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Pediatric Sepsis by Multi-Drugs Resistance Organism: Length of Stay, Prognosis, and Hospitalization Cost Evaluation

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ABSTRACT

Multi-Drugs Resistance (MDR) is a condition where bacteria are resistant to at least one type of antibiotic from three classes of antibiotics. One of the organisms included in the MDR is an Extended-Spectrum Beta Lactamase (ESBL) producing bacteria. Multi-drug resistance bacteria have been widely reported globally as a cause of severe infections. Still, information on the comparison of Length of Stay (LOS), hospitalization costs, and outcome status of the patients infected with MDR bacteria and infected with non-MDR bacteria is still limited. This study aimed to compare LOS, treatment costs, and outcome status of the BPJS pediatric sepsis patients infected with MDR bacteria and non-MDR bacteria in Dr. Soetomo General Academic Hospital, Surabaya. This study was observational research using medical records of hospitalized pediatric patients with BPJS insurance at the Dr. Soetomo General Academic Hospital from January 2015-July 2018 (n=49). The variables of this study were microbiology culture results and antibiotics sensitivity tests, LOS, INA-CBGs rates provided by BPJS, actual hospitalization cost, and outcome status. Statistical analyses were performed to compare LOS, INA-CBGs, actual cost, and outcome status of patients infected by MDR bacteria (ESBL and non-ESBL) or non-MDR bacteria. The results of this study include the average LOS value of non-MDR, MDR ESBL, and MDR non-ESBL cases, which were 30.55; 46.18; 32.41. Comparison of INA-CBGs and the actual cost of the three were 0.886 and 0.990, respectively, with $p>0.05$, and each percentage of the mortality patients was 27.3%, 45.5%, and 40.7%. There was no significant difference in the hospitalization cost and outcome status of patients infected by MDR bacteria (ESBL and non-ESBL) and non-MDR bacteria. Each percentage of LOS was also not much different. Still, MDR patients tended to be treated longer, require higher costs, and have a worse prognosis.

Keywords: MDR, ESBL, LOS, BPJS

INTRODUCTION

Multi-Drugs Resistance (MDR) bacteria is a condition where bacteria are resistant to at least one type of antibiotic from three classes of antibiotics. This resistance can be caused by several things: the use of antibiotics that do not meet the predetermined rules, namely the correct dose, the proper diagnosis, and the right bacteria. Many antibiotics are used for therapy, resulting in the selection of pathogenic bacteria that are resistant to many drugs. Two mechanisms can cause this: Bacteria can accumulate various genes, each coding resistance to one drug, in a single cell. This accumulation usually occurs in plasmid resistance (R); An increase in the expression of genes that encodes the MDR bacteria to pump out various drugs.[1]

Multi-drugs resistance cases have increased significantly in recent years. Data in 2009 shows Indonesia ranking 8th out of 27 countries with the highest MDR predicate in the world, while in Dr. Soetomo General Academic Hospital, Surabaya, the prevalence of MDR is mainly due to the bacteria *K.pneumonia* (also a cause of Urinary Tract Infection (UTI) in pediatric patients), has reached 60.7%.[2]

Extended-Spectrum Beta lactamase (ESBL) is an enzyme that can hydrolyze Penicillin; first, the second, and the third generation of Cephalosporins; and Aztreonam groups (excluding cephamycin and Carbapenem). Extended-spectrum beta lactamase is most widely produced by *Enterobacteriaceae* (mainly *Escherichia coli*) and *Klebsiella pneumonia*. Most of the published research today came from more than 30 different countries, all of which reflect the distribution of organisms that produce ESBL worldwide.[3]

Antibiotic resistance is also an economic burden to the health care system. Infections that are resistant to various drugs make the treatment costs more expensive and can also prolong the use of health care.[4] Based on this, the researchers aim to compare the duration and cost of hospitalization and the mortality of pediatric sepsis patients, with MDRO agents or not. The targeted observation was patients

with BPJS insurance in the Dr. Soetomo General Academic Hospital ward, Surabaya.

METHODS

This research was an observational study with data collected retrospectively. Sampling was done by purposive sampling. The existing samples were divided into non-MDR, ESBL, and MDR (non-ESBL). Inclusion criteria were medical records of patients who had microbiological culture examination data (sterile culture results were not included in the inclusion criteria), financial data, length of treatment, and mortality data. Financial data is a breakdown of total costs for all patient care provided through the hospital patient accounting system. Overall hospital costs for patients include drugs, laboratory and medical tests, inpatient rooms, and other patient care procedures. All fees were reported in rupiah. The total costs reported were general and not only related to the cost of each diagnosis of infection suffered. Patient outcome status was the patient's condition after undergoing treatment in the hospital with the category of survivors and non-survivors. The number of samples obtained was 49 samples. Total costs and the difference with BPJS budgeting were then calculated through the INA-CBGs system.

Duration of treatment data is presented in the form of mean±standard deviation to determine the length of treatment range for each category. Normality tests for data on maintenance costs used Shapiro-Wilk. Data that were not normally distributed were analyzed using the Kruskal-Wallis test and were considered statistically significant if the p-value <0.05. Data for each category were displayed as a percentage. Gender, age, and type of bacteria were displayed as characteristic data.

This study was approved by the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital with number 0316/KEPK/V/2018. Statistical tests used SPSS 13.0 version.

RESULTS AND DISCUSSIONS

This study used 49 samples with characteristics, as shown in Table 1. Characteristic data comprised age, gender, and bacteria as a source of pathogenic infection for patients. There was a variation in the age of the patients, with the youngest and eldest range of 0 and 16 years, especially in patients with MDR pathogen non-ESBL, which were also more prominent in number.

Table 1. Subject characteristics and pathogenic bacteria

	Group			Total
	Non-MDR	ESBL Pathogen	Non-ESBL MDR Pathogen	
Age (mean)	11 (4.18±4,579)	11 (2.55±3,387)	27 (2.63±4,096)	49
Gender				
Male	8 (72.7%)	2 (18.2%)	14 (51.9%)	24 (49%)
Female	3 (27.3%)	9 (81.8%)	13 (48.1%)	25 (51%)
Gram-negative bacteria				
Acinetobacter baumanii	3 (27.3%)	0 (0%)	5 (18.5%)	8 (16.3%)
Acinetobacter junii	0 (0%)	0 (0%)	1 (3.7%)	1 (2.0%)
Aeromonas hydrophila	1 (9.1%)	0 (0%)	0 (0%)	1 (2.0%)
Burkholderia cepacia	1 (9.1%)	0 (0%)	2 (7.4%)	3 (6.1%)
Enterobacter cloacae	1 (9.1%)	0 (0%)	0 (0%)	1 (2.0%)
Eschericia coli	0 (0%)	4 (36.4%)	0 (0%)	4 (8.2%)
Klebsiella pneumoniae	1 (9.1%)	7 (63.6%)	0 (0%)	8 (16.3%)
Pseudomonas aeruginosa	3 (27.3%)	0 (0%)	0 (0%)	3 (6.1%)
Gram-positive bacteria				
Corynebacterium bovis	0 (0%)	0 (0%)	1 (3.7%)	1 (2.0%)
Kocuria kristinae	1 (9.1%)	0 (0%)	0 (0%)	1 (2.0%)
Staphylococcus aureus	0 (0%)	0 (0%)	3 (11.1%)	3 (6.1%)
Staphylococcus epidermidis	0 (0%)	0 (0%)	5 (18.5%)	5 (10.2%)
Staphylococcus hemoliticus	0 (0%)	0 (0%)	5 (18.5%)	5 (10.2%)
Staphylococcus hominis	0 (0%)	0 (0%)	4 (14.8%)	4 (8.2%)
Staphylococcus klosii	0 (0%)	0 (0%)	1 (3.7%)	1 (2.0%)

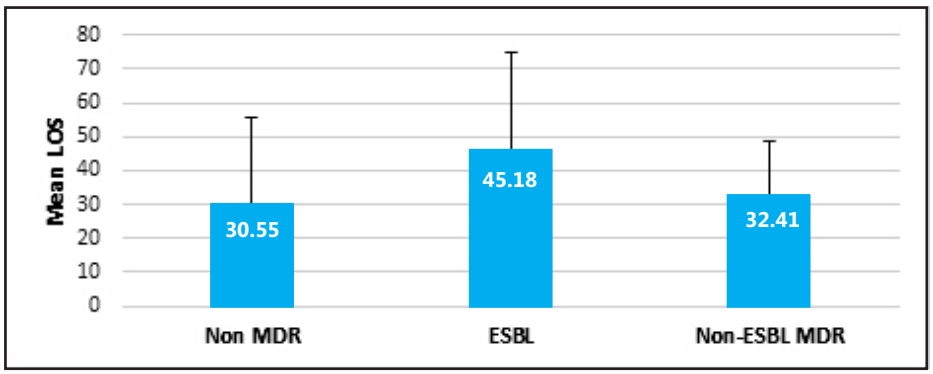

Figure 1. The distribution of LOS based on the resistance pattern of pathogen
*Kruskall-Wallis test (p-value 0.771)

The number of female patients was not much different from male patients, with a percentage of 51% and 49%, respectively. This result shows that the gender of the patients does not influence the type of infection. Table 1 details the gender of pediatric patients with sepsis and results in almost the same number. Also, the predominance of bacteria that cause non-MDR and MDR infections (ESBL and non-ESBL) in pediatric sepsis patients was mentioned. Bacteria that caused most infections in the non-MDR group were *Acinetobacter baumanii* (27.3%) and *Pseudomonas aeruginosa* (27.3%). The bacteria that caused infection in the ESBL group were *Klebsiella pneumonia* (63.6%) and *Escherichia coli* (36.4%). In contrast, the dominant bacteria in the non-ESBL MDR group were *Staphylococcus epidermidis, Staphylococcus hemoliticus*, and *Acinetobacter baumanii*, with the same percentage (18.5%). Coagulase-negative *Staphylococcus* (ConS) was not found on the patient's medical record, and neither was Carbapenemase.

Figure 1 describes the results of the analysis of the Length of Stay (LOS) of pediatric patients suffering from sepsis from both MDR and non-MDR, in which the three groups were equally broad. However, the mean LOS value of the MDR ESBL group was higher, meaning ESBL patients had more extended treatment compared to patients infected with non-MDR and MDR non-ESBL bacteria.

Three categories of inter-group treatment costs were analyzed, naming: actual cost, INA-CBGs, and the difference between real cost and INA-CBGs. Kruskal-Wallis test results showed no differences in the costs of INA-CBGs, actual costs, and the difference in costs between groups (p>0.05) (Table 2). The wide range of each group causes this. However, the minimum treatment costs needed by the MDR group showed a higher rate than the non-MDR group, which means there is a tendency for MDR patients to need higher treatment costs.

Analysis of the patient's outcome status data was divided into two categories: survivors and

Table 2. Comparison of intergroup costs using the Kruskal-Wallis test

	Group	n	Median (min-max)	p-value
INA CBGs	Non-MDR pathogen	11	20.718.900 (4.991.700 – 178.007.700)	0.886
	ESBL pathogen	11	32.236.700 (4.851.800 – 178.007.700)	
	Non-ESBL MDR pathogen	27	24.581.400 (7.833.800 – 381.777.760)	
Real cost	Non-MDR pathogen	11	42.290.900 (4.917.700 – 213.986.941)	0.990
	ESBL pathogen	11	32.669.740 (7.013.700 – 256.237.413)	
	Non-ESBL MDR pathogen	27	42.355.322 (10.585.700 – 381.777.760)	
Difference	Non-MDR pathogen	11	0 (-35.979.241 – 17.873.352)	0.921
	ESBL pathogen	11	0 (-222.924.613 – 41.490.828)	
	Non-ESBL MDR pathogen	27	0 (-57.175.457 – 86.988.336)	

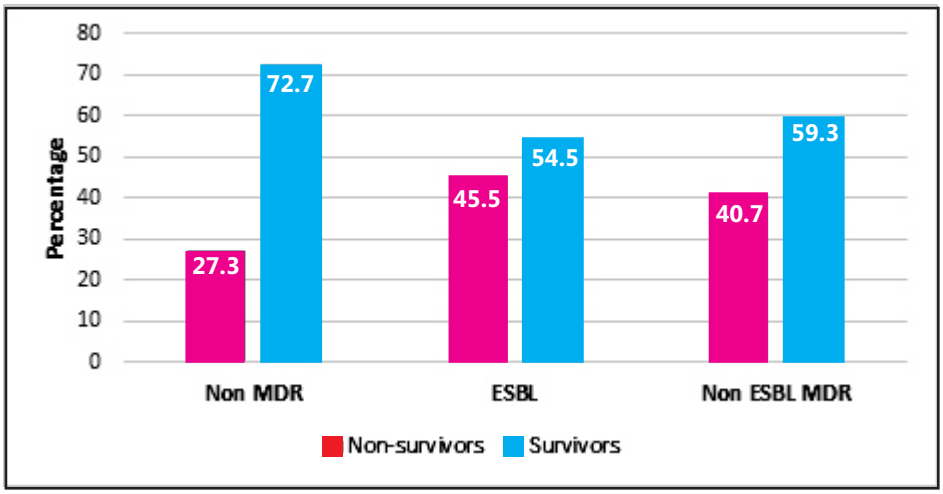

Figure 2. Survival comparison between resistant types of pathogen

non-survivors. Figure 2 shows that the outcome status of patients between groups was not significantly different (p=0.735 where p>0.05 was deemed not significant) because the number of survivors in each group was more than non-survivors. Still, the percentage of results showed a tendency for patients to be infected more by MDR bacteria (both ESBL and non-ESBL), having worse conditions (even ending up with death) than patients in the non-MDR group.

The incidence of infection by MDR-producing bacteria, including ESBL, is recently increasing worldwide; therefore, many studies have examined the risk factors for ESBL due to the following conditions:[5] Severity of the disease; LOS in hospital; Invasive medical equipment (hemodialysis, urine catheters, endotracheal tubes, and central venous lines); Antibiotics.

Antibiotic resistance is also an economic burden to the health care system. Infection resistance to various drugs causes treatment costs to be more expensive and prolongs the use of health care facilities.[4]

The characteristic data in Table 1 show that the number of MDR patients with non-ESBL bacteria is more significant than non-MDR and MDR ESBL patients. A variety of pathogenic bacteria can cause this. Bacteria that caused the most infections in the non-MDR group were *Acinetobacter baumanii* (27.3%) and *Pseudomonas aeruginosa* (27.3%). *Acinetobacter* is a species of Gram-negative bacteria that can cause infection in hospitalized patients and often become resistant to many antibiotics. Still, in this study, *Acinetobacter* bacteria found have not reached the stage of inducing resistance to many antibiotics.[6] The bacteria that caused infection in the MDR ESBL group were *Klebsiella pneumonia* (63.6%) and *Escherichia coli* (36.4%). In contrast, the dominant bacteria in the MDR non-ESBL group were *Staphylococcus epidermidis, Staphylococcus hemoliticus,* and *Acinetobacter baumanii,* with the same percentage (18.5%). The previous studies also mentioned that most ESBL were produced by *Enterobacteriaceae* (primarily *Escherichia coli*) and *Klebsiella pneumonia*.[3]

Comparison of LOS in these three groups showed the same treatment length, which is due to the wide range in each group. There are non-MDR cases that require a long period of treatment. One of the things that can affect the length of treatment for non-MDR sepsis cases is the complications of the disease and the medical treatment needed, causing complicated and long-term care. The average results showed that MDR patients were treated longer than non-MDR patients. A comparison of medical costs and outcome status between infected patients with non-MDR, MDR ESBL, and non-ESBL bacteria showed no significantly different results. The cost required by the three groups was considerable, but from the minimum costs perspective needed for the three groups, MDR patients had a higher actual cost than non-MDR. It can be concluded that MDR patients need more medical treatment costs, proving the statement of previous studies that antibiotic resistance is also an economic burden to the health care system. Various drug resistance makes treatment costs more expensive and can also extend the use of health care facilities.[4] Centers for diseases control and prevention stated that antibiotic-resistant infections could be complicated and sometimes impossible to treat. In addition to increased morbidity and mortality, resistant infections also add considerable costs to the U.S. health care system. These infections require extended hospital stays, additional follow-up visits to

health care providers, and the use of treatments that may be more costly and potentially more toxic.[6]

A few non-MDR cases require high costs. This is caused by medical treatment needed due to the complications of the infection, affecting statistical results, resulting in no significant difference between the three groups' INA-CBGs, actual cost, or the difference between the two. Figure 2 shows that the outcome status of patients between groups was not significantly different (p=0.735) because the number of discharged patients in each group was more than patients with poor prognosis. Still, the results showed that patients infected by MDR bacteria, both ESBL and non-ESBL, tend to have poorer prognoses than patients in the non-MDR group. This result indicates that bacteria resistant to many antibiotics have a poorer prognosis compared to bacteria that are not resistant to many drugs, in line with previous studies that concluded that the mortality rate of patients infected with *E.coli* producing ESBL bacteria was higher than patients infected by non-ESBL *E.coli*.[7]

The results above only slightly describe the management of both MDR and non-MDR pediatric patients suffering from sepsis being treated in Dr. Soetomo General Academic Hospital due to the small number of samples. This study also does not divide groups based on the medical treatment given to the patient. Further studies with larger sample sizes and groups based on medical treatment are needed.

CONCLUSIONS AND SUGGESTIONS

The MDR cases are a matter of concern. Although this study result shows no significant difference in terms of duration, cost of care, and outcome status of MDR and non-MDR patients, it can be seen that MDR cases tend to experience longer LOS, higher treatment costs, and worse prognosis. Further study with a more significant number of samples is needed to describe the condition of the treatment of pediatric sepsis patients in Dr. Soetomo General Academic Hospital. Uniformity of the patient's age, primary and secondary diagnosis, and medical measures are essential for future research data.

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