Comparison of microbial pattern in early and late onset neonatal sepsis in referral center Haji Adam Malik hospital Medan Indonesia

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Abstract. Neonatal sepsis contributes a significant rate of infants mortality and morbidity. The pathogens are diverse from region to another and change time to time even in the same place. To analyze the microbial pattern in early and late onset neonatal sepsis and the pattern of antibiotic resistance of the causative microbes at one of referral center hospital in Indonesia, Haji Adam Malik Hospital, a cross-sectional descriptive study was conducted on neonates with sepsis diagnosis proven with positive blood culture within one year period (2015-2016). Among 626 neonates admitted to perinatology unit, the total of 154 neonates was proven to have neonatal sepsis with positive blood culture with the incidence rate 24.6%. Seventy-nine (51.3%) neonates were diagnosed with early onset sepsis while 75 (48.7%) neonates had late-onset sepsis. Klebsiella pneumonia was the most commonly isolated organism in both early and late onset sepsis, encompassing 19.5% of cases. Periodic surveillance of the causative agents of neonatal sepsis is needed to implement the rational, empirical choice of antibiotic prescription while waiting for blood culture result to come out.

1. Introduction
Neonatal sepsis remains a major problem in neonates worldwide, including in developing the country in particular.[1-4] In spite of the advance of health care and treatment nowadays, neonatal sepsis contributes a significant rate of infants mortality and morbidity both in term and preterm infants.[1,3,5] Sepsis caused 0.421 million neonatal deaths in 2013, as it was the third leading cause of neonatal mortality after preterm birth complication and intrapartum-related complication.[6] It is one of the most common causes of neonatal mortality in the developing country, contributing to 30-50% of neonatal deaths.[7]

Neonatal sepsis is a result of bacterial infection invading bloodstream causing some nonspecific systemic signs and symptoms, including temperature instability, respiratory distress, cyanosis, apnea, bradycardia or tachycardia, feeding difficulties, hypotonia, lethargy, irritability, seizures, bulging fontanel, long capillary refill time, paleness, mottled skin, abdominal distention, and unexplained jaundice.[1,2]

According to the time of appearance of the signs and the symptoms, neonatal sepsis is classified into early onset sepsis (EOS) and late onset sepsis (LOS).[4,6] EOS defines the onset of sepsis before 72 hours after birth while LOS presents after 72 hours of life.[2] Generally, EOS results from vertical maternal infection and LOS are acquired from the community or nosocomial source.[4]
To achieve the Sustainable Development Goals target, the Neonatal Mortality Rate must decline to the rate of 12 per 1000 livebirths in 2030. Thus strategy against all the preventable causes of neonatal deaths such as neonatal sepsis should be studied thoroughly.[8] Early diagnosis and prompt treatment are quite challenging. It needs initial empirical antibiotic treatment before the result of microbial culture showing sensitive antibiotic choice come out.[2]

The pathogens are diverse from region to another and change time to time even in the same place. Source of infection accurate identification, prompt antibiotic treatment, aggressive management, and earlier recognition of general antibiotic resistance pattern can prevent neonatal sepsis complication and increase the success rate in management.[2]

The aim of this study was to analyze the microbial pattern in early and late onset neonatal sepsis along with the pattern of antibiotic resistance of the causative microbes at one of referral center hospital in Medan, Indonesia, Haji Adam Malik Hospital. The result can be implemented as a guideline for effective, prompt treatment strategies.

2. Methods
In this study, a cross-sectional descriptive study was performed to assess the incidence of neonatal sepsis and the causative microbial pattern of neonatal sepsis at Haji Adam Malik Hospital, Medan. The subjects were neonates with proven neonatal sepsis cases with positive blood culture result that admitted to the perinatology unit at Haji Adam Malik Hospital, Medan from 2015 to 2016. Data were collected from the patients’ medical records for the following variables: demographic profile, types of sepsis (early or late), outcome and culture result. Data analysis were performed using Statistical Package for Social Sciences (SPSS) software version 22.

3. Results
During the study period, the total of 626 neonates was admitted to perinatology unit at Haji Adam Malik Hospital, Medan. Out of which, 154 neonates were proven neonatal sepsis with positive blood culture. Ninety-four (61%) were male, and 96 (62.3%) had normal birth weight. The incidence of sepsis at Haji Adam Malik Hospital, Medan was 24.6%. Among 154 cases of neonatal sepsis, 79 (51.3%) cases were diagnosed with early-onset sepsis, and 75 (48.7%) cases were late-onset sepsis. Table 1 shows characteristics of neonates.

| Characteristics              | Frequency: n (%) |
|------------------------------|------------------|
| **Gender**                   |                  |
| Male                         | 94 (61.0)        |
| Female                       | 60 (39.0)        |
| **Birth weight, gram**       |                  |
| <1500                        | 11 (7.1)         |
| 1500 - 2499                  | 46 (29.9)        |
| 2500 - 3999                  | 96 (62.3)        |
| ≥4000                        | 1 (0.6)          |
| **Classification of sepsis** |                  |
| Early onset sepsis           | 79 (51.3)        |
| Late-onset sepsis            | 75 (48.7)        |
| **Outcome**                  |                  |
| Resolved                     | 96 (62.3)        |
| Died                         | 31 (20.1)        |
| Lost to follow up            | 27 (17.5)        |
| **Total**                    | **154 (100)**    |
From 154 blood cultures, 26 different bacteria were isolated. *Klebsiella pneumonia* was the most commonly isolated organism in both, early onset sepsis (16/79) and late-onset sepsis (14/75), followed by *Acinetobacter baumannii* and *Enterobacter cloacae* (Table 2).

### Table 2. Comparison of microbial pattern.

| Microbial Pattern           | Early Onset Sepsis n (%) | Late Onset Sepsis n (%) |
|-----------------------------|--------------------------|-------------------------|
| *Pseudomonas aeruginosa*    | 9 (11.4)                 | 3 (4.0)                 |
| *Staphylococcus haemolyticus* | 1 (1.3)             | 3 (4.0)                 |
| *Klebsiella pneumonia*      | 16 (20.3)                | 14 (18.7)               |
| *Serratia moreseus*         | 4 (5.1)                  | 3 (4.0)                 |
| *Acinetobacter baumannii*   | 12 (15.2)                | 14 (18.7)               |
| *Salmonella sp*             | 4 (5.1)                  | 4 (5.3)                 |
| *Burkholderia cepacia*      | 3 (3.8)                  | 0 (0.0)                 |
| *Bacillus cereus*           | 6 (7.6)                  | 1 (1.3)                 |
| *Corynebacterium amylolatum*| 1 (1.3)                  | 2 (2.7)                 |
| *Corynebacterium jeikeium*  | 0 (0.0)                  | 1 (1.3)                 |
| *Elisabeth king*            | 2 (2.5)                  | 2 (2.7)                 |
| *Enterobacter cloacae*      | 5 (6.3)                  | 8 (10.7)                |
| *Enterobacter faecali*      | 2 (2.5)                  | 1 (1.3)                 |
| *Eschericia coli*           | 1 (1.3)                  | 3 (4.0)                 |
| *Kocuria kristinae*         | 1 (1.3)                  | 0 (0.0)                 |
| *Pseudomonas oryzihab*      | 1 (1.3)                  | 1 (1.3)                 |
| *Staphylococcus aureus*     | 4 (5.1)                  | 3 (4.0)                 |
| *Staphylococcus epidermidis*| 4 (5.1)                  | 6 (8.0)                 |
| *Staphylococcus lentus*     | 0 (0.0)                  | 1 (1.3)                 |
| *Staphylococcus kloos*      | 0 (0.0)                  | 1 (1.3)                 |
| *Flavimonas oryzi habitans*| 1 (1.3)                  | 0 (0.0)                 |
| *Pasteurella pneumoti*      | 0 (0.0)                  | 1 (1.3)                 |
| *Cupriavidus pauculus*      | 1 (1.3)                  | 0 (0.0)                 |
| *Pantoea, spp*              | 1 (1.3)                  | 1 (1.3)                 |
| *Bacteroides stercois*      | 0 (0.0)                  | 1 (1.3)                 |
| *Rhizonium radiobacter*     | 0 (0.0)                  | 1 (1.3)                 |
| **Total**                   | **79 (100)**             | **75 (100)**            |

Table 3 shows antibiotic resistance in all bacteria cultured. Antibiotic with the highest resistance was Ampicillin (78.6%), followed by 3rd generation cephalosporins (cefotaxime 75.3%, ceftriaxone 69.5%, ceftazidime (64.3%) and aminoglycoside (gentamicin 63%).

### Table 3. Antibiotic resistance in all samples.

| Antibiotics               | Resistance; n (%) |
|---------------------------|-------------------|
| Ampicillin                | 121 (78.6)        |
| Cefotaxime                | 116 (75.3)        |
| Amoxicillin-Clavulanic acid | 60 (39.0)       |
| Ceftazidime               | 99 (64.3)         |
| Ceftriaxone               | 107 (69.5)        |
| Gentamisin                | 97 (63.0)         |
| Meropenem                 | 55 (35.7)         |
| Vancomycin                | 12 (7.8)          |
| Amikacin                  | 26 (16.9)         |
| Amoxicillin               | 46 (29.9)         |
| Erythromycin              | 3 (1.9)           |
| Penicillin                | 6 (3.9)           |
4. Discussion

Sepsis is one of the most common reasons for neonatal hospital admissions and estimated to cause 26% of all neonatal deaths worldwide. During the waiting for the results of blood culture, it is necessary to initiate an empirical antibiotics treatment based on the epidemiology of causative agents and antibiotic sensitivity pattern.[9]

In this study, the incidence of neonatal sepsis was 24.6%, which is similar to the results of previous studies by Singh HK et al. [10] in India that incidence of neonatal sepsis was 16.78%. Bukhari and Alrabiaah reported a much lower incidence of 5% in Saudi Arabia.[11] Whereas in Nigeria, the incidence of neonatal sepsis was higher than the previous study, 43.5% of the 233 neonates admitted in Special Care Baby Unit (SCBU) were proven neonatal sepsis with positive blood culture.[9] West and Tabansi in Port Harcourt, in Nigeria also reported similar result, the incidence of neonatal sepsis was 41.6%.[12]

In this study, males were found to have a higher incidence of sepsis compared to female. Other researchers in Nigeria [13], Ethiopia [14], Iraq [15] reported similar findings. Whereas, Omorogie et al. [16] found no significant difference in the incidence of bacterial sepsis.

About 51.3% cases were early-onset sepsis, and 48.7% cases were late-onset sepsis, which is similar to the result of study by West and Tabansi in Port Harcourt that EOS was more likely to happen than LOS [12], but different from Muhammed et al [17] study in Pakistan and Jumah and Hassan [15] study in Iraq that reported a higher incidence of LOS.

The most common isolated organism in neonatal sepsis was Klebsiella pneumonia (19.5%), followed by Acinetobacter baumannii (16.9%) and Enterobacter cloacae (8.4%). In EOS, the most common isolated organism was K. pneumonia (20.3%), followed by Acinetobacter baumanii (15.2%), Pseudomonas aeruginosa (11.4%). Whereas in LOS, the most common isolated organism was K. pneumonia (18.7%), followed by Acinetobacter baumanii (18.7%) and Enterobacter cloacae (10.7%). The results were same as Singh HK et al. [10] that K. pneumonia was the most common isolated organism. In Nigeria [9], the most frequently isolated organism was Staphylococcus aureus.

In this study, we found high resistance in Amoxicillin (78.6%). This high resistance rate of amoxicillin here was similar to study by Shah et al. in one Indian neonatal ICU tertiary care hospital in 2012 (75%).[18] Increased resistance was also found in commonly used empirical therapies such as 3rd generation cephalosporins (cefotaxime, ceftriaxone, ceftazidime) and gentamicin. This high resistance of cefotaxime and ceftriaxone also found by Najeebet al. in Pakistan [19], where the resistance of cefotaxime and ceftriaxone were 63.1% and 66.9% respectively.

5. Conclusion

Neonatal sepsis remains a major problem in neonates. Gram-negative bacteria were the most common cause of early and late onset sepsis in Haji Adam Malik Neonatal ICU setup with K. pneumonia being the most common pathogen. Regular periodic surveillance of the causative organisms of neonatal sepsis is needed to implement the rational empirical choice of antibiotic prescription while waiting for blood culture result to come out.

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