

## CHARACTERISTICS OF NEONATAL SEPSIS CAUSED BY MULTI-DRUG RESISTANT ORGANISMS (MDRO) IN THE NEONATAL INTENSIVE CARE UNIT (NICU) OF NGOERAH HOSPITAL

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### ABSTRACT

**Introduction:** Neonatal sepsis caused by MDRO is a clinical syndrome where a newborn infant experiences systemic inflammation caused by a pathogen that has adapted to resist several classes of antimicrobial drugs. The mortality rate of MDRO neonatal sepsis is significantly higher compared to non-MDRO cases due to having less treatment choices. This study was conducted to determine the characteristics of neonatal sepsis caused by MDRO in the NICU of Ngoerah Hospital, to provide clinical and microbiological data as a basis for prevention and formulation of new treatment regimens. **Methods:** This study uses a descriptive quantitative method with a cross-sectional approach. Data was collected from the medical records of neonates who were treated in January 2022 to August 2024, using the consecutive sampling technique. **Results:** A total of 34 samples were included in the study. The most common isolated gram-positive pathogen was *Staphylococcus epidermidis* (14.7%), while the most common gram-negative pathogens were *Klebsiella pneumoniae ssp. pneumoniae* (29.4%) and *Acinetobacter baumannii* (23.5%). The antibiotic classes that faced the most resistance were penicillin (100%), cephalosporin (97.1%), and aminoglycosides (88.2%). **Conclusion:** Other characteristics found a predominance in female infants (52.9%), low birth weight (29.4%), very preterm (32.4%), early onset sepsis (76.5%), duration of treatment 7-88 days, blood culture (91.2%), history of using invasive ventilatory devices (38.2%), no history of invasive surgery (76.5%), history of using a peripherally inserted venous catheter (41.2%), congenital anomalies of the circulatory system (55.9%), no subsequent case of meningitis (64.7%), and an outcome of death (67.7%).

**Keywords:** Neonatal sepsis, multi-drug resistant organism (MDRO), characteristics

### INTRODUCTION

Neonatal sepsis is a serious condition in neonatal patients characterized by the presence of life-threatening systemic infections.<sup>1</sup> Multi-drug resistant organisms (MDRO) are a group of organisms that have developed a resistance towards at least one antibiotic from three or more classes of antibiotics.<sup>2</sup> These organisms occur due to the inappropriate use of antibiotics.<sup>3</sup>

According to the World Health Organization (WHO), neonatal sepsis is the third leading cause of death in neonates.<sup>4</sup> Previous studies roughly estimated a prevalence of 14.2 million cases and 203 thousand deaths caused by neonatal sepsis in 2017.<sup>5,6</sup> Lower-middle-income countries, including Indonesia, constitute a third of the total neonatal sepsis cases found in the world.<sup>7</sup> This high morbidity and mortality rate is partially attributed to increasing cases of multi-drug resistant (MDR) neonatal sepsis with resistance to first-line antibiotics.<sup>4</sup> A previous study conducted in Jordan found 69% of MDR cases in 68 patients diagnosed with neonatal sepsis. The mortality rate of the MDR group reached 60%, while the non-MDR group had a lower mortality rate of 13%.<sup>8</sup>

Neonatal sepsis caused by MDRO is difficult to treat due to limited treatment options. Studies conducted in hospitals of developing countries found that more than 50% of MDROs that

cause neonatal sepsis are resistant to the WHO-recommended first-line antibiotics used to treat bacterial infections. These antibiotics are ampicillin and gentamicin.<sup>9</sup> The high mortality rate and challenges in handling MDR neonatal sepsis underline the urgency to conduct further research regarding this specific topic.

This study aimed to observe the characteristics of neonatal sepsis caused by MDRO in the NICU of Ngoerah Hospital.

### MATERIALS AND METHODS

This descriptive cross-sectional study was conducted from August to October 2024 at the Medical Records Installation of Ngoerah Hospital. The selection of samples was done using the consecutive sampling method. This study included all neonatal sepsis patients treated in the NICU of Ngoerah Hospital during the period of January 2022 to August 2024 with microbiological examination results that proved the infection was caused by a MDR pathogen. Patients with an incomplete medical record were excluded from the study. Demographic, clinical, and microbiological data were obtained from the patients' medical records.

The sample size was determined with the following assumption: the proportion of neonatal sepsis caused by MDRO in the population was 0.5, the estimated number of samples found

in a population of under 10,000 was 46, and a margin of sampling error tolerated 10% at 90% confidence interval; which required a minimum sample size of 27 neonates.

This research proposal was approved by the Research Ethics Committee (KEP) of the Faculty of Medicine, Universitas Udayana/Ngoerah Hospital on February 1, 2024, under the reference number 0426/UN14.2.2.VII.14/LT/2024.

**Table 1.** Demographic characteristics of patients

| Characteristics                        | Results         |
|----------------------------------------|-----------------|
| <b>Sex (%)</b>                         |                 |
| Male                                   | 16 (47.1)       |
| Female                                 | 18 (52.9)       |
| <b>Birth weight, median (range)</b>    | 1585 (740-4200) |
| Extremely low                          | 7 (20.6)        |
| Very low                               | 9 (26.5)        |
| Low                                    | 10 (29.4)       |
| Normal                                 | 7 (20.6)        |
| High                                   | 1 (2.9)         |
| <b>Gestational age, median (range)</b> | 32 (25-40)      |
| Extremely preterm                      | 5 (14.7)        |
| Very preterm                           | 11 (32.4)       |
| Moderate to late preterm               | 10 (29.4)       |
| Term                                   | 8 (23.5)        |

**Table 2** presents the clinical characteristics of the research subjects. The results of the laboratory examinations used in this study were those that were closest to when an MDRO pathogen was detected via microbiological examination. Total leukocyte count results found a normal amount of leukocytes in 28 patients (82.4%), whereas 5 patients (14.7%) experienced leukopenia, and 1 patient (2.9%) experienced leukocytosis. Thrombocyte count results found that the majority of patients experienced thrombocytopenia, with a total 19 patients (55.9%). Normal

## RESULTS

There were 36 patients that fulfilled the inclusion criteria. Two patients were excluded due to having incomplete medical records, leaving a total of 34 samples for observation. **Table 1** presents the demographic characteristics of the research subjects.

thrombocyte levels were found in 11 patients (32.4%), while 4 patients (11.8%) experienced thrombocytosis. All 34 patients' (100%) serum C-reactive protein (CRP) levels were elevated. Absolute neutrophil count (ANC) results found 20 patients (58.8%) with normal results, 8 patients (23.5%) with neutrophilia, and 6 patients (17.7%) with neutropenia. The ratio of immature to true (I/T) neutrophils was normal in 20 patients (58.8%), while 14 patients (41.2%) showed elevated results.

**Table 2.** Clinical characteristics of patients

| Characteristics                                                                  | Results         |
|----------------------------------------------------------------------------------|-----------------|
| <b>Onset of sepsis, n (%)</b>                                                    |                 |
| Early                                                                            | 26 (76.5)       |
| Late                                                                             | 8 (23.5)        |
| <b>Duration of treatment, n (%)</b>                                              | 26 (7-88)       |
| <b>Culture specimen, n (%)</b>                                                   |                 |
| Blood                                                                            | 31 (91.2)       |
| Sputum                                                                           | 3 (8.8)         |
| <b>Total leukocyte count (<math>10^3/\mu\text{L}</math>), median (range)</b>     | 13.9 (1.4-30.7) |
| <b>Platelet count (<math>10^3/\mu\text{L}</math>), median (range)</b>            | 132 (7-745)     |
| <b>Serum C-reactive protein (mg/L), median (range)</b>                           | 377 (10-3,068)  |
| <b>Absolute neutrophil count (<math>10^3/\mu\text{L}</math>), median (range)</b> | 6.7 (0.4-26.8)  |
| <b>I/T ratio, median (range)</b>                                                 | 0.15 (0.04-0.6) |
| <b>History of using mechanical ventilation devices, n (%)</b>                    |                 |
| Invasive                                                                         | 13 (38.2)       |
| Non-invasive                                                                     | 8 (23.5)        |

|                                                     |           |
|-----------------------------------------------------|-----------|
| Both                                                | 9 (26.5)  |
| None                                                | 4 (11.8)  |
| <b>History of surgery, n (%)</b>                    |           |
| Gastrointestinal                                    | 7 (20.6)  |
| Thorax                                              | 1 (2.9)   |
| None                                                | 26 (76.5) |
| <b>History of intravenous catheter usage, n (%)</b> |           |
| CVC                                                 | 11 (32.4) |
| PICC                                                | 6 (17.7)  |
| PIVC                                                | 14 (41.2) |
| CVC and PICC                                        | 3 (8.8)   |
| <b>Congenital malformations, n (%)</b>              |           |
| Yes                                                 | 24 (70.6) |
| Circulatory system                                  | 19 (55.9) |
| Digestive system                                    | 8 (23.5)  |
| Reproductive system                                 | 3 (8.8)   |
| Other                                               | 1 (2.9)   |
| No                                                  | 10 (29.4) |
| <b>Meningitis, n (%)</b>                            |           |
| Yes                                                 | 12 (35.3) |
| No                                                  | 22 (64.7) |
| <b>Outcome n (%)</b>                                |           |
| Survivors                                           | 11 (32.4) |
| Non-survivors                                       | 23 (67.7) |

Congenital malformations were found in 24 patients, with one patient exhibiting a chromosomal abnormality in the form of trisomy 16. Results also found that a third of the patients also experienced meningitis. Most of the patients observed in this study died from neonatal sepsis.

All of the isolates found in this study were bacterial. Both gram-positive and gram-negative microorganisms were isolated (**Table 3**).

**Table 3.** Isolated pathogens from culture

| Pathogen                                      | Sample |      |
|-----------------------------------------------|--------|------|
|                                               | n      | %    |
| <b>Gram-positive</b>                          | 8      | 23.5 |
| <i>Staphylococcus epidermidis</i>             | 5      | 14.7 |
| <i>Staphylococcus haemolyticus</i>            | 1      | 2.9  |
| <i>Staphylococcus cohnii ssp. urealyticus</i> | 1      | 2.9  |
| <i>Staphylococcus capitis</i>                 | 1      | 2.9  |
| <b>Gram-negative</b>                          | 26     | 76.5 |
| <i>Klebsiella pneumoniae ssp. pneumoniae</i>  | 10     | 29.4 |
| <i>Acinetobacter baumannii</i>                | 8      | 23.5 |
| <i>Escherichia coli</i>                       | 4      | 11.8 |
| <i>Salmonella sp.</i>                         | 2      | 5.9  |
| <i>Serratia marcescens</i>                    | 1      | 2.9  |
| <i>Pandoraea spp.</i>                         | 1      | 2.9  |

**Table 4** presents the resistance rates of MDR pathogens towards each antibiotic class. All of the isolated pathogens were resistant towards at least one drug of the penicillin class.

Cephalosporins and aminoglycosides also faced high resistance rates.

**Table 4.** Antibiotic resistance frequency

| Class           | Gram-positive | Gram-negative | Total |      |
|-----------------|---------------|---------------|-------|------|
|                 |               |               | n     | %    |
| Penicillin      | 8             | 26            | 34    | 100  |
| Cephalosporin   | 8             | 25            | 33    | 97.1 |
| Aminoglycosides | 6             | 24            | 30    | 88.2 |
| Fluoroquinolone | 6             | 19            | 25    | 73.5 |
| Trimethoprim    | 6             | 9             | 15    | 44.1 |
| Carbapenem      | 3             | 9             | 12    | 35.3 |
| Monobactam      | 0             | 12            | 12    | 35.3 |
| Macrolides      | 8             | 0             | 8     | 23.5 |
| Lincosamides    | 7             | 0             | 7     | 20.6 |
| Glycylcycline   | 0             | 5             | 5     | 14.7 |
| Ansamycin       | 1             | 0             | 1     | 2.9  |

The antibiotic resistance pattern of Gram-positive (**Table 5**) and Gram-negative (**Table 6**) bacteria are shown below.

**Table 5.** Resistance pattern in isolated Gram-positive pathogens

| Species                                     | PEN        | CEP        | MAC        | LIN         | AMG        | FQ         | TMP        | CBP         | ANS         |
|---------------------------------------------|------------|------------|------------|-------------|------------|------------|------------|-------------|-------------|
| <i>S. epidermidis</i> , n=5 (%)             | 5<br>(100) | 5<br>(100) | 5<br>(100) | 5<br>(100)  | 4<br>(80)  | 4<br>(80)  | 3<br>(60)  | 1<br>(20)   | -           |
| <i>S. haemolyticus</i> , n=1 (%)            | 1<br>(100) | 1<br>(100) | 1<br>(100) | 1<br>(100)  | 1<br>(100) | 1<br>(100) | 1<br>(100) | -           | 1<br>(100)  |
| <i>S. cohnii ssp. urealyticus</i> , n=1 (%) | 1<br>(100) | 1<br>(100) | 1<br>(100) | -           | -          | -          | 1<br>(100) | 1<br>(100)  | -           |
| <i>S. capitis</i> , n=1 (%)                 | 1<br>(100) | 1<br>(100) | 1<br>(100) | 1<br>(100)  | 1<br>(100) | 1<br>(100) | 1<br>(100) | 1<br>(100)  | -           |
| Total, n=8 (%)                              | 8<br>(100) | 8<br>(100) | 8<br>(100) | 7<br>(87.5) | 6<br>(75)  | 6<br>(75)  | 6<br>(75)  | 3<br>(37.5) | 1<br>(12.5) |

PEN, penicillin; CEP, cephalosporin; MAC, macrolide; LIN, lincosamide; AMG, aminoglycoside; FQ, fluoroquinolone; TMP, trimethoprim; CBP, carbapenem; ANS, ansamycin

**Table 6.** Resistance pattern in isolated Gram-negative pathogens

| Species                                         | PEN         | CEP          | AMG          | FQ           | MON          | CBP         | TMP         | G           |
|-------------------------------------------------|-------------|--------------|--------------|--------------|--------------|-------------|-------------|-------------|
| <i>K. pneumoniae ssp. pneumoniae</i> , n=10 (%) | 10<br>(100) | 10<br>(100)  | 10<br>(100)  | 5<br>(50)    | 7<br>(70)    | -           | 4<br>(40)   | 1<br>(10)   |
| <i>A. baumannii</i> , n=8 (%)                   | 8<br>(100)  | 8<br>(100)   | 8<br>(100)   | 8<br>(100)   | -            | 8<br>(100)  | -           | 4<br>(50)   |
| <i>E. coli</i> , n=4 (%)                        | 4<br>(100)  | 3<br>(100)   | 3<br>(100)   | 3<br>(100)   | 2<br>(100)   | -           | 4<br>(100)  | -           |
| <i>Salmonella sp.</i> , n=2 (%)                 | 2<br>(100)  | 2<br>(100)   | 2<br>(100)   | 2<br>(100)   | 2<br>(100)   | -           | 1<br>(50)   | -           |
| <i>S. marcescens</i> , n=1 (%)                  | 1<br>(100)  | 1<br>(100)   | -            | 1<br>(100)   | -            | -           | -           | -           |
| <i>Pandoraea spp.</i> , n=1 (%)                 | 1<br>(100)  | 1<br>(100)   | 1<br>(100)   | -            | 1<br>(100)   | 1<br>(100)  | -           | -           |
| Total, n=8 (%)                                  | 26<br>(100) | 25<br>(96.2) | 24<br>(92.3) | 19<br>(73.1) | 12<br>(46.2) | 9<br>(34.6) | 9<br>(34.6) | 5<br>(19.2) |

PEN, penicillin; CEP, cephalosporin; AMG, aminoglycoside; FQ, fluoroquinolone; MON, monobactam; CBP, carbapenem; TMP, trimethoprim; G, glycylcycline

Resistance towards at least one drug of the penicillin, cephalosporin, and macrolide classes were found in all 8 Gram-positive isolates. High resistance rates were also found in lincosamides, aminoglycosides, fluoroquinolone, and

trimethoprim. This study also found one case of resistance towards rifampicin from the ansamycin class.

Resistance towards at least one drug of the penicillin class was found in 100% of the Gram-negative isolates. Cephalosporins and aminoglycosides also faced high resistance rates. None of the *K. pneumoniae* and *E. coli* isolates in this study were resistant towards carbapenems. The isolate with the highest rate of resistance in this study was *A. baumannii*, with a 100% resistance rate towards at least one drug from the penicillin, cephalosporin, aminoglycoside, fluoroquinolone, and carbapenem classes.

## DISCUSSION

This study has a nearly equal distribution of male and female patients. Previous studies in Surabaya and Tuzla showed similar results, in which the gender distribution was almost equal.<sup>10,11</sup> Another study conducted in Neyshabour had slightly different results, where male patients dominated the study.<sup>12</sup> All three previous studies found that gender was not a significant risk factor for MDR neonatal sepsis.<sup>10-12</sup>

The results of the birth weight characteristics observed in this study are similar to a previous study conducted in Bandung. The study found that neonates with a birth weight below 2500 grams were 1.42 times at risk of experiencing neonatal sepsis compared to neonates with a normal birth weight. This is due to the tendency of babies born with low birth weight to lose body heat, experience difficulties in eating, have lower glucose levels, and have a higher risk of experiencing hypoglycemia. In addition, low birth weight is heavily associated with other risk factors for neonatal sepsis, such as prematurity, history of maternal infections, history of premature rupture of membranes, and asphyxia.<sup>13</sup> A similar study conducted in Tuzla discovered that low birth weight is one of the most significant risk factors for MDR neonatal sepsis.<sup>11</sup>

The gestational age of the patients observed in this study has similar results to the Tuzla study, in which there were more premature neonates.<sup>11</sup> A study by Merlyana et al. conducted in Banjarmasin also found similar results. The study also found that premature neonates have a 1.258 times greater risk of experiencing neonatal sepsis compared to term neonates.<sup>14</sup> This is due to premature babies having an immune system that has not fully developed. In addition, premature babies have lower IgG levels, because maternal IgG levels that are passed down to the neonates increase along with their gestational age.<sup>15</sup>

This study found more early-onset neonatal sepsis (EOS) cases compared to late-onset cases (LOS). This aligns with the findings of a study by Miranda et al.<sup>10</sup> Different results were found in the Tuzla study by Hadžić et al., in which there were more cases of LOS.<sup>11</sup> According to previous studies, the onset of neonatal sepsis is not a significant risk factor for MDR neonatal sepsis.<sup>10</sup> EOS is usually attributed to chorioamnionitis, multiple births, and a history of group B *Streptococcus* infection. On the other hand, LOS is attributed to risk factors found in the neonates'

external environment, such as a history of intravenous catheter usage, undergoing invasive procedures, and mechanical ventilator usage.<sup>16</sup>

The prolonged duration of treatment observed in this study is attributable to the patient's delivery method, comorbid conditions, and a history of premature rupture of membranes. Low birth weight is also heavily associated with a prolonged duration of treatment.<sup>17</sup> Patients with a longer course of treatment are at a higher risk of developing sepsis due to nosocomial infection. This is especially common in immunocompromised patients, such as premature neonates and term neonates with other comorbid conditions present.<sup>18</sup> Furthermore, neonatal sepsis caused by MDRO requires a longer duration of treatment. This is apparent in the Tuzla study, which compared the duration of treatment between MDR and non-MDR neonatal sepsis patients. The MDR group had a longer duration of treatment.<sup>11</sup> Contrarily, prolonged treatment also increases a patient's risk of developing MDR neonatal sepsis.<sup>10</sup>

Most of the culture specimens used in this study were blood, with an exception of 2 cases in which sputum was used instead. Blood culture is the gold standard in the diagnosis of neonatal sepsis.<sup>19</sup> Previous comparable studies observed the patient's blood culture results.<sup>10,11,20</sup> Other specimens that are less commonly used include urine, cerebrospinal fluid, and sputum. The use of sputum as an alternative specimen may be considered in patients with respiratory distress who require mechanical ventilation.<sup>16</sup>

The findings of leukocyte levels in this study are in line with a previous study done by Miranda et al., in which most patients had normal leukocyte levels. The only abnormal finding detected in a few patients was leukopenia. Total leukocyte count is not an effective standalone indicator, because normal results do not fully rule out the possibility of patients experiencing sepsis.<sup>20</sup> This is also apparent in a study conducted in Riyadh, which found that most of the observed patients had normal leukocyte levels.<sup>21</sup> In terms of abnormal findings, leukopenia is a better predictor of neonatal sepsis compared to leukocytosis.<sup>19</sup>

The results of platelet levels in observed patients are in accordance with the results obtained in a study conducted at Dr. Soetomo Hospital, Surabaya, which found that thrombocytopenia was present in 75% of neonatal sepsis patients with positive cultures.<sup>20</sup> A study conducted in Abbottabad also found similar results in which 68.9% of the observed patients experienced thrombocytopenia.<sup>22</sup> Although the pathogenesis of thrombocytopenia in neonatal sepsis cases is not fully understood yet, several studies theorize that endotoxins produced by Gram-negative bacteria are related to the occurrence of thrombocytopenia.<sup>23</sup> This is especially apparent in *K. pneumoniae* cases, which have a higher tendency to display abnormal findings such as anemia, leukopenia, and thrombocytopenia compared to cases caused by other pathogens.<sup>20</sup>

The findings related to CRP levels in this study are in accordance with results obtained in a case-control study conducted by Hakiem et al.<sup>24</sup> The previous study found that

CRP is able to detect 90% of sepsis cases, with a cut-off value of 6.4 mg/L. A study conducted by Al-Matary et al. found similar results, especially in LOS in which 84.1% of patients experienced increased serum CRP levels. C-reactive protein is produced by the liver as a response to acute inflammation and tissue damage. This laboratory examination is generally used to establish the diagnosis of acute infections that are difficult to diagnose using only clinical findings.<sup>21</sup> Serum CRP levels exceeding 500 mg/L often indicate the presence of an acute bacterial infection.<sup>25</sup>

The ANC results in this study are in line with the results of a study conducted in Riyadh. The study found that only 15.2% of EOS and 13.7% of LOS patients experienced neutropenia.<sup>21</sup> Neutropenia is considered a more specific abnormal finding in EOS compared to neutrophilia. Although ANC is not regarded as a septic marker at Ngoerah Hospital, several studies have found that neutropenia is an abnormal finding commonly found in EOS.<sup>16</sup>

The results of I/T ratio in this study resemble the results obtained by studies conducted in Ambon.<sup>26</sup> The study found 58% of patients with normal results and 42% of patients with an elevated I/T ratio. This laboratory examination has a high sensitivity for detecting EOS, especially since it is not easily influenced by non-infectious factors compared to other neutrophil indicators.<sup>19</sup>

The majority of neonates in this study had a history of using invasive mechanical ventilation devices. Similar results were found in the study conducted by Miranda et al. The previous study found that neonates with a history of using invasive mechanical ventilation devices are 2.678 times at higher risk of developing MDR infections compared to those with a history of using non-invasive devices.<sup>10</sup> A systematic review by Araújo and Guimarães found an association between the occurrence of neonatal sepsis and the use of mechanical ventilators. This may be attributed to the colonization of Gram-positive bacteria via nasal trauma due to the installation of ventilators, as well as frequent suctioning of patients that may transmit bacteria from their surrounding environment.<sup>27</sup> The Tuzla study found that almost all patients with MDR neonatal sepsis required mechanical ventilation. This is due to the tendency of MDR neonatal sepsis patients to experience multi-organ dysfunction, thus requiring more supportive therapy.<sup>11</sup>

According to a systematic review conducted by Araújo and Guimarães, three studies from 2006, 2012, and 2015 found that a history of undergoing surgery was a risk factor for developing neonatal sepsis. Patients who have undergone surgery need to be monitored and observed more closely.<sup>18</sup> However, this risk factor is still rarely studied.

The findings of this study regarding the patients' history of using intravenous catheters are in accordance with the study conducted by Miranda et al. The previous study found no significant association between intravenous catheter usage as a risk factor for MDR neonatal sepsis.<sup>10</sup> Venous catheter usage is one of the primary causes of LOS, due to its risk of contaminating the patients' intravenous

fluids.<sup>28</sup> According to a systematic review conducted by Araújo and Guimarães, the history and duration of CVC use are significant risk factors attributing to the development of neonatal sepsis, while the association of PICC use and neonatal sepsis showed inconclusive results.<sup>18</sup>

This study found different results regarding congenital malformations when compared to a similar study conducted in Northern Ethiopia. The previous study found that the majority of patients did not have any congenital abnormalities, as opposed to our study that found a majority of congenital malformations in the observed patients. However, this previous study also found that patients with congenital malformations had a 3.1 times higher risk of developing neonatal sepsis compared to patients with no abnormalities. This may be caused by several types of congenital malformations that support the growth of infectious microorganisms, as well as the long duration of treatment in patients with congenital malformations which makes them more susceptible to nosocomial infections.<sup>28</sup> The difference in characteristics between this study and the previous study could be attributed to various factors, such as differences in clinical interventions and management at the two sites, as well as differences in inclusion criteria.

The findings of this study regarding meningitis in MDR neonatal sepsis patients are similar to the results of a study by Hadžić et al.<sup>11</sup> Neonatal meningitis can be found in about one-third of neonatal sepsis cases.<sup>29</sup> This is in accordance to the results of this study. Prematurity is one of the most significant risk factors for meningitis to occur in neonatal sepsis patients.<sup>29</sup> This may explain why several meningitis cases were found in our patients, considering that most of the patients observed in our study were preterm neonates.

The mortality rate found in this study is similar to a previous study by Miranda et al.<sup>10</sup> Another study in North India found that only 56.5% of patients with MDR sepsis successfully underwent the treatment process and were discharged from the hospital.<sup>31</sup> Higher mortality rates are found in MDR sepsis compared to non-MDR cases. This may be attributed to the fact that MDR cases often experience delays in administering appropriate antibiotics because broad-spectrum antibiotics are not effective against MDROs. The treatment regimen must be readjusted after obtaining culture and resistance tests results.<sup>8</sup>

Pathogens attributing to neonatal sepsis may vary according to geographical locations. Our study found more gram-negative isolates compared to gram-positive isolates. These findings are in accordance with the study of Hadžić et al. in which most cases were caused by gram-negative bacteria.<sup>11</sup> A similar study by Miranda et al. found that *K. pneumoniae* was the leading cause of MDR neonatal sepsis.<sup>10</sup> This species is the dominant causative pathogen of neonatal sepsis in lower-middle-income countries, including Indonesia. Similar results were seen in a study conducted in three major cities in Indonesia. This study by Putri et al. also found *K. pneumoniae* as the most isolated pathogen in MDR neonatal sepsis patients.<sup>23</sup> Another study conducted in North

India found that the most found gram-positive MDR bacteria was methicillin-resistant *Staphylococcus aureus*.<sup>30</sup>

The antibiotic resistance pattern found in this study showed similar results to a study conducted at King Abdullah Hospital, Jordan. The previous study found that most *A. baumannii* cases observed had resistance towards all drug classes except for colistin. Several *A. baumannii* cases in the Jordan study were also sensitive to tigecycline, an antibiotic belonging to the glycylcycline group. The study also found that most of the isolated *K. pneumoniae* and *E. coli* had the ability to produce extended-spectrum  $\beta$ -lactamase. The results of this study are also in accordance with a similar study conducted in Cairo, Egypt. In that study, it was found that gram-positive bacteria tend to have resistance to penicillin and aminoglycoside groups, while Gram-negative bacteria tend to be resistant to penicillin and cephalosporins.<sup>31</sup>

The first-line antibiotics recommended by the WHO to treat neonatal bacterial infections are ampicillin from the penicillin group, and gentamicin from the aminoglycoside group. Third-generation cephalosporins are the recommended second-line antibiotics.<sup>9</sup> The Clinical Practice Guidelines at Ngoerah Hospital also use the same antibiotic recommendations.<sup>32</sup> However, this study found high resistance to these three classes of antibiotics. To determine alternative regimes that are effective in treating neonatal sepsis, further research is needed regarding the epidemiology and antibiotic resistance patterns of MDROs that often cause neonatal sepsis.

This study has several limitations. First, this descriptive study cannot analyze risk factors and causal relationships between various factors related to the incidence of MDR neonatal sepsis. Second, the results of this study only describe the characteristics of MDR neonatal sepsis patients in the NICU of Ngoerah Hospital. These results cannot be generalized to a wider population.

## CONCLUSION AND SUGGESTION

Based on the results of the study to determine the characteristics of neonatal sepsis caused by MDROs in the NICU of Ngoerah Hospital, several conclusions were drawn. The patients' demographic characteristics are predominantly female, low birth weight, and very preterm. Clinical characteristics showed a predominance in early onset sepsis, the use of blood as the culture specimen, history of using invasive ventilation device, no history of invasive surgery, history of using a peripherally inserted venous catheter, congenital anomalies of the circulatory system, no subsequent case of meningitis, and an outcome of death. The most common isolated pathogens in this study were *Klebsiella pneumoniae* ssp. *pneumoniae*, *Acinetobacter baumannii*, and *Staphylococcus epidermidis*. The antibiotic classes with the highest resistance rates were penicillin, cephalosporin, and aminoglycosides.

Several recommendations are proposed to address the issue related to MDR neonatal sepsis. First, it is crucial to implement more comprehensive evaluations of antibiotic administration policies in hospitals. Second, increased efforts in educating

patients regarding the proper use of antibiotics should be done. Furthermore, future studies are needed to investigate the risk factors of MDR neonatal sepsis. Longitudinal studies with more complex designs, such as cohort and case-control studies, are recommended. These studies are able to compare the characteristics of MDR neonatal sepsis patients compared to non-MDR and healthy patients.

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