonia has never been carried out, so it is interesting to conduct research.

METHODS

This study is a retrospective cohort study by collecting medical record data of patients with community acquired bacterial pneumonia from July through December 2019 at Dr. Moewardi General Regional Hospital Surakarta. Total sampling method was applied with the inclusion criteria of patients aged 18–64 years, undergoing hospitalization with a diagnosis of community pneumonia, and having sputum culture results and antibiotic resistance. The exclusion criteria were incomplete medical records, currently undergoing treatment for pulmonary tuberculosis, on steroid and oral chemotherapy, having a Charlson comorbidity index (CCI) score of 4, receiving empiric antibiotic therapy, not following the community pneumonia antibiotic guidelines of the Indonesian Lung Doctors Association (Indonesian Lung Doctors Association) receiving initial therapy for sepsis which did not comply with The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).

The dependent variable in this study was sepsis, hospital mortality, and the time of onset of sepsis, while the independent variable was antibiotic resistance. The relationship between two nominal variables was tested by using the Chi-Square test with Fisher's exact test correction. The magnitude of association between two variables was estimated with a relative risk (RR). Survival analysis and log-rank test were used to examine the differences between the two-time curves for the onset of sepsis. All statistical tests used a 95% confidence interval value or a value limit of the significance of $P<0.05$.

RESULTS

The study included 220 patients who met the inclusion criteria. The research subjects were assigned into two groups, the MDRO group and the non-MDRO group respectively. Each group was evaluated for the occurrence of sepsis, the time of sepsis, and death in the hospital. The flow of the results of this study can be seen in Figure 1.

Participant’s characteristics of this study included gender, age, CCI score, and type of germ. Non-MDRO group had the highest number of male patient (64.8%), while MDRO group had the highest number of female participant (39.5%). The mean age in the MDRO group was 47.24 years, while in the non-MDRO group was 49.32 years.

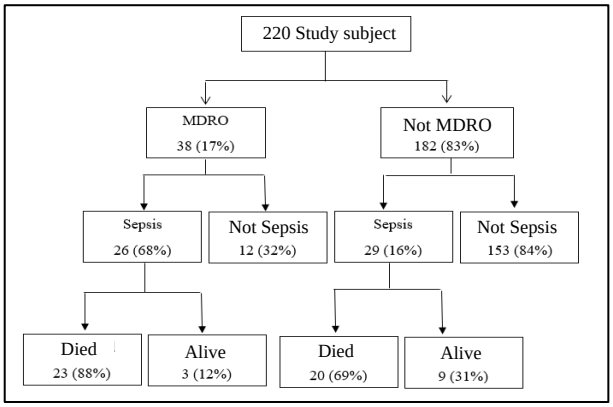

Figure 1. Flow of research results

The highest CCI score in the MDRO group was 1 at 34.2%, while in the non-MDRO group, the highest CCI score was 0. The MDRO group had the most comorbid of cerebrovascular disease at 15.8%. The non-MDRO group had the most comorbid of diabetes mellitus without complications at 16.5%. All of the above baseline data did not have a significant correlation in the two groups except for the CCI scores for the moderate and severe chronic liver disease, which, although it had a significant correlation (*P*=0.023), the correlation was very weak (r=0.152).

The most common type of MDRO bacteria was Acinetobacter baumannii at 21.1%, followed by Klebsiella pneumonia ESBL (+) and Escherichia coli with the same number at 18.4%. The non-MDRO group had the most types of bacteria, Klebsiella pneumonia at 37.9%, followed by Pseudomonas aeruginosa at 12.6% and Enterobacter cloacae at 9.9%. Participant's characteristics is presented in Table 1.

Table 2. Correlation between antibiotic resistance and sepsis

Antibiotic resistance	Sepsis		Total	r	*P*
	Yes	No			
MDRO	26 (47,3%)	12 (7,3%)	38 (17,3%)	0,417	0,0001
Not MDRO	29 (52,7%)	153 (92,7%)	182 (82,7%)		
Total	55 (100%)	165 (100%)	220 (100%)		

The correlation test between antibiotic resistance and sepsis in this study revealed r=0.417 and *P*=0.0001, which implies a significant correlation with a fairly strong correlation value (r=0.417) with a unidirectional relationship and RR=4.294 (95% CI=2.886–6.390). The correlation between antibiotic resistance and sepsis is outlined in Table 2.

The correlation test between antibiotic resistance and hospital mortality in this study revealed r=0.229 and *P*=0.081, which implies no significant correlation with the RR=1.283 (95% CI=0.969–1.699). The correlation between antibiotic resistance and hospital mortality is presented in Table 3.

Table 3. Correlation between antibiotic resistance and mortality in hospital

Antibiotic resistance	Died in the hospital		Total	r	*P*
	Died	Alive			
MDRO	23 (53,5%)	3 (25%)	26 (47,3%)	0,229	0,081
Not MDRO	20 (46,5%)	9 (75%)	29 (52,7%)		
Total	43 (100%)	12 (100%)	55 (100%)		

The median occurrence of sepsis in the MDRO group was 0 days (95% CI=0.000–0.000), while the non-MDRO group was 4 days (95% CI=3.402–4.598), with the log-rank test results revealed *P*=0.0001 which suggests that there was a difference in the median time of occurrence of sepsis in both groups.

Table 4. Median and log-rank test for the time of sepsis

Antibiotic resistance	Median		*P*
	95% *Confidence Interval*		
	Lower Bound	*Upper Bound*	
MDRO	0.000	0.000	0,0001
Not MDRO	3.402	4.598	
Total	0.683	3.317	

The median and log-rank test for the time of sepsis is delineated in Table 4. The Kaplan Meier curve for the time of sepsis is described in Figure 2.

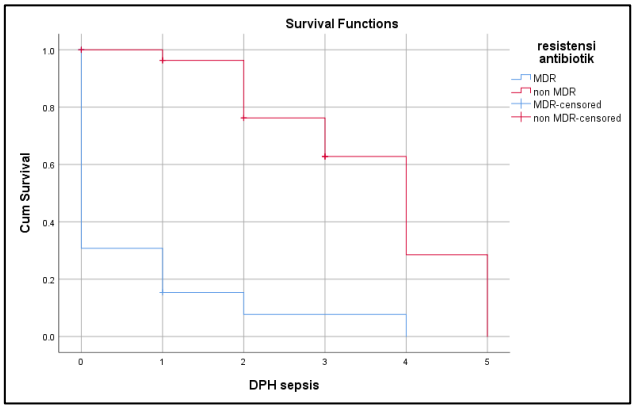

Figure 2. Kaplan Meier curve at the time of sepsis

Table 1. Characteristics of participants

Variables	MDRO n=38 (%)	Not MDRO n=182 (%)	r	*P*
Gender				
Male	23 (60.5%)	118 (64.8%)	0,034	0,615
Female	15 (39.5%)	64 (35.2%)		
Mean age	47.24	49.32	-	0,346
CCI Score				
Score 0	12 (31.6%)	75 (41.2%)	-	
Score 1	13 (34.2%)	67 (36.8%)	-	0,220
Score 2	8 (21.1%)	31 (17.0%)	-	
Score 3	5 (13.2%)	9 (4.9%)	-	
Myocardial infarction	0 (0%)	10 (5.5%)	0,099	0,139
Congestive heart failure	5 (13.2%)	23 (12.6%)	0,006	0,930
Peripheral artery disease	0 (0%)	1 (0.5%)	0,031	0,647
Dementia	0 (0%)	0 (0%)	-	-
Cerebrovascular disease	6 (15.8%)	28 (15.4%)	0,004	0,950
Chronic obstructive pulmonary disease	2 (5.3%)	9 (5%)	0,005	0,941
Connective tissue disease	0 (0%)	1 (0.5%)	0,031	0,647
Uncomplicated diabetes mellitus	5 (13.2%)	30 (16.5%)	0,034	0,610
Decubitus ulcer	0 (0%)	2 (1.1%)	0,044	0,516
Mild chronic liver disease (Child Pough A)	0 (0%)	0 (0%)	-	-
Hemiplegia	0 (0%)	0 (0%)	-	-
Chronic renal failure	4 (10.5%)	6 (3.3%)	0,130	0,052
Diabetes mellitus with complications	1 (2.6%)	2 (1.1%)	0,050	0,459
Malignant tumor without metastases	2 (5.3%)	2 (1.1%)	0,117	0,081
Leukemia	2 (5.3%)	7 (3.8%)	0,027	0,688
Lymphoma	1 (2.6%)	5 (2.7%)	0,003	0,968
Moderate and severe chronic liver disease (Child Pough B-C)	2 (5.3%)	1 (0.5%)	0,152	0,023
Malignant tumor (cancer), metastases	0 (0%)	0 (0%)	-	-
AIDS	0 (0%)	0 (0%)	-	-
Types of germs				
Klebsiella pneumoniae	2 (5.3%)	69 (37.9%)	-	-
Klebsiella pneumoniae ESBL (+)	7 (18.4%)	0 (0%)	-	-
Pseudomonas aeruginosa	4 (10.5%)	23 (12.6%)	-	-
Acinetobacter baumanii	8 (21.1%)	14 (7.7%)	-	-
Staphylococcus aureus	1 (2.6%)	9 (4.9%)	-	-
MRSA	2 (5.3%)	0 (0%)	-	-
Staphylococcus haemolyticus	4 (10.5%)	9 (4.9%)	-	-
Escherichia coli	7 (18.4%)	13 (7.1%)	-	-
Escherichia coli ESBL (+)	2 (5.3%)	0 (0%)	-	-
Enterobacter cloacae	1 (2.6%)	18 (9.9%)	-	-
Others	0 (0%)	27 (14.8%)	-	-
Sepsis	26 (68.4%)	29 (15.9%)	-	-
Sepsis and died	23 (88.4%)	20 (68.9%)	-	-
Time of onset of sepsis (median)	0	4	-	-

DISCUSSION

The MDRO group had 81.5% gram-negative bacteria (31 patients), while the non-MDRO group had 87.3% (159 patients). Gram-negative bacteria affected majority of patients in both groups. The result is comparable to SARI sentinel surveillance data which obtained from several hospitals in Indonesia (2012), and Luan Y et al., which stated that gram-negative bacteria are the most common cause of community pneumonia.[1,3,4]

MDRO infection in this study was 17% which is higher than result reported by Prina E et al. (2015), which found 6% of the causes of community pneumonia were MDRO bacteria but almost similar to a study by Capsoni N et al. which found MDRO

infection up to 17% in community pneumonia. Sepsis caused by MDRO in this study was 47% higher than a study by Tores A et al., which revealed that MDRO caused only 10% of the incidence of sepsis in community pneumonia patients. This may be due to the differences in the germ map in each region.[8–10]

This study found a significant correlation (*P*=0.0001) between antibiotic resistance and the incidence of sepsis with a fairly strong correlation value (r=0.417) and a unidirectional relationship in which if antibiotic resistance increased, the incidence of sepsis also increased. The presence of risk factors for antibiotic resistance increased the risk of sepsis by four times (RR=4.294; 95% CI=2.886-6.390) compared to those without risk factors for antibiotic resistance.

This may be due to ineffective therapy in eliminating MDRO germs, as reported by Torres A et al., which stated that MDRO sepsis was significantly associated with the administration of therapy that was ineffective in eliminating bacteria (*P*<0.001). Zilberberg MD et al. also revealed that MDRO infection had a strong relationship with the administration of inappropriate therapy (AOR=13.05; 95% CI=7.00-24.31). Failure to eliminate bacteria keeps the inflammatory process running and causes sepsis. Study that addresses the link between risk factors of antibiotic resistance with sepsis has never been conducted.[7,8]

This study found no significant correlation between antibiotic resistance and hospital mortality (*P*=0.081). A relative risk value of 1 (RR=1.283;95% CI=0.969-1.699) indicated that antibiotic resistance was not a risk factor for in-hospital mortality. The result disproves a study conducted by Capsoni et al., which stated that MDRO infection was an independent risk factor related to death in hospitals in sepsis patients (OR=4.6; *P*<0.001). In addition, the study by Prina et al. stated that MDRO infection was independently associated with an increased risk of 30-day mortality (AOR=2.51; 95% CI=1.20-5.25; *P*=0.015), they also only included MDR bacteria of Pseudomonas aeruginosa, ESBL, and MRSA in their study while in this study it was not limited to those three. In addition, in Prina et al.'s study, the mortality criteria used were mortality from any cause. In contrast, in this study, death in the hospital was used as the leading cause of sepsis.[9,10]

The absence of correlation between antibiotic resistance and hospital mortality in this study suggests that there may be other factors affecting hospital mortality. Firmansyah MA at Cipto Mangunkusumo Hospital reported significant independent predictors of mortality in multivariate analysis, including severe pneumonia (OR=29.42; 95% CI=20.81-41.58), sepsis (OR=3.65; 95% CI=2.57-5.19), respiratory failure (OR=3.2; 95% CI=1.9-5.37), CCI score 5 (OR=2.25; 95% CI=1.6-3.15) and albumin levels <3 g/dL (OR=1.42; 95% CI=1.04-1.95) in community pneumonia patients.[11] Presence of sepsis, the severity of sepsis, or severity of comorbidities may influence in-hospital mortality in this study.

Most MDRO germs in this study were Acinetobacter baumannii at 21.1%, where a study by Zilberberg MD et al. stated that MDR Acinetobacter baumannii increased the risk of ineffective therapy more than five times (ARRR=5.5; 95% CI=4.0-7.7; *P*<0.001) and inappropriate therapy almost doubled hospital mortality (ARRR=1.8; 95% CI=1.4-2.3; *P*<0.001). Busani S et al. also found in a multivariate analysis of MDR infection with Acinetobacter baumannii an increased risk of 30-day mortality (OR=3,197) in septic shock due to MDRO infection.[12,13] The presence of Acinetobacter baumannii infection, which was commonly found in the MDRO group, may have a relationship with hospital mortality in this study.

The median time of occurrence of sepsis in this study in the MDRO group was 0 days (95% CI=0.000-0.000), while in the non-MDRO group was 4 days (95% CI=3.402-4.598) with the log-rank test revealed a significant difference in the median time of occurrence of sepsis in both groups (*P*=0.0001). The incidence of sepsis in the MDRO group on day 0 was more than 50% after having risk factors for antibiotic resistance, while more than 50% of the incidence of sepsis in the non-MDRO group was on day 4. This study shows that the MDRO group had a higher risk of developing sepsis faster than the non-

MDRO group, although, in this study, the early onset of sepsis was difficult to predict with certainty because participants might have had sepsis for several days before being hospitalized. Administration of antibiotics before participant is hospitalized may also affect the onset of sepsis, which was not included in study analysis. The survival analysis of sepsis has never been done before.

LIMITATION

The limitation of this study is the retrospective cohort design in which observations were made indirectly, only relying on medically recorded data, which cannot be controlled for data quality. In addition, indirect observations make it difficult to accurately determine onset of sepsis. This study also does not rule out the influence of genetic factors, microbiome factors, or environmental factors that may influence the occurrence of sepsis and hospital mortality.

CONCLUSION

This study suggests that there was a relationship between antibiotic resistance and the incidence of sepsis in community-acquired bacterial pneumonia, but there was no significant relationship between antibiotic resistance and hospital mortality. Antibiotic resistance affects the timing of sepsis in community-acquired bacterial pneumonia.

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CONFLICT OF INTEREST

None.

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REFFERENCES

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