

# Evaluation of antibiotic prescriptions for sepsis in the Neonatal Intensive Care Unit in a Tertiary Hospital in North Sumatera, Indonesia

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**A** – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

**Summary Background.** Neonatal sepsis is a leading cause of morbidity and mortality worldwide. The evaluation of antibiotic prescription in neonatal intensive care units (NICUs) is important for reducing inappropriate antibiotic use and minimizing the development of antibiotic resistance. Antimicrobial stewardship programs potentially promote a prudent use of antibiotics; however, the approach in NICUs is not yet optimal.

**Objectives.** The aim of our study was to evaluate antibiotic prescriptions for neonatal sepsis in a tertiary hospital in North Sumatera, Indonesia.

**Material and methods.** In our retrospective study, we collected data from medical records and enrolled 324 neonatal sepsis patients who received one or more antibiotics.

**Results.** Gentamycin and cefotaxime were the two most common antibiotics prescribed in the NICU (72.22% and 71.60%, respectively). However, high levels of resistance to gentamycin and cefotaxime were found among common pathogens circulating in the NICU (55.56% and 82.81%, respectively). Only 40.33% of the antibiotic prescriptions were appropriate: approximately 15.11% of the patients had received antibiotics with incorrect indications and 16.16% of the antibiotics had been administered without sufficient duration.

**Conclusions.** The appropriate use of antibiotic prescriptions in the NICU was low, which may lead to high mortality in neonatal sepsis patients. Continued evaluation of antibiotic usage by implementing antimicrobial stewardship programs in the NICU is important.

**Key words:** anti-bacterial agents, neonatal sepsis, prescriptions.

Pasaribu AP, Syofiani B, Fahmi F, Dalimunthe FA, Nasution MJ, Pasaribu S. Evaluation of antibiotic prescriptions for sepsis in the Neonatal Intensive Care Unit in a Tertiary Hospital in North Sumatera, Indonesia. *Fam Med Prim Care Rev* 2021; 23(3): 337–340, doi: <https://doi.org/10.5114/fmpr.2021.108200>.

## Background

Neonatal sepsis is one of the major causes of infant mortality, accounting for 13% of neonatal deaths worldwide, especially in developing countries [1]. Antibiotics are the most commonly used medications in newborn wards and neonatal intensive care units (NICUs) [2]. Neonatal sepsis has nonspecific manifestations and results in serious complications. Therefore, clinicians often administer antibiotics to infants at high risk of sepsis during hospitalization, despite only 5% of culture results returning positive [2, 3]. Approximately 60% of antibiotics are administered for more than 72 hours even in the presence of a negative blood culture, and a prolonged use of antibiotics is known to increase the risk of late-onset sepsis, necrotizing enterocolitis, and even death [3, 4]. Some studies have found that the overuse of antibiotics in NICUs is common in developing countries, where 35% of neonates received at least one inappropriate antibiotic during their stay [5, 6]. Inappropriate use of antibiotics is associated with the development and spread of resistant pathogens [7, 8]. Multidrug-resistant strains causing sepsis are associated with increased mortality, excessive cost, and therapeutic challenges [9]. A prudent use of antibiotics in

the NICU is very important for the protection of this vulnerable population [10].

## Objectives

The aim of this study was to evaluate antibiotic prescriptions for neonatal sepsis in a tertiary hospital in North Sumatera, Indonesia. The assessment of antibiotics prescribed in the NICU as part of antimicrobial stewardship programs is necessary to evaluate the appropriate choice of antibiotics.

## Material and methods

The Adam Malik Hospital is a tertiary hospital in North Sumatera, Indonesia. It has a special ward for babies and an NICU with 30 beds. Each month, 30–60 babies are treated in this ward. The majority of the diagnoses are for sepsis, and the patients are prescribed various antibiotics. We conducted a retrospective study based on medical records. All neonates who were hospitalized in 2018 and diagnosed with sepsis – either confirmed by blood culture results or clinically suspected



– and who received one or more antibiotics were included in this study. Incomplete data or medical records that could not be found were grounds for exclusion. Sensitivity to various antibiotics was also found in the culture results. Empirical antibiotics were considered inappropriate if the pathogens were resistant to the antibiotic used. Demographic variables such as sex, type of sepsis, and pathogens found were analyzed, as well as variables associated with the use of antibiotics such as type of antibiotics, dosage, duration, and reason for switching or stopping.

We assessed the quality of antibiotic use according to the method of Gyssens et al. to evaluate each parameter of importance associated with antibiotic use [11, 12]. Antibiotic usage was evaluated based on the Gyssens flowchart as follows: appropriate use (0), incomplete data for evaluation (VI), no antibiotic indication (V), improper choice of antibiotic (IVA–IVD), inadequate duration (IIIA–IIIB), and improper dosage interval (IIA–IIC, I).

Prescriptions were considered therapeutic if the medical record contained information that the antibiotic was prescribed for treatment or that any clinical sign of infection occurred. Antibiotics were considered prophylactic if the medical record stated that the antibiotic was prescribed for prevention. Three investigators, one Pediatric Infectious Diseases Consultant and two clinical pharmacologists, independently reviewed the medical records. The assessment of each reviewer was summarized in a combined evaluation when at least two reviewers evaluated the prescription as appropriate, not indicated, or inappropriate.

All statistical procedures were performed using STATA version 15.1 (Stata Corporation, College Station, Texas, USA). Descriptive data are expressed as the mean and percentage (%).

The Universitas Sumatera Utara Institutional Review Board (IRB) approved the protocol for this study (no. 239/TGL/KEPK FK USU-RSUP HAM/2019).

## Results

A total of 351 neonates were admitted to the NICU in 2018, and 324 of them were diagnosed with sepsis and administered one or more antibiotics. Approximately half (58.6%) of them were female and 83.65% had been diagnosed with clinical sepsis. Detailed characteristics of the patients are shown in Table 1.

Characteristics	Number of patients (n = 324)	Percent of patients
Sex		
male	134	41.36
female	190	58.6
Type of sepsis		
EOS	55	16.98
LOS	269	83.02
Diagnosis		
confirmed sepsis	53	16.36
clinical sepsis	271	83.65
Outcome		
discharged	214	66.05
died	80	24.69
discharged by request	30	9.26

EOS – early onset sepsis; LOS – late onset sepsis.

About 50% (165/324) of the patients received antibiotics without any culture being performed. Only 49.1% (159/324) of the samples from the patients were cultured. The most common pathogen isolated was *Klebsiella pneumoniae* (15 out of 159 samples, 9.43%). Approximately 62% of the blood cultures performed showed no growth of any bacteria (Table 2).

The most commonly used antibiotic in the NICU was gentamycin, which was prescribed 234 times, followed by cefotaxime (232) and metronidazole (55) as the second and third most used

antibiotics, respectively. A total of 14 different antibiotics were used in the NICU in 2018 (Table 3).

Table 2. Result of blood culture and most common pathogen found (n = 159)

Pathogen	Number of samples, n (%)
No growth	99 (62.26)
<i>Klebsiella pneumoniae</i>	15 (9.43)
<i>Escherichia coli</i>	9 (5.66)
<i>Salmonella sp.</i>	9 (5.66)
<i>Acinetobacter baumannii</i>	8 (5.03)
<i>Staphylococcus aureus</i>	4 (2.52)
Other	15 (9.43)

Table 3. Top five most common antibiotics prescribed

Antibiotics	Number of prescriptions, n (%)
Cefotaxime	232 (71.60)
Gentamycin	234 (72.22)
Metronidazole	55 (16.98)
Amikacin	50 (15.43)
Meropenem	39 (12.04)
Other	52 (16.07)

Overall, 324 medical records containing 662 antibiotic prescriptions were reviewed. Among the different kinds of antibiotics, ampicillin (62.5%) and cefotaxime (82.81%) were used inappropriately most frequently, while fosfomycin (100%) was used appropriately (Table 4).

Table 4. Appropriate use of antibiotics based on the Gyssens flowchart

Antibiotics	Appropriate use, n (%)	Inappropriate use, n (%)
Cefotaxime (n = 232)	41 (17.67)	191 (82.81)
Gentamycin (n = 234)	104 (44.44)	130 (55.56)
Amikacin (n = 50)	31 (62)	19 (38)
Meropenem (n = 39)	23 (58.97)	16 (41.03)
Metronidazole (n = 55)	39 (70.91)	16 (29.09)
Ampicillin (n = 8)	3 (37.50)	5 (62.50)
Ampicillin-sulbactam (n = 30)	18 (60)	12 (40)
Cefoperazone-sulbactam (n = 2)	2 (100)	0 (0)
Clindamycin (n = 3)	2 (66.67)	1 (33.33)
Cefazolin (n = 3)	0 (0)	3 (100)
Ceftazidime (n = 3)	2 (66.67)	1 (33.33)
Vancomycin (n = 2)	1 (50)	1 (50)
Fosfomycin (n = 1)	1 (100)	0 (0)
Total	102	560

Table 5. Reasons for inappropriate use of antibiotics

Reason for inappropriate use	Number of prescriptions (n = 662)	Percentage (%)
Improper choice of antibiotic	183	27.63
Inadequate duration	107	16.16
No antibiotic indication	100	15.11
Improper dosage interval	3	0.45
Cannot be evaluated (data incomplete)	2	0.30
Appropriate use of antibiotics	267	40.33

Antibiotic therapy was found to be inappropriately used in 59.67% of the prescriptions. The most common reason for inappropriate use was that more effective antibiotics could have been chosen (27.63%). The second most common reason was ineffective/inadequate duration of antibiotic administration against the suspected infection (16.6%). Approximately 15% of the antibiotics used were without indication (Table 5).

## Discussion

This study was conducted to evaluate antibiotic prescriptions in the NICU of Adam Malik General Hospital. Complete documentation of clinical features, neonatal sepsis risk factors, laboratory examinations, and management were retrieved from the medical records of all neonatal sepsis patients in 2018 that met the inclusion and exclusion criteria. In our study, we found that more females (58.6%) were admitted to the NICU than males. This finding was different from a study performed by Tank et al. in Kenya and Pokhrel et al. in Nepal [13, 14]. Pokhrel et al. found that early-onset sepsis patients were admitted more frequently to the NICU than late-onset sepsis patients; however, in our study, we found that more neonates with late-onset sepsis were admitted to our NICU [13]. This may be explained by our hospital being a tertiary hospital that receives referral cases from other hospitals. Sepsis was confirmed in only 16.36% of all cultures included in our study. This rate was higher than the one found by Tank et al., who reported only 4% culture positivity, but it was similar to that reported by Prusakov et al., citing 20% confirmed sepsis cases in their study [2, 14]. Low culture positivity is a common problem in pediatric patients, particularly in neonates. The difficulty of the procedure for blood sampling, especially obtaining the optimal volume, is a subject of controversy due to several obstacles, such as low intravascular volume and the risk of causing anemia [15].

*Klebsiella pneumoniae* was the most common pathogen that we found (4.63%). This finding was similar to the study conducted by Almohammady et al. in Cairo, who reported an incidence rate of 45.3% for *K. pneumoniae* among all isolates [16]. However, a study by Yadav et al. found that *Staphylococcus aureus* was the most common isolate among neonatal sepsis patients in Nepal [17]. Approximately 30% of our patients did not show any microbial growth. This finding was higher than the rate found in studies by Yadav et al. and Weldu et al. [17, 18].

Antibiotics are the most common drugs prescribed for neonates in the NICU [19]. Given the high mortality associated with neonatal sepsis and the presence of maternal and neonatal risk factors, empirical antibiotics are frequently administered to neonates in the NICU [20]. Gentamycin was the most common antibiotic prescribed in our NICU (72.22%), followed by cefotaxime (71.60%). This finding was similar to the results of studies conducted by Prusakov et al. [2]. A combination of meropenem and amikacin was the recommended antibiotic therapy in a study by

Weldu et al., while in our study the most commonly selected combination antibiotic in the NICU was cefotaxime and gentamycin [18]. The different choices of empiric antibiotics were based on the pathogen distributions in particular hospitals.

Antibiotic resistance is a serious global health problem caused by overusing antibiotics. Microbial resistance to antibiotics has increased rapidly over the last few decades with the emergence of super-resistant microbial strains that commonly do not respond to general antibiotics [21]. The overuse of antibiotics is also found in the NICU, where neonates are frequently exposed to antibiotics prescribed for a suspected or proven infection [22]. Cefotaxime was one of the most commonly used antibiotics in our NICU. Surprisingly, we discovered that 82.81% of the pathogens found in the cultures were resistant to cefotaxime, followed by 55.56% which were resistant to gentamycin. Therefore, we concluded that the choice of antibiotics for treating neonatal sepsis in our NICU was inappropriate. Our finding was in line with the results of sensitivity tests of antibiotics performed by Pokhrel et al., but was different from the results of a study by Yadav et al. [13, 17].

In our study, only 40.33% of antibiotic prescriptions were appropriately prescribed based on qualitative analysis, according to the Gyssens flowchart. This finding was lower than that of a study conducted by Tank et al. [14]. Approximately 59.67% of antibiotics prescribed in our NICU were inappropriately used for various reasons. One hundred neonates (15.11%) received antibiotics even though there was no information on the clinical manifestation, risk factors, or any laboratory results supporting the presence of infection. Our finding was similar to a multicentre study by Hashmi et al. [23]. One hundred seven neonates (16.16%) in our study were prescribed an inadequate duration of antibiotic treatment. Despite the improvement of the clinical manifestation of sepsis in neonates, a prolonged use of antibiotics was observed. A similar observation was also reported by Al-Turkait et al. [24]. Because neonatal sepsis could negatively impact mortality, many physicians are sometimes hesitant to discontinue antibiotic administration despite improvement in infection symptoms or clinical appearance [24, 25].

## Conclusions

In conclusion, neonatal sepsis is a life-threatening condition, and antibiotics are essential for clearing infections. However, antibiotic administration is not without risk. The inadequate use of antimicrobial agents will contribute to an increase in neonatal drug-resistant bacterial infections in the NICU, which will lead to high mortality. A comprehensive approach consisting of a rational use of empirical therapy and the discontinuation of therapy when appropriate, the evaluation of antibiotic consumption, and an antimicrobial stewardship program in the NICU are needed to prevent the emergence of drug resistance in the NICU.

Source of funding: This study was supported by RISTEKDIKTI grant scheme DRPM 2019 3/UN5.2.3.1/PPM/KP-DRPM/2019.

Conflicts of interest: The authors declare no conflicts of interest.

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Tables: 5

Figures: 0

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Received: 03.04.2021

Reviewed: 18.04.2021

Accepted: 13.06.2021

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