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Bacterial patterns and antibiotic susceptibility among neonatal sepsis in Prof. Dr. I.G.N.G. Ngoerah Hospital, Bali, Indonesia



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I Gusti Amanda Jaya¹, I Wayan Gustawan^{1*}, Made Sukmawati¹,
Ni Nengah Dwi Fatmawati²

¹Child Health Department, Faculty of Medicine, Universitas Udayana, Prof. dr. I.G.N.G Ngoerah Hospital, Denpasar, Bali, Indonesia;

²Clinical Microbiology Department, Faculty of Medicine, Universitas Udayana, Prof. Dr. I.G.N.G. Ngoerah Hospital, Denpasar, Bali, Indonesia.

*Corresponding author:

I Wayan Gustawan;

Child Health Department, Faculty of Medicine, Universitas Udayana, Prof. dr. I.G.N.G Ngoerah Hospital, Denpasar, Bali, Indonesia;

iwayangustawan@gmail.com

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ABSTRACT

Background: Neonatal sepsis has the main cause of mortality and morbidity in neonates worldwide; the most frequent cause is bacteria. This study examined the bacterial patterns and antibiotic susceptibility in neonatal sepsis at Prof Ngoerah Hospital, Bali.

Methods: This observational, descriptive study was conducted in Prof Ngoerah Hospital, Bali, Indonesia involving neonatal sepsis confirmed with blood culture. Data on antibiotic susceptibility and bacterial patterns were collected retrospectively from the registry of neonates patients with neonatal sepsis from January 2021 to August 2022.

Results: The predominance of gram-negative bacteria was *Acinetobacter baumannii* (29.17%), *Klebsiella pneumoniae* (10.42%), and the predominance of gram-positive bacteria was *Staphylococcus haemolyticus*

(14.58%), *Staphylococcus epidermidis* (8.35%). The susceptibility was Gentamicin (57.29%), Ciprofloxacin (56.84%), Levofloxacin (55.21%), Trimethoprim/sulfamethoxazole (54.17%), Amikacin (50%), Meropenem (39.58%), Ampicillin/sulbactam (34.38%), Cefepim (32.29%), Piperacillin/Tazobactam (28.13%), Cefoperazone sulbactam (25%), Tigecycline (25%), Ceftriaxone (23.96%), and Vancomycin (22.92%).

Conclusion: Gram-negative bacteria were a common infection. This study suggests that the reconsideration of gentamicin still can be an option as an empirical antibiotic, but ampicillin has low sensitivity; another broad-spectrum antibiotic with better sensitivity is another option due to its significantly higher susceptibility.

Keywords: antibiotic susceptibility, bacterial pattern, neonatal sepsis.

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INTRODUCTION

Neonatal sepsis is a systemic response that responds to infection in newborns, which is one of the main causes of mortality and morbidity in neonates worldwide. The incidence of neonatal sepsis worldwide reaches around 3 million neonates (22 per 1000 live birth group).¹ The incidence of neonatal sepsis is still relatively high in developing countries, reaching 1.8-18 per 1,000 live births.² The incidence in several referral hospitals in Indonesia reaches 1.5%-3.7% with a mortality rate of 37.1%-80%. The incidence of neonatal sepsis at Prof Ngoerah Hospital Denpasar in 2010 reached 5% with a mortality rate of up to 30.4%, and in 2011 reached 48% with positive blood culture.³

Based on the onset of symptoms, neonatal sepsis is divided into 2: early-

onset neonatal sepsis (EONS) and late-onset neonatal sepsis (L.O.N.S.).⁴ This systemic infection arises due to various causative pathogens such as viruses, bacteria, or fungi that can be detected in blood culture, and the most frequent is bacteria. Pathogenic bacteria differ from one country to another or between hospitals and impact the choice of antibiotic therapy. Excessive use of antibiotics can increase the consequences of increased morbidity, mortality, costs, and length of stay in the hospital, and the use of antibiotics is quite high, closely related to the increase in the problem of antibiotic resistance.⁵⁻⁷

Until now, the empirical antibiotics used for neonatal sepsis patients at Prof Ngoerah Hospital, Bali, are ampicillin and gentamicin. Based on the description

above, this study aims to evaluate the bacterial patterns and antibiotic susceptibility in neonatal sepsis at Prof Ngoerah Hospital, Bali. The results can be used as a reference as the basis for giving empirical antibiotics for neonatal sepsis.

METHODS

This observational, descriptive study was conducted in Prof Ngoerah Hospital, Bali. This study sample was selected by consecutive sampling. The inclusion criteria were neonates, examined for culture and antibiotic sensitivity with blood specimens. If data from medical records were incomplete or could not be read, the samples were excluded. Data were collected retrospectively from the blood culture registry of patients with neonatal

sepsis from January 2021 to August 2022. The sample size was determined using a single population proportion formula with the following assumption: proportion of neonatal sepsis that confirmed with positive blood culture in the population to be 48% margin of sampling error tolerated 5% at 95% confidence interval; this required sample size of 96 neonates.

Data collection was analyzed using the S.P.S.S. program for Windows, version 25.0. This study was approved by the Research Ethics Committee of the Faculty of Medicine University of Udayana and Prof Ngoerah Hospital with ethical clearance number 2187/UN14.2.2.VII.14/L.T./2022.

RESULTS

The characteristics of the research subjects

There were 690 with sign and symptom neonatal sepsis, 96 patients (13.91%) with confirmed blood culture and fulfilled inclusion and exclusion criteria. Bacterial patterns and antibiotic susceptibility were collected retrospectively (January 2021 to August 2022) from a blood culture registry from neonatal sepsis. Table 1 summarizes the characteristics of our research subjects (96 patients).

Identification of Microorganisms in the positive culture

The bacterial pattern was categorized into gram-positive and gram-negative microorganisms. As shown in Table 2, we found a higher proportion of gram-negative organisms (66; 68.75%) than gram-positive organisms (30; 31.25%).

Antibiotic sensitivity among isolated microorganisms

This study investigated the antibiotic sensitivity pattern among 96 isolated bacteria. Antibiotic with highest sensitivity rates overall were Gentamicin (57.29%), Ciprofloxacin (56.25%), Levofloxacin (55.21%), Trimethoprim/sulfamethoxazole (TMP/SM) (54.17%), Amikacin (50%), Meropenem (39.58%), Ampicillin/sulbactam (34.38%), Cefepim (32.29%), Piperacillin/Tazobactam (28.13%), Cefoperazone sulbactam (25%), Tigecycline (25%), Ceftriaxon (23.96%), Vancomycin (22.92%) as seen in Figure 1.

Table 1. Characteristics of research subjects

Characteristics	Total (n=96)
Gender	
- Male	52 (54.17%)
- Female	44 (45.83%)
Gestational age	
- Term	42 (43.75%)
- Preterm	54 (56.25%)
Birth weight	
- ≥ 2500 grams	46 (47.92%)
- < 2500 grams	50 (52.08%)
Outcome	
- Survived	39 (40.62%)
- Demised	57 (59.38%)
Onset	
- EONS	77 (80.20%)
- L.O.N.S.	19 (19.80%)

Table 2. Isolated pathogens from blood cultures

General	Species	Total (N=96)	Percentage (%)
Gram-positive bacteria			
	<i>Enterococcus faecalis</i>	2	2.08
	<i>Staphylococcus aureus</i>	2	2.08
	<i>Staphylococcus coagulase negative</i>	1	1.04
	<i>Staphylococcus epidermidis</i>	8	8.35
	<i>Staphylococcus haemolyticus</i>	14	14.58
	<i>Staphylococcus hominis</i>	1	1.04
	<i>Streptococcus dysgalactiae</i>	1	1.04
	<i>Streptococcus pyogenes</i>	1	1.04
Gram-negative bacteria			
	<i>Achromobacter xylosoxidans</i>	1	1.04
	<i>Acinetobacter baumannii</i>	28	29.17
	<i>Acinetobacter iwoffii</i>	4	4.17
	<i>Acinetobacter junii</i>	1	1.04
	<i>Burkholderia cepacia</i>	1	1.04
	<i>Enterobacter cloacae</i>	5	5.21
	<i>Escherichia coli</i>	4	4.17
	<i>Klebsiella oxytoca</i>	1	1.04
	<i>Klebsiella pneumoniae</i>	10	10.42
	<i>Pantoea agglomerans</i>	2	2.08
	<i>Pseudomonas aeruginosa</i>	2	2.08
	<i>Pseudomonas oryzae</i>	1	1.04
	<i>Serratia marcescens</i>	4	4.17
	<i>Sphingomonas paucimobilis</i>	1	1.04
	<i>Stenotrophomonas maltophilia</i>	1	1.04

Antibiotics with highest sensitivity rates in gram-negative bacteria were Amikacin (72.73%), Gentamicin (60.61%), Meropenem (57.58%), Ciprofloxacin (53.03%), TMP/SM (51.52%), Levofloxacin (48.48%), Ampicillin/sulbactam (39.39%), Cefepim (39.39%), Cefoperazone sulbactam (36.36%), Piperacillin tazobactam (30.30%), Tigecycline (27.27%) as seen in Figure 2.

Antibiotics with highest sensitivity rates in gram-positive bacteria were Vancomycin (73.33%), Levofloxacin (70%), Ciprofloxacin (63.33%), TMP/SM (60%), Clindamycin (60%), Tetracycline (56.67%), Linezolid (50%),

Gentamicin (50%), Doxycycline (43.33%), Moxifloxacin (43.33%), Erythromycin (30%) as seen in Figure 3.

DISCUSSION

Neonatal sepsis is a systemic response to infection in newborns, one of the main causes of mortality and morbidity in neonates worldwide.¹ In this study, 52 (54.17%) subjects were male, and the other 44 (45.8%) were female. Compared to the results of a study in India in 2015, it was found that male neonates had a higher rate than female neonates.^{8,9} It is because the factors that regulate the

synthesis of gammaglobulin may be located on the X chromosome, providing more immunological protection in female infants.¹⁰

The preterm group (56.25%) had higher results than the term group (43.75%) in this study. According to a study in 2017, preterm neonates are more

common than term neonates.¹¹ Low birth weight (52.08%) was higher than normal. It is caused by immaturity of the immune system, prolonged mechanical ventilation,

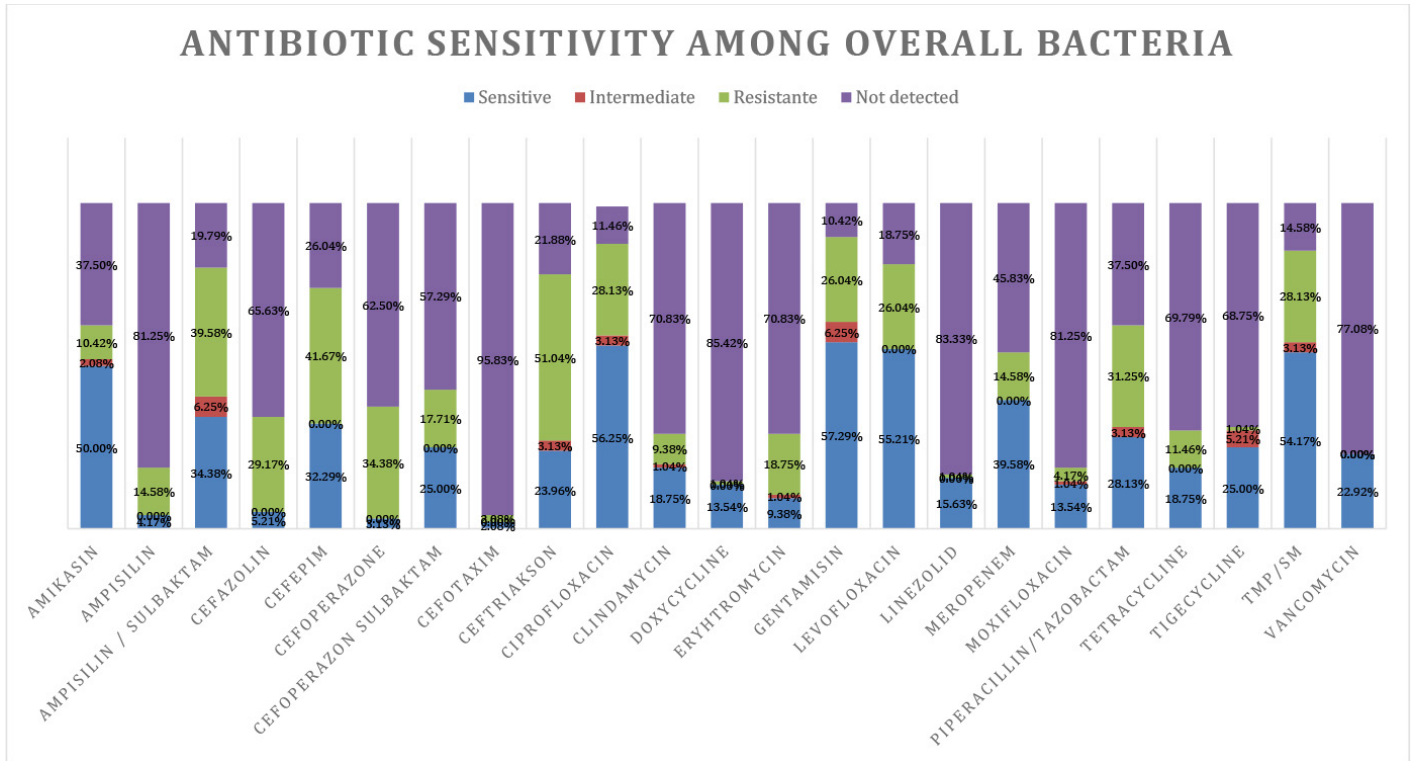


Figure 1. Antibiotic sensitivity among overall bacteria.

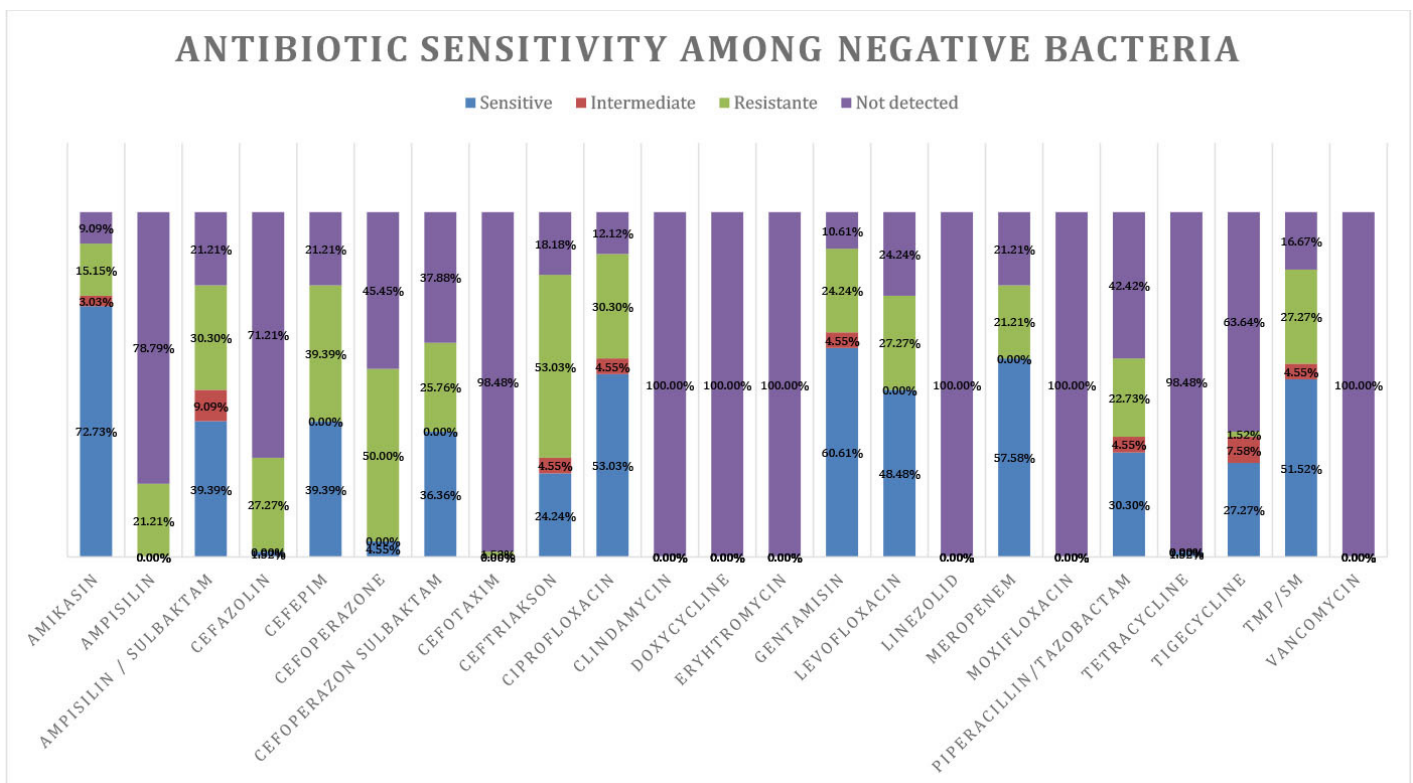


Figure 2. Antibiotic sensitivity among gram-negative bacteria.

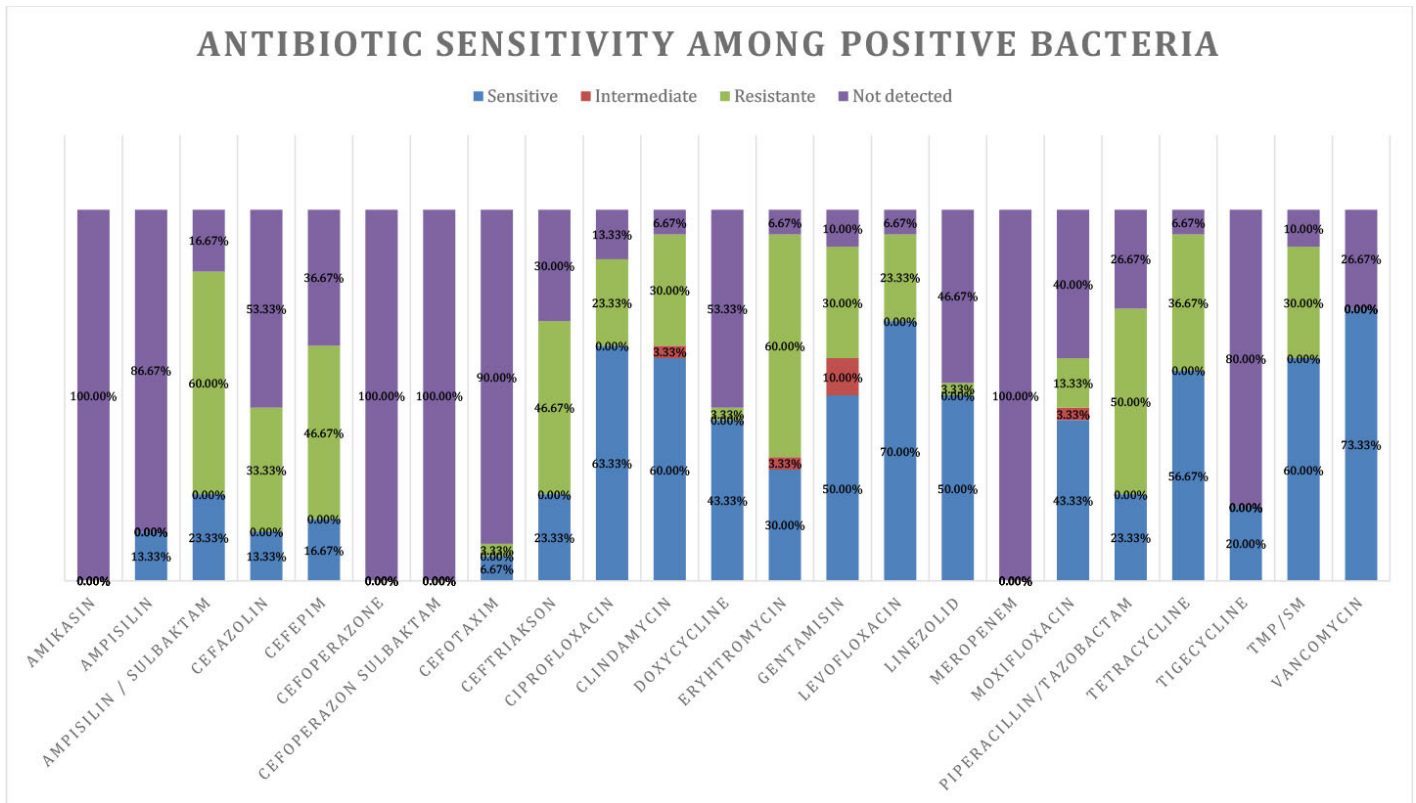


Figure 3. Antibiotic sensitivity among gram-positive bacteria.

long hospital stays, use of catheters and other invasive procedures.¹²

In this study, the survival rate was only 40.62%. Similar findings in a study in Tanzania in 2010 found that 28.5% of neonates with positive blood cultures died compared to only 8.6% of those with negative blood cultures ($p = 0.0001$). Gram-negative sepsis has been associated with severe sepsis and increased mortality. The outcome is usually determined by the duration of the inflammatory response to the offending pathogens, with severe and worse outcomes in gram-negative sepsis.¹³ We found mostly (80.20%) neonates had EONS than L.O.N.S. (19.80%), and gram-negative had a higher mortality rate.

This study found a higher proportion of gram-negative organisms (68.75%) than gram-positive organisms (31.25%). The findings are consistent with a study in Pakistan in 2016 that found 78.6% of isolates were gram-negative bacteria, while gram-positive bacteria accounted for 27.2% of cases of neonatal septicemia ($P = 0.00$).¹⁴ It may also indicate some of these infections are hygiene-related, including poor infection control practices, which can be challenging in limited resource

settings. Thus, a key area of focus in trying to reduce the prevalence of neonatal sepsis could be improving infection control policies, including overall hygiene around routine and high-risk newborn care.^{15,16}

In this study, the predominance of gram-negative bacteria is *Acinetobacter baumannii*, followed by *Klebsiella pneumoniae*, and gram-positive bacteria is *Staphylococcus haemolyticus*, followed by *Staphylococcus epidermidis*. Mishra A et al. found the incidence of *acinetobacter* accounted for 31.5% of causes of neonatal sepsis, followed by *Escherichia coli* (26.3%), *Klebsiella pneumoniae* (10.7%) and *Pseudomonas aeruginosa* (7.2%).¹⁷ In another study at Adam Malik Hospital (2020), the pattern of bacteria was dominated by *Klebsiella pneumoniae* (34.1%), followed by *Acinetobacter baumannii* (29.3%).¹⁸ Another study in Germany (2021) contained most of the isolates; 99 (73.9%) were gram-positive bacteria. The most predominant isolates were *Staphylococcus epidermidis*, 51 (38.1%), followed by *Escherichia coli*, 23 (17.2%); *Staphylococcus haemolyticus*, 15 (11.2%); and *Staphylococcus aureus*, 11 (8.2%).¹⁹

The other study by Kardana IM in Prof Ngoerah Hospital was dominated by gram-negative bacteria (68.3%), mostly *Serratia marcescens* (23.5%). The proportion of gram-positive bacteria, only 31.7%, such as *Staphylococcus coagulase positive* (16.4%), *Staphylococcus coagulase negative* (10.2%), and *Streptococcus viridans* (4.6%).²⁰

Acinetobacter baumannii is the most common type of gram-negative bacteria found in this study. Bacterial colonization is commonly found in hospital equipment and the hands of health workers.²¹ Meanwhile, *Klebsiella pneumoniae* is commonly found in the respiratory tract and feces in about 5% of normal individuals. *Klebsiella pneumoniae* can cause extensive hemorrhagic necrotizing consolidation of the lungs.²²

Staphylococcus haemolyticus and *Staphylococcus epidermidis* are this study's most common type of gram-positive bacteria. Despite multiple studies over the past decade suggesting that *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* are important causes of nosocomial and bloodstream infections in neonates in the gram-positive bacteria group.²³⁻²⁵

Indonesia did not have a national registry for the incidence of neonatal sepsis up until this point. The rise of multi-drug-resistant infections in neonatal units has also recently sparked concerns. To determine the most suitable empiric treatment, it is crucial to monitor antibiotic and pathogen sensitivity levels, which vary from one unit to another.

As a first line of therapy for neonatal sepsis, the World Health Organization (WHO) recommends using a combination of the narrow-spectrum medications penicillin and an aminoglycoside.^{7,26-28} In our center, ampicillin and gentamicin are the first-line empirical antibiotic, and our result showed that their susceptibility rate was 4.17% and 57.29%, which means ampicillin had low sensitivity, but gentamicin still had high sensitivity. It had the same result as previous research by Suarca et al., that ampicillin had no longer sensitive to bacteria that cause sepsis.²⁵ This study found that *Acinetobacter baumannii* is the most common type of gram-negative sensitive to Amikacin (75%). It is the same with another study that showed *Acinetobacter baumannii* is sensitive to Amikacin (78.9%).^{18,29,30}

Our data was based on single-center experience. Thus, the results are most likely related to the local epidemiological conditions. Differences observed in the bacterial spectrum and antibiotic resistance pattern of the isolates between recent studies and previous studies can be attributed to epidemiological differences, the prevalence of resistant strains in the region, and the type of antibiotic treatments. Our study showed that implementing a local epidemiological survey plays an important role in treating neonatal sepsis. The pattern of antibiotic sensitivity appears to be different in various research reports and, at other times, possibly due to the emergence of resistant strains due to the indiscriminate use of antibiotics.

CONCLUSION

This study found gram-negative bacteria were the most frequent cause of neonatal sepsis. The most sensitive antibiotics were gentamicin, ciprofloxacin, levofloxacin, TMP/SM, Amikacin, Meropenem, ampicillin/sulbactam, cefepime,

piperacillin/tazobactam, cefoperazone sulbactam, Tigecycline, ceftriaxone, vancomycin. This study results in gentamicin still being an option as an empirical antibiotic, but ampicillin had low sensitivity; another broad-spectrum antibiotic with better sensitivity is considered another option due to its significantly higher susceptibility. Bacterial surveillance and resistance patterns must be carried out routinely to determine policies for the use of antibiotics in each neonatal care unit.

CONFLICT OF INTEREST

There is no competing interest regarding the manuscript.

ETHICAL CONSIDERATION

Ethics approval was obtained from the Ethics Committee, Faculty of Medicine, Universitas Udayana, Prof. Dr. I.G.N.G. Ngoerah Hospital, Bali, Indonesia, before the study was conducted.

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None.

AUTHOR CONTRIBUTIONS

All authors equally contribute to the study from the conceptual framework, data acquisition, and data analysis until reporting the study results through publication.

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