Research Article

The relationship between preterm birth and the incidence of Multidrug Resistance Organisms (MDRO) in neonates at Dr. Moewardi Hospital Surakarta.

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ABSTRACT

Background: Infection cases caused by Multi-drug Resistant Organisms (MDRO) have increased in the last few decades. Antimicrobial resistance is responsible for 30% of neonatal mortality worldwide. Preterm birth discovered as independent risk factor for MDRO in neonates associated with immature immune system. However, other studies suggested conversely.

Aims: To investigate the relationship between preterm birth and the incidence of MDRO in septic neonates at Dr. Moewardi Hospital Surakarta.

Methods: A retrospective analytic observational study with case control design conducted. The subjects were septic neonates proven by blood cultures hospitalized during January to December 2021 at Dr. Moewardi hospital Surakarta. This study used SPSS 25.0 with Chi Square bivariate analysis followed by multivariate logistic regression analysis.

Results: The subjects were 60 neonates, consisted of 30 MDRO and 30 non-MDRO neonates. There were 21 MDRO neonates (70%) born prematurely and 8 premature neonates (26,6%) in non-MDRO group. Chi square bivariate analysis found that low birth weight (OR=3.755, 95%CI=1.239–11.385, p=0.017), preterm birth (OR=6.417, 95%CI=2.084-19.755, p=0.001) and duration of antibiotic administration >7 days (OR=5.231, 95%CI=1.657-16.515, p=0.003) had p<0.05. Results continued with multivariate logistic regression analysis showed that preterm birth (OR=7.632, 95%CI=1.158-50,293, p=0.035) and duration of antibiotic administration >7 days (OR=3.939, 95%CI=1.106-14.032, p=0.034) had significant correlation with the incidence of MDRO in neonates.

Limitations: We had not been able to analyze medical personnel's hand hygiene adherence because the data used is retrospective data.

Conclusion: Preterm birth was associated with the incidence of MDRO in neonates at Dr. Moewardi hospital Surakarta.

Keywords: MDRO, preterm birth, neonates, neonatal sepsis, antimicrobial resistance

INTRODUCTION

Infection cases caused by Multi-drug Resistant Organisms (MDRO) have increased in the last few decades. This requires more attention because alternative antibiotics as a treatment are limited.[1,2]

Inappropriate administration of antibiotics can affect the worsening of the patient's condition. This can be life-threatening and increase in the burden of patients' treatment costs.[3,4]

Based on the International Expert Proposal for Interim Standard Definitions for Acquired Resistance, MDRO is a condition which a bacterial isolate is resistant to at least one agent of antibiotic from ≥ 3 classes of antibiotics from these following antimicrobial categories: Carbapenems, Penicillins, Broad-spectrum Cephalosporins, Monobactams, Aminoglycosides, Fluoroquinolones, Chloramphenicol, folate pathway inhibitors, Tetracyclines, Macrolides and Glycopeptides.[1,5,6]

Neonates are susceptible to infectious diseases because their immune system has not fully developed yet. Therefore, neonates at risk for developing antimicrobial resistance which causes high morbidity and mortality compared to the older children.[4,7] Antimicrobial resistance has been reported to be responsible for around 30% mortality of neonatal sepsis worldwide.[8,9]

There are various risk factors for MDRO infection in neonates in several studies. Previous studies have identified extremely low birth weight, preterm birth, and long-term antibiotic administration as independent risk factors associated with the increase of antimicrobial resistance incidences.[3] The preterm baby has an immature immune system, lack of innate and adaptive immunity, which can be further linked by various factors associated with preterm birth. The immune system of preterm neonates has a smaller pool of monocytes and neutrophils, impaired ability of these cells to destroy pathogens, and lower production of cytokines that limit T-cell activation and reduced capability to destruct bacteria and detect viruses in cells, compared to full-term neonates. Intrauterine inflammation is a major contributor to preterm birth, and leads to premature immune activation and cytokine production. This can induce immune tolerance which leads to decreased immune function in newborns.[10-12] Thantrimontrichai et al (2019) found that preterm birth as an independent risk factor for the occurrence of gram-negative rods MDRO associated with immature immune system.[7] However, in a study by Giuffre et al (2016) stated otherwise that preterm birth was not the independent risk factor for MDRO in neonates. The absence of a significant association may indicate cross-transmission during treatment in the Neonatal Intensive Care Unit (NICU).[12] Study of Tsai et al (2014) also stated that premature birth was not the independent risk factor for the incidence of MDRO in neonates, but they found that the history of administration of third-generation cephalosporin antibiotics and carbapenems as the independent risk factor.[3] Other risk factors of MDRO were Length of Stay (LOS), history of invasive procedures, using of mechanical ventilators, APGAR scores, duration of central venous access, parenteral nutrition, and formula feeding.[13,14]

This study was purposed to determine the relationship between preterm birth and the incidence of MDRO in neonates at Dr. Moewardi hospital Surakarta.

Methods

This research was a retrospective analytic observational study with case control design. Data collection was obtained from patient's medical record data. The subjects were neonates who were treated in the neonatal High Care Unit (HCU) and NICU diagnosed neonatal sepsis proven by patient's blood cultures found organism at Dr. Moewardi hospital Surakarta during the hospitalization period from January to December 2021. Sampling was carried out by purposive sampling. This study used patient medical record data. The sample size was calculated using the sample size formula for multivariate analysis involving ≥ 6 predictors with formula is shown below:

$n > 10\ m$

where,

n = minimum sample size or minimum number of subjects

m = number of variables studied

In this study, six variables were used, consisting of one independent variable and five confounding variables which were included in the study, so that the minimum sample size in this study required a minimum of 60 subjects.

Inclusion criteria included data on gestational age at birth, duration of previous antibiotic administration, LOS, using of invasive mechanical ventilators, birth weight, and APGAR scores from patient's medical record data. Incomplete medical record data have been excluded. Medical record data that fulfilled the inclusion criteria divided into two groups, namely the MDRO group as the case group and the non-MDRO group as the control group. This study used SPSS 25.0 with Chi Square bivariate analysis followed by multivariate logistic regression analysis with a p value <0.05 was statistically significant.

Results

This study involved sixty neonates diagnosed as neonatal sepsis proven by blood culture found organisms at Dr. Moewardi Surakarta during the hospitalize period from January to December 2021. There were thirty neonates with MDRO and thirty non-MDRO neonates. The characteristics of the subjects in both groups are shown in Table 1.

The most common organism found was *Klebsiella pneumoniae* both in the MDRO group there were ten neonates (33.3%) and also in the non-MDRO group there were three neonates (10%). Other

Table 1. Characteristic of subjects

Variables	Resistance		p-value
	MDRO	Non-MDRO	
Gender			0.438
Males	14 (46.7%)	17 (56.7%)	
Females	16 (53.3%)	13 (43.3%)	
Birth weight			0.014*
Very Low (VLBW) (<1500 g)	15 (50.0%)	5 (16.7%)	
Low (LBW) (<2500 g)	8 (26.7%)	9 (30.0%)	
Normal (NBW) (>2500 – 3999 g)	7 (23.3%)	16 (53.3%)	
Gestational Age (weeks)			0.006*
Extremely preterm (<28)	1 (3.3%)	0 (0.0%)	
Very preterm (28-<32)	9 (30.0%)	2 (6.7%)	
Moderate to late preterm (32-<37)	11 (36.7%)	6 (20.0%)	
At term (37-<42)	9 (30.0%)	22 (73.3%)	
Delivery			0.598
Spontaneous	13 (43.3%)	11 (36.7%)	
Cesarean	17 (56.7%)	19 (63.3%)	
Length of Stay (LOS)			0.067
> 15 days	16 (53.3%)	9 (30.0%)	
< 15 days	14 (46.7%)	21 (70.0%)	
Outcome			0.184
Mortality	21 (70.0%)	16 (53.3%)	
Survived	9 (30.0%)	14 (46.7%)	
Mechanical ventilation			0.781
Invasive mechanical ventilation	9 (30.0%)	10 (33.3%)	
Without invasive mechanical ventilation	21 (70.0%)	20 (66.7%)	
Duration of antibiotic administration			0.003*
> 7 days	17 (56.7%)	6 (20.0%)	
< 7 days	13 (43.3%)	80.0%)	

*p-value <0.05

organisms found in the group of neonates with MDRO were *Staphylococcus haemolyticus* (16.7%), *Acinetobacter baumannii* (13.3%), and *Staphylococcus hominis* (13.3%), and the rest being other types of organisms with a percentage of less than 10%. In the group of non-MDRO neonates, many fungi were found, namely *Candida parapsilosis* (30.0%), followed by *Klebsiella pneumoniae* organisms (10.0%) and the rest were other types of organisms with a percentage of less than 10%. The species of organisms found are shown in Table 2.

Table 2. Organisms isolated from blood culture

Organisms	Resistance	
	MDRO	Non-MDRO
Klebsiella pneumoniae	10 (33.3%)	3 (10.0%)
Acinetobacter baumannii	4 (13.3%)	2 (6.7%)
Citrobacter koseri	1 (3.3%)	0 (0.0%)
Enterobacter cloacae	2 (6.7%)	0 (0.0%)
Enterobacter faecalis	1 (3.3%)	2 (6.7%)
Pseudomonas aeruginosa	1 (3.3%)	2 (6.7%)
Pseudomonas stutzeri	0 (0.0%)	2 (6.7%)
Staphylococcus aureus	0 (0.0%)	2 (6.7%)
Staphylococcus epidermidis	2 (6.7%)	0 (0.0%)
Staphylococcus haemolyticus	5 (16.7%)	0 (0.0%)
Staphylococcus hominis	4 (13.3%)	2 (6.7%)
Staphylococcus saprophyticus	0 (0.0%)	1 (3.3%)
Streptokokkus agalactiae	0 (0.0%)	1 (3.3%)
Acinetobacter spp	0 (0.0%)	1 (3.3%)
Acinetobacter wolfii	0 (0.0%)	1 (3.3%)
Eschericia coli	0 (0.0%)	1 (3.3%)
Fungus		
Candida haemulonii	0 (0.0%)	1 (3.3%)
Candida parapsilosis	0 (0.0%)	9 (30.0%)

The bivariate analysis showed a significant correlation between the incidence of MDRO in neonates on LBW group (OR= 3.755, 95%CI=1.239–11.385, p=0.017), preterm birth group (OR=6.417, 95%CI=2.084-19.755, p=0.001), and duration of antibiotic administration >7 days group (OR=5.231, 95%CI=1.657-16.515, p=0.003) were shown in Table 3. To discover the dominant variable at risk for incidence of MDRO, a multivariate logistic regression analysis was performed.

Table 3. Bivariate analysis of factors associated with the incidence of MDRO

Variables	Resistance		OR (95% CI)	p-value
	MDRO	Non-MDRO		
Sex				
Males	14 (46.7%)	17 (56.7%)	0.669 (0.242-1.852)	0.438
Females	16 (53.3%)	13 (43.3%)	Ref.	
Birth weight				
LBW/VLBW (<2500 g)	23 (76.7%)	14 (46.7%)	3.755 (1.239-11.385)	0.017*
NBW (>2500 – 3999 g)	7 (23.3%)	16 (53.3%)	Ref.	
Gestational age (weeks)				
Preterm (<37)	21 (70.0%)	8 (26.7%)	6.417 (2.084-19.755)	0.001*
Aterm (37-<42)	9 (30.0%)	22 (73.3%)	Ref.	
Delivery				
Spontaneous	13 (43.3%)	11 (36.7%)	1.321 (0.469- 3.721)	0.598
Cesarean	17 (56.7%)	19 (63.3%)	Ref.	
Length of Stay (LOS)				
>15 days	16 (53.3%)	9 (30.0%)	2.667 (0.924- 7.699)	0.067
<15 days	14 (46.7%)	21 (70.0%)	Ref.	
Mechanical ventilation				
Invasive mechanical ventilation	9 (30.0%)	10 (33.3%)	0 .857 (0 .288- 2.547)	0.781
Without invasive mechanical ventilation	21 (70.0%)	20 (66.7%)	Ref.	
Duration of antibiotic administration				
> 7 days	17 (56.7%)	6 (20.0%)	5.231 (1.657-16.515)	0.003*
< 7 days	13 (43.3%)	24 (80.0%)	Ref.	

*p-value <0.05

The multivariate analysis showed a significant correlation between preterm birth (OR=7.632, 95%CI=1.158-50.293, p=0.035) and duration of antibiotics administration >7 days (OR=3.939, 95%CI=1.106-14.032, p=0.034) with the incidence of MDRO in neonates were shown in Table 4.

Table 4. Logistic regression multivariate analysis of factors associated with the incidence of MDRO*

Variables	OR (95%CI)	p-value
LBW/VLBW	0.540 (0.077-3.797)	0.535
Preterm birth	7.632 (1.158-50.293)	0.035*
Duration of antibiotic administration > 7 days	3.939 (1.106-14.032)	0.034*

*Only variables with p-value <0.05

The description of the APGAR score based on the incidence of MDRO in this study used the Mann Whitney test. Mann Whitney test was conducted to see whether there was a difference in APGAR scores in the MDRO group and the non-MDRO group. Our study found that the 1st minute APGAR score had p value=0.662 (p>0.05), the 5th minute got p value=0.514 (p>0.05) and the 10th minute had p value=0.306 (p>0.05) were not significantly related to the incidence of MDRO in neonates at Dr. Moewardi hospital Surakarta is shown in Table 5.

Table 5. APGAR scores based on incidence of MDRO

Variable	Resistance		p-value
	MDRO	Non-MDRO	
1st minute APGAR score			0.662
Mean +SD	5.37 +1.85	5.60 +1.65	
Median (min-max)	6.00 (2.00-8.00)	6.00 (3.00-8.00)	
5th minute APGAR score			0.514
Mean +SD	6.60 +1.57	6.97 +1.35	
Median (min-max)	7.00 (3.00-9.00)	7.00 (4.00-9.00)	
10th minute APGAR score			0.306
Mean +SD	7.80 +1.42	8.30 +1.02	
Median (min-max)	8.00 (4.00-10.00)	8.00 (6.00-10.00)	

Discussion

Our study found that the most common types of organisms in the group of neonatal sepsis patients with MDRO were *Klebsiella pneumoniae* (33.3%), *Staphylococcus haemolyticus* (16.7%), *Acinetobacter baumannii* (13.3%), and *Staphylococcus hominis* (13.3%), and the rest were other types of organisms with a percentage of less than 10%. This is different from the research by Estiningsih et al in 2016, it was observed that the bacterias that infected NICU patients at dr. Soeradji Tirtonegoro hospital were *Pseudomonas sp* (30.4%), *Klebsiella sp* (23.9%), *Serratia sp* (15.2%), and *Enterobacter sp* (15.2%). This differences because each hospital has a different pattern of organisms.[15,16] In our study, it was observed that the *Klebsiella pneumonia* was most commonly organism found in MDRO patients where

the organisms were gram-negative bacterium which is in line with study by Litzow et al (2009) in the Philippines, Tsai et al (2014) in Taiwan, Thatrimontrical et al (2019) in Thailand and research by Giuffre et al (2016) in Italy which stated that there was a tendency for a rapid increase in gram-negative bacterial infections that cause MDRO conditions in neonatal patients treated in the NICU.[3,7,13,17] Our study also was in line with the research by Ballot et al in 2019 in Johannesburg, South Africa and Yuse et al (2016) in Jordan, that the most commonly found organism was *Klebsiella pneumoniae*.[18,19]

Based on the gestational age in the bivariate analysis between preterm birth and the incidence of MDRO in neonates in our study, the results obtained OR = 6.417 (95%CI=2.084 –19.755) with p=0.001 (p <0.05) then followed by multivariate analysis with the results obtained OR=7.632 (95%CI=1.158-50.293) with value of p = 0.035 (p <0.05) which mean that preterm birth had risk of 7.632 times the incidence of MDRO, thus preterm birth was one of the dominant factors at risk of MDRO incidence. Our research result is in line with Begum et al's study in 2016 where premature infants had a correlation with the incidence of sepsis, both early onset and late onset sepsis due to an immature immune system which was at risk for MDRO.[10,13,19] In the 2016 study by Giuffre et al, it was stated diverse that preterm birth was not the independent risk factor for MDRO incidence in neonates. The absence of a significant association might indicate cross-transmission phenomenon during treatment in the NICU.[13]

In the bivariate analysis between the duration of antibiotics administration >7 days and the incidence of MDRO in neonates in our study, the results obtained OR=5.231 (95%CI=1.657–16.515) with p=0.003 (p <0.05). Then proceed by multivariate analysis and then obtained OR=3.939 (95%CI=1,106-14,032) with p=0.034 (p<0.05) which mean that duration of antibiotics administration >7 days had risk of 3.939 times the incidence of MDRO, thus the duration of antibiotics administration >7 days was one of the dominant risk factors for the occurrence of MDRO. Our research results are in accordance with the study of Giuffre et al in 2016 which stated that the average duration of administration of Ampicillin-Gentamicin antibiotics was 7.4 days as the independent risk factor for MDRO in neonates.[13] The bacterial selective pressure comes from the use of antibiotic doses. When the doses of antibiotics used reach or are close to sublethal doses, the selective pressure of antibiotics can force changes in the body's behavior, physiology and biochemistry. Genes and proteins in the expression of resistant bacteria will change, the body's protective and immune defenses will gradually weaken, and the risk of MDRO increases.[2]

Based on birth weight in bivariate analysis between LBW/VLBW and MDRO incidences in neonates in our study, the results obtained OR=3.755 (95%CI=1.239–11.385) with p=0.017 (p<0.05). Furthermore, multivariate analysis was performed to obtain OR=0.540 (95%CI=0.077-3.797) with p value=0.535 (p>0.05) which mean that LBW was not the dominant factor at risk for MDRO. Our results were not the similiar as the study by Ballot et al in 2019 which stated that there was a correlation between the incidence of LBW, prematurity, maternal HIV infection and oxygenation in the initial 28 days with the incidence of multidrug resistant *Enterobacteriace*.[21] Intrauterine growth disorders could affect birth weight and development of the respiratory, cardiovascular, neurological, hematological

and immunological systems. Neonates with VLBW have the highest risk of infection due to low immunity.[22] This difference might be due to the large discrepancy in the number of subjects in that study were 2437 neonates, while the total subjects of our study were 60 neonates.

LOS in the MDRO group obtained a value of OR=2.667 (95%CI=0.924–7.699) p=0.067 (p>0.05) which mean that there was no significant correlation between LOS and the incidence of MDRO. This is not in line with the study of Abdel-Hady et al which stated that the total number of days in the hospital was an independent risk factor for *Klebsiella pneumoniae* caused infection of Extended Spectrum Beta-Lactamase (ESBL). The study said that the hospital environment played an important role in the transmission of these pathogens, especially the spread from medical personnels.[22,23] This difference may be due to the group of MDRO neonates in our study who obtained LOS <15 days because there was mortality of 21 neonates in MDRO group, while in the non-MDRO group there were 16 neonates died.

In the using of invasive mechanical ventilation in the MDRO group, the value was OR=0.857 (95%CI=0.288–2.547) p=0.781 (p > 0.05) which mean that there was no significant relationship between the using of invasive mechanical ventilation with MDRO incidence. Our study is different from the research by Wang et al in 2020 and Tsai et al in 2014 which stated that there was an effect of using invasive mechanical ventilation on the incidence of MDRO, with the longer the duration of ventilator use, then the higher the incidence of MDRO. This might happen because both the group of patients with MDRO and not MDRO used only small number of ventilators in our study. This may be due to differences in the number of research subjects which are very different where in the 2014 Tsai's study with total sample size 1106 neonates and differences in research methods where the study was a prospective cohort study conducted for eight years.[2,3]

APGAR score in the 1st minute had p=0.662 (p>0.05), in the 5th minute got p=0.514 (p>0.05) and in the 10th minute had p=0.306 (p>0.05). All three there were no significant difference between the MDRO group and the non-MDRO group, thus the 1st minute, 5th minute, and 10th minute APGAR scores were not associated with the MDRO incidence, although the APGAR scores of MDRO group tended to be lower (mean score 1-5-10 minutes = 5.37–6.6–7.8) compared to the non-MDRO group (mean score 1-5-10 minutes = 5.60–6.97–8.3) in our study. This is not in line with the study of Geyesus et al (2017) in Egypt which stated that the APGAR score in the 5th minute with a score <7 was an independent risk factor for sepsis which then led to an MDRO condition in neonates.[19] This difference occurred perhaps because in our study the average APGAR score obtained in both the MDRO and non-MDRO groups at 5th minutes both obtained a score of <7.

The incidence of MDRO caused by nosocomial hospital infections commonly referred to as hospital-acquired infections (HAI's) which one of the preventions of this condition is isolation precautions that is evaluation of hand hygiene adherence, which can be a risk factor for MDRO incidence in neonates.[16,25,26] The longer the patient was hospitalized, the exposure to HAI's will increase as well as the MDRO incidence in neonates.[26] In our study,

we had not been able to analyze medical personnel's hand hygiene adherence because the data used is retrospective data which there was no data on hand hygiene compliance.

Conclusions

Preterm birth (OR=7.632, 95%CI=1.158-50.293, p value=0.035) and duration of antibiotics administration >7 days (OR=3.939, 95%CI=1.106-14.032, p value=0.034) had significant correlation with the incidence of MDRO in neonatal patients at Dr. Moewardi hospital Surakarta. *Klebsiella pneumoniae* was the most common organism found to cause MDRO incidence in neonatal patients at Dr. Moewardi hospital Surakarta.

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Conflict of interest

None declared.

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