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Clinical Manifestations of Neonatal Sepsis and Antibiotics Management in Newborn at Dr. Soetomo General Hospital Surabaya, Indonesia

Martono T. Utomo, Ni Luh Putu Herli Mastuti, Hodimatum Mahiroh, Talitha Y. Aden

Department of Child Health, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

Abstract

Background: Neonatal sepsis is a problem of morbidity and mortality that still occurs in neonates. This neonatal sepsis can cause 1/4 of the total deaths in neonates in the world. The incidence can increase to 13-27 cases per 1000 live births in babies born weighing <1500 grams.
Objective: This study was conducted to describe laboratory and culture results, clinical manifestations, and antibiotic management in infants diagnosed with neonatal sepsis.
Material and Methods: This research is an observational study with a case series retrospective study method. The subjects observed were 9 newborns and diagnosed with sepsis. Data were collected from medical records from June to August 2021. Most of the neonatal sepsis was early-onset, namely 6 neonates. .
Results: A total of 4 neonates were included in the Low Birth Weight and 6 neonates were born prematurely. A total of 4 neonates had hyperbilirubinemia, 2 neonates had leukopenia, and 4 neonates had thrombocytopenia. The most common microorganisms causing sepsis in neonates were Acinetobacter baumannii (4), Klebsiella pneumoniae (3), and Staphylococcus epidermidis (3). The most common clinical manifestation is fever (7). For antibiotic treatment, all neonates received initial antibiotic treatment of Ampicillin and Gentamicin with administration between 3-9 days. While the second antibiotic, as many as 7 neonates received antibiotics Cefoperazone sulbactam and Amikacin between 4-18 days.
Conclusion: From the results of the study, it can be concluded that culture and laboratory results are important for the proper administration of antibiotics. Surveillance of organisms causing sepsis should also be carried out regularly to plan appropriate treatment. Then there is a need for further research with a longer period to fully describe neonatal sepsis. Increased adherence to antibiotic stewardship also needs to be considered to prevent antibiotic resistance and improve patient outcomes.

Keywords: Neonatal Sepsis; Clinical Manifestation; Antibiotic

Introduction

Neonatal sepsis is a substantial cause of morbidity and mortality. The clinical manifestations of neonatal sepsis range from subclinical infection to severe manifestations of focal or systemic disease. The pathogenic source of sepsis may be related to in-utero infection, acquisition of maternal flora, or postnatal acquisition from the hospital or the immediate environment.[1] Neonatal sepsis causes 1/4 of the total deaths in neonates. The annual incidence of neonatal sepsis is 2-6 per 1000 live births in developed countries, whereas, in developing countries, the mortality rate due to neonatal sepsis is between 11-68/1000 live birth.[2] According to the World Health Organization (WHO), there are 10 million neonatal deaths out of 130 million babies born each year. WHO also estimates that of the five million neonatal deaths each year, developing countries account

for up to 98% of the percentage. The incidence can increase to 13-27 cases per 1000 live births in infants born weighing <1500 grams.[3]

Neonatal sepsis is defined as a clinical syndrome in infants aged 28 days or younger, which is manifested by systemic signs of infection and isolation of pathogenic bacteria from the bloodstream. Group B Streptococcus (GBS), a gram-positive organism, is the most common organism causing neonatal sepsis in Europe and North America. However, in developing countries, the organisms are dominated by gram-negative organisms.[2] The most common pathogenic bacteria causing sepsis in Dr. Soetomo General Hospital were coagulase-negative Staphylococci, E. Coli, Klebsiella Pneumonia, Enterococcus, Pseudomonas, and Staphylococcus aureus.[4]

Blood culture is considered the gold standard for diagnosis, but it is quite time-consuming.[2] Neonatal sepsis and early antibiotic therapy may influence bacterial colonization and immune activation after birth.[5] Alertness to clinical manifestations is very important because they can often represent early signs of sepsis. Staff involved in the Neonatal Intensive Care Unit (NICU) need to identify these signs of sepsis, in addition to other factors for a faster diagnosis.[2] This study aims to describe the characteristics of subjects diagnosed with neonatal sepsis, characteristics of supporting laboratories and culture results, clinical manifestations, and antibiotic treatment given to the subjects. So that appropriate and maximum treatment can be carried out to overcome neonatal sepsis.

Methods

The number of subjects that the researchers observed were 9 newborns diagnosed with neonatal sepsis and treated in the NICU of Dr. Soetomo General Hospital Surabaya. Data were collected from medical records from June to August 2021 which included culture results and supporting laboratory results starting from babies being treated in the NICU as well as outcomes from treatment. The method of this observation is a case series retrospective study. Clinical results, culture results, and laboratory results were investigated in this study.

Subject characteristics of 9 neonates consisting of onset, gender, birth weight, gestational age, mode of delivery, and outcome are presented in Table 1. While the characteristics of supporting laboratories and culture results are presented in Table 2. Clinical manifestations are presented in Table 3 and antibiotic treatment starting from the initial antibiotic to the fifth antibiotic is presented in Table 4. The role of the analyzed laboratory parameters consisted of hyperbilirubinemia, hypoglycemia, anemia, leukopenia, and thrombocytopenia.

Result

Most of the sepsis in neonates was early-onset, with as many as 6 neonates. A total of 4 neonates were included in the Low Birth Weight and 6 neonates were born prematurely. Five of these neonates were born spontaneously and 1 neonate was declared dead, but 2 neonates recovered after receiving intensive care at Dr. Soetomo General Hospital Surabaya (Table 1).

From the supporting laboratory results, some neonates had abnormal laboratory results. A total of 4 neonates had hyperbilirubinemia, 2 neonates had leukopenia, and 4 neonates had thrombocytopenia. The most common microorganism causing sepsis in neonates is Acinetobacter baumannii, which causes sepsis in 4 neonates. In addition, there were also Klebsiella pneumoniae ssp: ESBL which caused sepsis in 3 neonates, and Staphylococcus epidermidis which caused sepsis in 3 neonates (Table 2). The most common clinical manifestation in neonates with sepsis was fever, which was 7 neonates. A total of 5 neonates experienced

respiratory distress and 4 neonates also experienced a shock. In addition, 1 neonate had asphyxia and 1 neonate had seizures (Table 3).

Table 1. Subject Characteristics

Characteristics	(n)
Onset	
Early-onset (<=72 hours)	6
Late-onset (>72 hours)	3
Sex	
Male	5
Female	4
Birth Weight	
Normal	3
LBW (<2500 g)	4
VLBW (<1500 g)	2
Gestation Age	
Term (37-40 weeks)	3
Preterm (<37 weeks)	6
MOD	
Spontan	5
Caesarean Section	4
Outcome	
Recovered	2
Died	1
Under Treatment	6

Table 2. Laboratorium and Culture Result

Description	(n)
Laboratorium Results	
Hyperbilirubinemia	4
Hypoglicemia	1
Anemia	5
Leukopenia	2
Thrombocytopenia	4
Culture Results	
Klebsiella pneumoniae	3
Acinetobacter baumannii	4
Serratia marcescens	1
Staphylococcus epidermidis	3
Pseudomonas aeruginosa	2

All neonates with sepsis received initial antibiotic treatment of Ampicillin and Gentamicin with administration between 3 to 9 days. While the second antibiotic, as many as 7 neonates received antibiotics Cefoperazone sulbactam and Amikacin between 4 to 18 days. There was 1 neonate who received the second antibiotic Meropenem for 8 days. A total of 4 neonates received the third antibiotic Meropenem for 8 to 10 days, two neonates received the third antibiotic Fosfomycin and one neonate received Colistin, and two neonates

received the fourth and fifth antibiotics. The third antibiotic included culture results and antibiotic sensitivity. Of the 7 infants who received antibiotic treatment to the third, 3 of them showed Klebsiella pneumoniae culture results. Only 1 infant was given the third antibiotic according to the antibiotic sensitivity results (Table 4).

Table 3. Clinical Manifestation in Neonates with Sepsis

Clinical Manifestation	(n)
Fever	7
Shock	4
Respiratory Distress	5
Breathless	3
Asphyxia	1
Seizure	1

Table 4. Antibiotic Management in Neonates with Sepsis

Case	Initial Antibiotic (days)	Second Antibiotic (days)	Third Antibiotic (days)	Fourth Antibiotic (days)	Fifth Antibiotic (days)
1	Ampicilin (9) Gentamicin (9)	Cefoperazone sulbactam (4) Amikasin (14)	Meropenem (10) Endotracheal Tube culture result: Klebsiella Pneumoniae Sensitif: Amikasin, Tazobactam, Sulbactam.	Cotrimoxazole (9)	Levofloxacin (16)
2	Ampicilin (5) Gentamicin (5)	Cefoperazone sulbactam (4) Amikasin (4)	Meropenem (8) Sputum culture result Klebsiella pneumoniae Sensitif: Tazobactam, Cepoperazone, Sulbactam.	Colistin (2) Cotrimoxazole (2)	
3	Ampicilin (5) Gentamicin (5)	Cefoperazone sulbactam (4) Amikasin (4)	Meropenem (8) Sputum culture result: Klebsiella pneumoniae Sensitif: Amoxicillin, Clavulanic, Acid piperacilin, Tazobactam.		
4	Ampicilin (3)	Meropenem (8)			

	Gentamicin (3)				
5	Ampicilin (7) Gentamicin (7)	Cefoperazone sulbactam (8) Amikasin (8)	Fosfomycin (9) Blood culture result: Staphylococcus epidermidis Sensitif: Linezoid, Teicoplamin, Tetracyclin, Vancomycin.		
6	Ampicilin (8) Gentamicin (8)	Cefoperazone (7) Amikasin (7)	Colistin Blood culture result: batang gram negatif Hasil kultur ETT: Staphylococcus negatif Sensitif: -		
7	Ampicilin (6) Gentamicin (6)	Cefoperazone sulbactam (5) Amikasin (4)	Fosfomycin (9) Culture result: Staphylococcus epidermidis Sensitif: Chloramphenicol, Liprofloxacin, Fosfomycin.	Ceftazidim (7)	
8	Ampicilin (7) Gentamicin (7)				
9	Ampicilin (4) Gentamicin (4)	Cefoperazone sulbactam (18) Amikasin (18)	Meropenem (8) Culture result: Pseudomonas aeruginosa Sensitif: Cotrimoxazole.	Levofloxacin (8)	Colistin meropenem

Discussion

Most neonates develop early-onset sepsis because this can occur in utero either transplacental or due to ascending bacteria entering the uterus from the vaginal environment after rupturing of the membranes. In addition, newborns can become infected when exposed to potentially pathogenic bacteria, viruses, or fungi during passage through the birth canal. The human birth canal is colonized with aerobic and anaerobic bacterial

organisms that can be transmitted vertically from ascending amniotic fluid infection or neonatal natal infection during labor or delivery.[1] In addition, the majority of neonates include LBW and prematurity which are health risk factors for neonates in industrialized and developing countries.[6] Research conducted in Bangladesh and Bishoftu showed that infants with LBW can have a significant effect on neonatal sepsis.[7,8] Then babies born prematurely are susceptible to sepsis due to the immunological immaturity of the neonate which can result in impaired response to infectious agents, especially in premature infants who have a long stay in the hospital and require invasive procedures[1]. Several neonates died from sepsis, the main possible underlying causes of death from neonatal sepsis are conditions originating in the perinatal period and congenital malformations. Sepsis is associated with preeclampsia, urinary tract infection, Apgar at 1 and 5 minutes, and the occurrence of late death.[9] According to research conducted by Alves JB, *et.al.* (2017), sepsis was implicated in 2.3 deaths per 1,000 live births.[9]

Some neonates have hyperbilirubinemia, leukopenia, and thrombocytopenia. In a study conducted by Shresta A, Shresta S, and Basnet R in 2020, only 7% of infants with sepsis developed thrombocytopenia. Thrombocytopenia caused by Candida spp or K. pneumoniae is more serious than that caused by other bacteria.[10] Abnormal laboratory results consisting of hyperbilirubinemia, leukopenia, and thrombocytopenia were significantly associated with neonatal sepsis (p-value < 0.05).[2] Whereas in another study, leukopenia occurred in more than 40% of neonatal sepsis caused by E.coli, K. pneumoniae, or Candida spp and about 30% due to co-NS, S. agalactiae, or Enterococcus spp.[10] Therefore, laboratory parameters are also important to identify neonatal sepsis. According to research results, Acinetobacter baumanii is the organism that causes the most sepsis in neonates, followed by Klebsiella pneumoniae ssp: ESBL and Staphylococcus epidermidis. Meanwhile, in a study conducted by Shresta A, Shresta S, and Basnet R in 2020, the most common bacterial isolates causing sepsis were Klebsiella spp (48%) followed by CoNS (17%), Acinetobacter spp (14%), Enterobacter spp. (7%), Pseudomonas (7%) and Staphylococcus aureus (7%).[2]

The clinical manifestations of neonatal sepsis are highly variable and non-specific so that early diagnosis of neonatal sepsis is difficult. Clinical signs of neonatal sepsis include apnea, difficulty breathing, cyanosis, tachycardia or bradycardia, shock, irritability, lethargy, hypotonia, convulsions, abdominal distension, vomiting, food intolerance, gastric residue, hepatomegaly, jaundice, instability of body temperature, and purpura.[11] Clinical manifestations experienced by neonates with sepsis in this study were fever, respiratory distress, shock, asphyxia, and seizures. In the study of Fitriani EC, Amalia Y, & Andriana D in 2019, neonates with sepsis experienced asphyxia, 9 of them were alive and 3 of them died. According to research conducted by Li X, et. al. (2019), symptoms of respiratory distress occurred in 39.13% and asphyxia in 22.98% of neonates with early-onset sepsis. While febrile of 40.56% occurred in late-onset sepsis.[12] Diagnosis of neonatal sepsis is quite difficult because the clinical symptoms, especially in the early stages, are difficult to distinguish from other neonatal diseases. Therefore, for early diagnosis and treatment, there is a need for continuous evaluation of risk factors, clinical symptoms and manifestations, followed by laboratory results and culture results.[12] In a retrospective cohort study, neonates with bacteremia 19.4% of the population developed septic shock and were associated with 57.1% mortality.[13] Septic shock in newborns can cause morbidity and mortality depending on the causative organism and its primary transmission.[14]

The use of empirical antibiotics in neonates at Dr. Soetomo General Hospital Surabaya with a diagnosis of sepsis caused by coagulase-negative Staphylococcal pathogens, E coli, Klebsiella pneumonia, Enterococcus, Pseudomonas, and Staphylococcus aureus is Ampicillin and Gentamicin with a duration of 3-14 days and a dose of 50 mg/ kgBW /dose every 12 hours per day for Ampicillin, 5 mg/kgBW/dose for Gentamicin.[4] This is also consistent with a study conducted in Brazil that the antibiotics Ampicillin and Gentamicin were given as empiric antibiotics for neonatal sepsis patients.[11] As for the second antibiotic, namely Cefoperazone sulbactam at a dose of 50 mg/kgBW/dose every 8-12 hours per day and Amikacin at a dose of 7.5 mg/kgBW/dose with administration adjusted to the chronological age of the patient. Both antibiotics are given in 3-14 days. The third

antibiotic is Meropenem at a dose of 20-40 mg/kgBW/dose and is given according to age, while Amikacin is given at a dose of 7.5 mg/kg/time according to chronological age. Both antibiotics are given in 10-14 days as definitive therapy according to culture results or approval of the ASP team (PGA-KPRA).[4] Some neonates in this study received antibiotics Fosfomycin and Colistin on the third antibiotic administration. Evidence for the use of Fosfomycin in neonates is limited. Fosfomycin has a broad spectrum of activity and is used as a combination therapy for gram-positive neonatal sepsis. Several studies have described the successful use of Fosfomycin in neonatal gram-negative sepsis as monotherapy for a cohort of neonates with E coli enterocolitis. In this treatment, Fosfomycin is combined with Gentamicin, some are combined with Meropenem for intracranial Citrobacter infection.[15] In this study, some neonates received the antibiotic Colistin, according to a study conducted by Pokhrel B, et. al. (2018) Klebsiella showed good susceptibility to Colistin which was 88.8%.[16] Cotrimoxazole, Ceftazidime, and Levofloxacin antibiotics were used at the fifth administration in some of the patients in this study. Cotrimoxazole has been shown to have a sensitivity of 16.67% on Acinetobacter spp.[17] Five of the 7 gram-negative bacteria found in culture media were sensitive to Ceftazidime and 2/5 of the subjects had an improved response after receiving Ceftazidime.[18] Based on the results of the susceptibility test, gram-positive organisms showed moderate sensitivity to 55% Levofloxacin. Meanwhile, for staphylococci (CONS) Levofloxacin showed a sensitivity of 54%.[19]

In this study, infants with Klebsiella pneumoniae culture results on the third antibiotic treatment were treated with Meropenem. Klebsiella pneumoniae is an antibiotic-resistant bacterium and produces Extended-Spectrum Beta-Lactamase (ESBL).[4] In a study conducted by Yadav NS, et. al. In 2018, Meropenem is the drug of choice for the treatment of neonatal sepsis in particular Klebsiella pneumoniae and other Gram-negative strains.[20] Only 1 infant received antibiotic treatment according to their antibiotic sensitivity in this study. Most of the infants received the third antibiotic Meropenem, but this antibiotic was not included in the antibiotic sensitivity of these infants. This is not by the principle of antibiotic stewardship, because if it is not by the patient's antibiotic sensitivity, it will prolong the duration of treatment so that the use of antibiotics will be longer. Inappropriate administration of antibiotics and in the long term can trigger resistance. Inappropriate administration of antibiotics is caused by prescribing antibiotics by doctors based on clinical experience rather than culture results.[21] Therefore, it is important to comply with antibiotic stewardship to improve antibiotic policy compliance, reduce the duration of antibiotic administration, reduce treatment costs, improve patient outcomes, and reduce resistance. One of the antibiotic stewardship efforts that can be done is operational planning and monitoring.[21]

This was a retrospective design with a short period, which was the limitation of this study. Therefore, longer-term studies are needed to validate our findings.

Conclusion

Most neonatal sepsis is early-onset with some abnormal laboratory results. The most common microorganism causing neonatal sepsis is Acinetobacter baumanii. In addition, the most common clinical manifestation is fever. In this study, all neonates received empiric antibiotics Ampicillin and Gentamicin. The results of culture and laboratory results are very important for the proper and maximal administration of antibiotic treatment and the management of abnormal laboratory results. Surveillance of organisms causing sepsis should also be carried out regularly to plan appropriate treatment. In addition, it is necessary to increase adherence to antibiotic stewardship to prevent antibiotic resistance and improve patient outcomes.

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