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Original Article

Characteristics and Risk Factor of Multidrug-Resistant-Organism Infection in the Pediatric Intensive Care Unit of Dr. Kariadi Hospital Semarang

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Abstract

Background : The Pediatric Intensive Care Unit (PICU) that treats critical patients with various invasive procedures is a potential place for Multidrug Resistant Organism (MDRO) infections. This spesific unit, especially in tertiary care facilities may have higher prevalence of MDRO than non-PICU settings, causes serious disease and mortality. The aims of this study was to describe the characteristics and risk factor of MDRO infection in the PICU of dr. Kariadi Hospital Semarang,
Methods : Retrospective study in patients aged 1 month – 18 years with growth of germs on culture results during 2021–2022. Demographic data, use of central venous catheters and ventilator, length of stay, duration of antibiotic usage, and history of major surgery were investigated from medical records. The amount of risk expressed by the Odds Ratio (OR).
Results : From 544 culture examinations, 199 (36.5%) germs grew, consisting of 79 MDRO isolates (39.7%) and 120 non-MDRO isolates (60.3%). Gram-negative bacteria were found in 140 samples (70.4%) with *Klebsiella pneumoniae* as the most common germ (15.1%) and respiratory tract infection (56.3%) being the most common infection diagnosis. As many as 24 of 30 (80%) isolates that grew *Klebsiella pneumoniae* were MDRO. Mechanical ventilator use (OR 2.15; 95% CI 1.07 – 4.3; p=0.043) and length of stay in the PICU (OR 2.44; 95% CI 1.21 – 4.96; p=0.018) are risk factors for MDRO infection.
Conclusion : *Klebsiella pneumoniae* is the most common germ found from culture isolates and respiratory tract infection is the most common diagnosis. The use of mechanical ventilators and length of stay in the PICU are risk factors for MDRO infection.

Keywords : risk factor, culture, MDRO, PICU, antibiotic resistance

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INTRODUCTION

Multidrug Resistant Organism (MDRO) is defined as insensitivity or resistance of a microorganism to several antibiotic drugs.[1,2] Drug resistance can be occur due to natural phenomenon, selective pressure, and widespread distribution of pathogenic microorganisms.[3] These are several microorganism categorized as MDRO: Extended-spectrum beta-lactamase producing Enterobacteriaceae (ESBLs), methicilin-resistant Staphylococcus aureus (MRSA), Pseudomonas aeruginosa, Acinetobacter baumannii, Vancomycin-resistant Enterococci (VRE), dan Carbapenem-resistant enterobacteriaceae (CRE).[4]

Rising number of MDRO cases creating a emergent global problem nowadays.[5] World Health organization (WHO) predicted that MDRO cases causing 700.000 deaths in general population, while around 200.000 deaths in new born babies every year. It is estimated that 23.000 and 25.000 deaths per year in United States of America (USA) and Europe.[6] In Indonesia, prevalence of MDRO cases are rising every year. Based on National Survey on Antimicrobial Resistance by Ministry of Health in 2016, the prevalence of MDRO case especially for *E. coli* and *K. pnemunoiae* resulting ESBL are 50–82%. *Indonesia Antimicrobial Surveillance System* (INASS) in 2019–2020 showed that prevalence of cephalosporin-resistant and fluoroquinolone-resistant *E. coli* are 66.7% and 65.6%, respectively. While the number are higher for *K. pneumoniae*, 74.4% and 53.2%, respectively.[7,8]

Pediatric Intensive Care Unit (PICU) is a dedicated unit aimed to provide best care for critically ill patients with various invasive procedures and highly-potential place for MDRO cases to be found.[9] Immature immune system in children, prolong intensive care, such as intubation and central-venous catheter, and inappropriate wide-spectrum antibiotics are several causes that create PICU patients are highly vulnerable of being a MDRO case. MDRO cases are emerging problem in healthcare facilities, that causing more mortality, morbidity, prolonged length-of-stay, and increasing healthcare costs.[5] A study in Jordan showed that sepsis caused by MDRO had higher mortality than non-MDRO (60% vs 13%). Studies in Taiwan also showed that the Gram negative MDRO group had higher morbidity in neurological sequelae, kidney disease, use of parenteral nutrition, than the Non MDRO group. This study also found a longer duration of hospitalization in sepsis patients with MDRO compared to non-MDRO sepsis patients (27.6 days vs 20.7 days).[10]

MDRO infection case in PICU setting are vary. Infection pattern, hospitalized-cases complexity, bacterial pattern, and local antibiotic sensitivity creating vast major problem in MDRO infection. Several conditions are predicted to be the risk factor of MDRO indection in PICU setting, such as nutritional status, age, invasive device usage (intubation and mechanical ventilator, central venous catheter, and urine catheter), previous history of major surgical procedure, antibiotic use, and hospitalization period.[11–13]

This study aims to identify the characteristics and risk factor of MDRO infection in PICU setting of Dr. Kariadi General Hospital, which is a tertiary referral hospital in Central Java, where this kind of research has not been carried out much in this hospital. This research hopefully can be used as fundamental consideration for future prevention, management, and research of MDRO infection cases.

METHODS

This research was an analytical observational type with a retrospective approach, carried out in the PICU of RSUP Dr. Kariadi Semarang in all pediatric patients aged 1 month – 18 year during study period (January 2021 – December 2022). Patient with infection diagnosis (respiratory tract infections, abdominal infections, CNS infections, post-operative infections, urinary tract infections, skin infections) were taken based on antibiotic culture and lab results. Research subject characteristics data (gender, diagnosis of infection, type of germ, clinical outcome, and type of specimen) were extracted from medical records. The types of culture specimens taken include sputum, blood and urine specimens. Incomplete medical record data were excluded. Sample selection was carried out by total sampling. Data analysis were done using descriptive analysis and hypothesis testing. Analysis were done by dividing microorganism into two groups, MDRO and non-MDRO group. MDRO group is group of microorganism that has been proven to be resistant to at least one from ≥3 antibiotics.[4] The independent variables in this study were age, nutritional status, use of invasive medical equipment (CVC), use of a mechanical ventilator, length of treatment, duration of antibiotic use, and history of major surgery. Bivariate analysis were done by using Chi Square test. Odd Ratio and 95% Confidence Interval (CI) were defined as the risk of incidence of MDRO infection. This study has been approved by Ethical Committee of Faculty of Medicine, Diponegoro University, Semarang No. 1379/EC/KEPK-RSDK/2022 on January 13rd, 2023.

RESULTS

During the study period, the researcher has been able to register 544 culture examination from various specimens, 199 (36.5%) culture results were successfully grown microorganisms, consisting of 79 isolated MDRO microorganisms and 120 isolated non-MDRO microorganisms. Subjects' characteristics are shown in Table 1. There are 100 (50.3%) men and 99 (49.7%) women in this study. The most commonly found infection diagnosis are 112 cases (56.3%) of respiratory-tract

TABLE 1
Subjects Characteristics

Description		n (%)
Sex	Men	100 (50.3%)
	Women	99 (49.7%)
Clinical Diagnosis	Respiratory tract infection	112 (56.3%)
	Abdominal infection	21 (10.6%)
	Central nervous system infection	20 (10.1%)
	Urinary tract infection	22 (11.1%)
	Post-operative infection	21 (10.6%)
	Skin infection	3 (1.5%)
Causative Bacteria		
Gram-negative	*Klebsiella pneumoniae*	30 (15.1%)
	Pseudomonas Aeruginosa	27 (13.6%)
	Acinetobacter baumani	22 (11.1%)
	Eschericia coli	19 (9.5%)
	Stenotrophomonas maltophilia	18 (9.0%)
	Enterobacter spesies	10 (5.0%)
	Other species	8 (4.0%)
	Serratia marcescens	6 (3.0%)
Gram-positive	Other species	25 (12.6%)
	Staphylococcus epidermidis	17 (8.5%)
	Enterococus spesies	10 (5.0%)
	Staphylococcus aureus	7 (3.5%)
Outcomes	Survive	103 (51.8%)
	Death	96 (48.2%)
Culture specimen	Urine	20 (10.1%)
	Blood	69 (34.7%)
	Sputum	110 (55.3%)

infection, 22 cases (11.1%) of urinary tract infection, 21 cases (10.6%) of postoperative infection and abdominal infection, and 20 cases (10.1%) of central nervous system infection. Gram-negative bacteria were found in 140 sample (70.4%) and gram-positive bacteria were found in 59 sample (29.6%). From all examined culture specimens, *K. pneumoniae* (80%) is the most commonly found in MDRO infection cases.

After assigning each data based on the specimen type, it has been found that sputum is the most frequently examined specimen, followed by blood and urine culture. From 110 examined isolated sputum cultures, 85 of them were taken from patients using mechanical ventilators (773%), and 25 of the specimens were taken from patients without mechanical ventilators (22.7%). Bacterial groups are dominated with gram-negative bacteria with 91 isolate (84%), which 49 of them (44.5%) were assigned to MDRO group and 61 of them (55.5%) were assigned to non-MDRO group. The most commonly found bacterial in sputum culture are *K. pneumoniae* (20.9%). Gram-positive bacteria were found in 18 isolate (16%), which *Coagulase Negative Staphylococcus* has the largest numbers (6.4%).

Analysis results from 69 blood culture isolates, 21 of them are MDRO group isolates (30.4%) and 48 of them are non-MDRO group isolates (69.6%). Thirty five

TABLE 2
MDRO Prevalence in Various Infectious Pathogens

Microorganism		Non MDRO	Non MDRO
Gram-negative	*Klebsiella pneumoniae*	24 (80%)	6 (20%)
	Acinetobacter baumanii	16 (72.7%)	6 (27.3%)
	Pseudomonas Aeruginosa	5 (18.5%)	22 (81.5%)
	Enterobacter spesies	6 (60%)	4 (40%)
	Escherichia coli	16 (88.9%)	3 (11.1%)
	Stenotrophomonas maltophilia	0 (0%)	18 (100%)
	Serratia marcescens	3 (50%)	3 (50%)
Others	*Salmonella spesies*	2 (100%)	0 (0%)
	Chryseobacterium gleum	2 (66.7%)	1 (33.3%)
	Klebsiella aerogenes	0 (0%)	1 (100%)
	Aeromonas veronii bv veronii	0 (0%)	1 (100%)
	Burkholderia cepacia	0 (0%)	1 (100%)
Gram-positive	*Staphylococcus aureus*	0 (0%)	7 (100%)
	Staphylococcus epidermidis	2 (11.8%)	15 (88.2%)
	Enterococus spesies	3 (30%)	7 (70%)
Others	*Staphylococcus haemolyticus*	0 (0%)	7 (100%)
	Staphylococcus hominis	0 (0%)	8 (100%)
	Micrococcus luteus	0 (0%)	1 (100%)
	Streptococcus pneumoniae	0 (0%)	1 (100%)
	Staphylococcus capitis	0 (0%)	5 (100%)
	Staphylococcus cohnii	0 (0%)	1 (100%)
	Streptococcus mitis	0 (0%)	1 (100%)
	Streptococcus pyogenes	0 (0%)	1 (100%)

isolates were gram-positive (51%) and 34 were gram-negative (49%). The most commonly found gram-positive bacteria were *Coagulase Negative Staphylococcus* (24.6%) and *Staphylococcus epidermidis* (14.5%), while the most commonly found gram-negative bacteria were *A. baumanii* (11.6%), *P. aeruginosa* (10.1%), and *E. coli* (8.7%).

Urine specimens examination revealed that 9 out of 20 isolate were assigned to MDRO groups (45%). Fourteen isolates were gram-negative bacteria (70%) with the most commonly found bacteria are *E. coli* (30%) and *K. pneumoniae* (20%), while for gram-positive bacteria, *Enterococcus sp.* is the most common found in urine specimens.

Table 3 showed the results of bivariate analysis of study data. Data analysis revealed that nutritional status, CVC, previous history of major surgery, prolonged usage of antibiotics (≥7 days), and age were not significantly different in both study groups (p>0.05). While mechanical ventilator usage (OR 2.15; 95% CI 1.07 – 4.3; p = 0.043) and ≥ 9 days of length-of-stay (OR 2.44; 95% CI 1.21 – 4.96; p = 0.018) were significantly different in both study groups.

DISCUSSION

The percentage of MDRO varies in each country depending on the population and time of study. In 2021, a nation-wide study from Egypt reported that 9.2% prevalence of MDRO infection in PICU setting, while the previous study also mentioned that MDRO rates was 85.5% in septic patients treated in PICU and NICU

TABLE 3
Risk Factor of MDRO

Variables		MDRO		p	OR	95%CI
		Yes (n=79)	No (n=120)			
Nutritional Status	Malnutrition	33 (41.8%)	68 (53.3%)	0.147¥	0.6	0.35 – 1.11
	Normal	46 (60.8%)	56 (46.7%)			
Invasive Medical Devices Usage *(Central Venous Catheter)*	Yes	77 (97.5%)	114 (95%)	0.826¥	0.8	0.44 – 1.71
	No	2 (2.5%)	6 (15%)			
Mechanical Ventilator Usage	Yes	65 (82.3%)	82 (68.3%)	0.043¥*	2.1	1.07 – 4.3
	No	14 (17.7%)	38 (31.7%)			
Length-of-stay ≥ 9 days	Yes	66 (83.5%)	81 (67.5%)	0.018¥*	2.4	1.21 – 4.96
	No	13 (16.5%)	52 (26.1%)			
Antibiotic usage ≥ 7 days	Yes	35 (44.3%)	37 (30.8%)	0.074¥	1.7	0.99 – 3.21
	No	44 (55.7%)	83 (69.2%)			
Previous History of Major Surgery	Yes	17 (21.5%)	40 (33.3%)	0.100¥	0.5	0.28 – 1.05
	No	62 (78.5%)	80 (66.7%)			
Age	1 month-< 3 months old	9 (11.4%)	19 (15.8%)	0.206¥	–	–
	3 months-<3 years old	45 (57.0%)	53 (44.2%)			
	3–18 years old	25 (31.6%)	48 (40.0%)			

*Significance (p<0.05); ¥Chi Square

settings.[14]

Gram-negative bacteria are a world health problem because of their high resistance to antibiotics.[15] It is widely known that gram-negative bacteria caused 2.3 times more infection compared to gram-positive bacteria.[16] Meta-analysis studies in China show that 50% of gram-negatives are resistant to third generation of cephalosporins.[17] A 15-year cohort study in Germany showed that resistance of *E. Coli* and *K. pneumoniae* to third-generation cephalosporins increased every year, and in 2015 the rates were 16.3 and 15.7%.[18] Gram-negative bacteria were dominantly found in every specimen examined in this study. *K.pneumoniae*, *P. aeruginosa, A. baumanii,* and *E. coli* are the most commonly found. Research at Turkish Hospital also mentioned linear results with recent findings, that culture findings dominantly showed gram-negative bacteria (84.2%), with *P. aeruginosa*, *K.pneumoniae*, *A. baumanii*, and *E. coli* leading the list.[19] Previous literature from Surabaya, Indonesia revealed that in PICU setting, gram-negative bacteria were dominantly found in collected patients' specimens.[20]

K. pneumoniae is the most commonly found bacteria in this study (15%). Ranjeeta *et al*. revealed, in their meta-analysis study, that *K. pneumoniae* dominated the lab findings (16%), and 64% of them were ESBL producers.[21] Previous study located in Indonesia, Dr. Soeradji General Hospital, Klaten, revealed similar study results with 17.5% culture findings indicated for *K. pneumoniae* and 52.98% ESBL producers. The most examined isolates in previous study were sputum (40.45%),[22] which has similar numbers with recent study (55.3%). Normally, *K. pneumoniae* is easily found in the nasopharynx and digestive tract.[23] Immune-competent setting, this bacteria will never cause problems, as it is a normal flora inside of human body. However, once the immune system of host body is altered, especially in patients receiving invasive treatment such as endotracheal tubes and urinary catheters, *K. pneumoniae* poses great danger.[24] The most frequent form of complication is antibiotic resistance. Recent study found dominantly *K. pneumoniae* collected from patients with invasive treatment such as mechanical ventilators with endotracheal tubes attached to them. Colonization occurred as the result of biofilms formation at the endotracheal tube tip.[25]

Another ESBL-producing pathogens are *E. coli* with the ESBL group as much as 88.9%. This result is higher that a study conducted in a neonatal ward in China where 55% were in the ESBL-producing *E. coli* group.[26]

Similar study results were shown in a Polish national hospital.46 ESBL samples were taken for further analysis, which revealed that 43.5% of the samples were *E. coli*.[27] *E. coli* is the most commonly found bacteria in urinary tract culture samples. Turkish study reports similar findings, 73% urine isolates were dominated by gram-negative bacteria, with *E. coli* as the most commonly found bacteria.[20] *E. coli* mainly causes urinary tract infection (UTI) from both community-acquired and hospital-acquired UTI.[28] Uropathogenic *Escherichia coli* (UPEC) is the main causative agent of UTI. UPEC colonized and adheres to the urinary tract epithelium. These bacteria invade and replicate to form intracellular aggregates and cause biofilm formation. Biofilms cause bacteria to become resistant to antibiotics and host immune responses. UPEC can form biofilms on the surface of the catheter, urinary tract walls, and the epithelial lining of the bladder.[28,29]

The results of the blood isolates showed that gram positive bacteria were dominant with the most germ found were *Coagulase Negative Staphylococcus*. In line with research conducted at the PICU Hospital in Turkey from 2013–2016. 324 blood isolates were collected during the study period, 195 isolates were gram-positive (60.2%) and 107 isolates were gram-negative (33.0%). *Coagulase Negative Staphylococcus* (45.1%), *K. pneumoniae* (14.5%), *Enterococcus faecalis* (6.5%) were the most microorganisms found. This can be caused by gram-positive bacteria which are normal flora on human skin and mucosa and can contaminate blood cultures if culture specimens are not taken correctly. Gram-positive germs can also colonize and produce mucus which forms hydrophobic biofilms on medical devices such as intravenous catheters and causes infection.[30] A study in Soetomo General Hospital showed different outcomes, where the blood culture was dominated by gram-negative bacteria (66%) with *B. capea* (17.06%) as the most commonly found microorganisms. Meanwhile, gram-positive was dominated by *S. haemolyticus* (31.97%).[20]

Recent study reported that mechanical ventilators usage and prolonged length-of-stay (≥9 days) are risk factors of MDRO, sharing same results with a study by Wang *et al*.[31] who found that length of stay in the PICU, use of mechanical ventilators >5 days were risk factors for MDRO infection. A meta-analytic study also showed that a history of hospitalization within the last 3 months increases the likelihood of a carrier for antibiotic resistance.[13] The use of a mechanical ventilator which is an invasive medical procedure can remove the natural barrier of the upper airway and allow direct exposure of the lower respiratory tract to outside air, increasing the risk of colonization and invasion of bacteria in the airway epithelium.[32] Invasive procedures such as suctioning and fiberoptic bronchoscopy have been reported to increase the incidence of Ventilator-Associated Pneumonia (VAP).[31] Prolonged use of a ventilator is also associated with an increased incidence of MDR in Ventilator ventilator-associated pneumonia (VAP). One study showed that the MDR proportion of VAP patients with >5 days duration was greater (12.3%) compared to VAP patients with the duration of <4 days, namely 2.8%.[32]

Study by Qureshi *et al*[33] showed that the use of antibiotics >2 days, a stay in the ICU >3 days, and a history of using invasive medical devices (urinary catheters and CVC) are not risk factors for MDRO.[33] Another study on pediatric wards in Hospitals in Japan also showed similar results. History of administration of broad-spectrum intravenous antibiotics >2 days in 90 days, administration of short and long-term macrolide therapy (>1 month) is not a risk factor for MDR in children with pneumonia.[34] In contrast to the study by Ahmed *et al* [14] who found a significant relationship age with MDRO infection. Age <1 year is associated with an immature immune system and increased exposure to infection and environmental contamination in this study.[14] A meta-analysis study in America also showed a history of antibiotic exposure, duration of antibiotic administration, and combination antibiotics were associated with the risk of MDR occurring in pediatric patients.[35]

There was no significant difference in mortality between MDRO and non-MDRO patients. Different from previous literature results, a study conducted at the NICU Hospital in Jordan where neonatal sepsis mortality (age 0–90 days) in the MDRO group was higher than in the non-MDRO group (60% vs 13%).[36] In contrast to the study by Verma *et al*.[37] who assessed the risk factors for MDRO in children who received liver transplantation, found no significant differences between the 30-day, 90-day, and 1-year survival rates between the non-MDRO and MDRO groups.[37] Studies assessing MDRO mortality in Blood Stream Infection (BSI) in several Tertiary Hospitals in Indonesia showed the same thing. There was no difference in the risk of mortality in MDRO and non-MDRO BSI patients. This is expected due to several things such as: the use of carbapenems as empiric antibiotics can reduce the difference in risk between MDRO and non-MDRO patients, administration of empirical antibiotics without taking a culture first due to limited health insurance funding at the local hospital and the research is not specific enough to explore the differentiating factors between groups BSI MDRO and non MDRO.[38]

This study has limitations. In-depth analysis of the rationale and effectiveness for using third-generation cephalosporins as first-line empiric antibiotics in PICU setting and the analysis of factors affecting the mortality in each MDRO group has not been further elaborated in this study.

CONCLUSION

The results of this study showed that MDRO infections from various specimens were 39.7% with predominance of gram-negative germ. *K. pneumoniae* and *E. coli* as ESBL-producing bacteria had 80% and 88.9% resistance rates, respectively. Mechanical ventilators and prolonged length-of-stay are two main risk factors of MDRO in PICU setting in Dr. Kariadi General Hospital (p=0.043 and p=0.018).

Further research is needed regarding the effectiveness and rationality of using third generation cephalosporins as first-line empiric antibiotics in the PICU.

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