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Research Article

Quantitative and qualitative analysis of antibiotic use among neonatal patients in teaching hospitals in Indonesia

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Abstract

Patients in the neonatal intensive care unit (NICU) are at a heightened risk of bacterial infection. The administration of antibiotics in the NICU varies widely, and inappropriate use can cause resistance, underscoring the need to monitor rationale use through an antimicrobial stewardship program. Therefore, this study aimed to evaluate the quantity and quality of antibiotic prescriptions for neonates in the NICU at Airlangga University Hospital. A retrospective observational study was conducted on patients admitted to the NICU from January 1, 2021, to December 31, 2022. The quantity of antibiotics was determined using the defined daily dose (DDD) method, and the quality of prescriptions was evaluated using the Gyssens algorithm. The results showed that based on the quantitative analysis using the DDD 100 patient-days method, the most common antibiotic used was ampicillin-sulbactam. Meanwhile, the qualitative study using the Gyssens method showed that 91% of antibiotic use was in category 0 (rational).

Keywords

antibiotic use, AWARE, defined daily dose, Gyssens method, neonates

Introduction

Infectious diseases in neonates attributed to viruses, fungi, or bacteria are reported to cause approximately 550,000 deaths annually (WHO 2022b). Meanwhile, low-birth-weight infants treated in the NICU often have weak immune systems and are more susceptible to nosocomial infections. These patients are at high risk of colonization and infection caused by antibiotic-resistant organisms (Patel and Salman 2010). This heightened risk is due to the weak physical condition, high exposure to microbes, and underdeveloped immunity (Graus et al. 2022).

Antibiotics are among the most frequently prescribed drugs in the NICU (Graus et al. 2022), with the most common route being intravenous administration. This is because newborns and premature infants have a total body water compartment accounting for approximately 85% of body weight, with a high proportion being extracellular fluid. The great proportion of extracellular fluid is a critical parameter explaining the high distribution of hydrophilic drugs in neonates. Oral administration causes the absorption of most antibiotics in neonates to vary greatly, decreasing drug bioavailability (van den Anker 2014).

One way to control the prudent use of antibiotics in Indonesia is by grouping antibiotics into the AWaRe category, namely Access, Watch, and Reserve. This categorization supports WHO's plan to control antimicrobial resistance. The government has stipulated through the Regulation of the Minister of Health of the Republic of Indonesia Number 28/2021 to supervise and regulate the prudent use of antibiotics in healthcare facility environments (Kemkes 2021). Since 2011, WHO has established the anatomical therapeutic chemical (ATC) classification system and measurement using DDD as the standard for measuring the quantity of antibiotic use. While for quality evaluation using the Gyssens flowchart assessment. This evaluation aims to provide information related to antibiotic use patterns in healthcare facilities, both in terms of quantity and quality. So that it is expected that the quantity and quality of AWARE antibiotic uses can be evaluated.

Antibiotic treatment in the NICU varies widely, leading to inappropriate overuse (Graus et al. 2022). Broad-spectrum and long-term empirical antibiotic treatment are associated with adverse effects, including candidiasis, increased antimicrobial resistance, necrotizing enterocolitis, late-onset sepsis, and death (Tripathi and Cotten 2012). Furthermore, inappropriate use accounts for 50% of total antibiotic treatment over the past few decades, leading to increased healthcare costs. A study by the Department of Pediatric Health Sciences at Cipto Mangunkusumo Hospital in 2011 found that 48.3% of antibiotic use was inappropriate. Another study in 2016 reported that 37.8% of antibiotic use was inappropriate (Karyanti and Faisha 2022). Aside from using a qualitative approach, quantitative analyses have also been conducted on neonates. Based on a 2011 study conducted at an Italian hospital, the most commonly used antibiotic in neonates was from the J01CA group (extended-spectrum penicillin), followed by J01CR (penicillin and beta-lactam inhibitor), with values of 2.73 and 1.91 DDD/100 bed-days, respectively (Buccellato et al. 2015). Another study conducted in the NICU of Dr. Soetomo Hospital in 2018 found that the highest DDD was for gentamicin at 3.58 DDD/100 patient days, with a total of 10.93 DDD/100 patient days (Aprisa 2019). In contrast, a study at Purwakarta Hospital stated that the antibiotic with the highest DDD/100 patient-days was cefoperazone sulbactam at 4 DDD/100 patient-days, with a total of 12.9 DDD/100 patient-days (Hendiyani et al. 2021).

This study aimed to evaluate the use of antibiotics quantitatively and qualitatively among neonatal patients in the NICU at Airlangga University Hospital, Surabaya. Quantitative analysis was performed using the ATC/DDD, while qualitative study was conducted using the Gyssens method.

Method

This study used an observational method with a descriptive analysis design without any interventions being applied to the patients. Data collection was performed retrospectively by reviewing the medical records of neonatal patients hospitalized in the NICU at Airlangga University Hospital from January 1, 2021, to December 31, 2022. The total sampling technique was used, including all patients who met the established inclusion and exclusion criteria. The inclusion criteria were neonatal patients aged ≤ 28 days who received antibiotic treatment, and no exclusion criteria were established. This study received ethical approval No. 075/KEP/2023, and data on antibiotic use in the NICU patients was analyzed quantitatively with the DDD/100 patient-days method and qualitatively using the Gyssens method (Fig. 1) recommended by the WHO. DDD calculation in hospitals uses the formula:

$$\text{DDD/ 100 patients day} = \frac{\text{Total dose of antibiotics used (gram)}}{\text{WHO's standart of DDD (gram)}} \times \frac{\text{100 days}}{\text{Total length of stay (day)}}$$

Result

This study analyzed the use of antibiotics quantitatively and qualitatively in neonatal patients, obtaining a sample of 63. The characteristics of these patients were classified based on gender (male and female), gestational age at birth (premature, term, and post-term), age at admission, length of stay, and birth weight, as shown in Table 1.

Table 1. Patient characteristics.

Gender	Number of Patients	Percentage (%)
Male	39	61
Female	24	39
Age Range at admission		
Early Neonatal (0-7 days)	62	98
Late Neonatal (8-28 days)	1	2
Gestational Age at Birth		
Preterm (< 38 weeks)	38	60
Term (38–42 weeks)	24	38
Post-term (> 42 weeks)	1	2
Birth Weight Range (grams)	**Number of Patients**	**Percentage (%)**
Overweight (> 4000 grams)	1	1
Normal Birth Weight (2500 to 4000 grams)	22	35
Low Birth Weight (< 2500 grams)	34	54
Very Low Birth Weight (< 1500 grams)	6	10
Length of Stay (Days)		
1-5 days	8	13
6-10 days	39	62
11-15 days	6	9
16-20 days	7	11
> 20 days	3	5

Table 2 shows the profile of antibiotic types used among neonatal patients at Airlangga University Hospital from 2021 to 2022. This table provides information on the type of antibiotic, route of administration, frequency of use, and percentages. Based on the profile, ampicillin was the most used antibiotic, accounting for 32%.

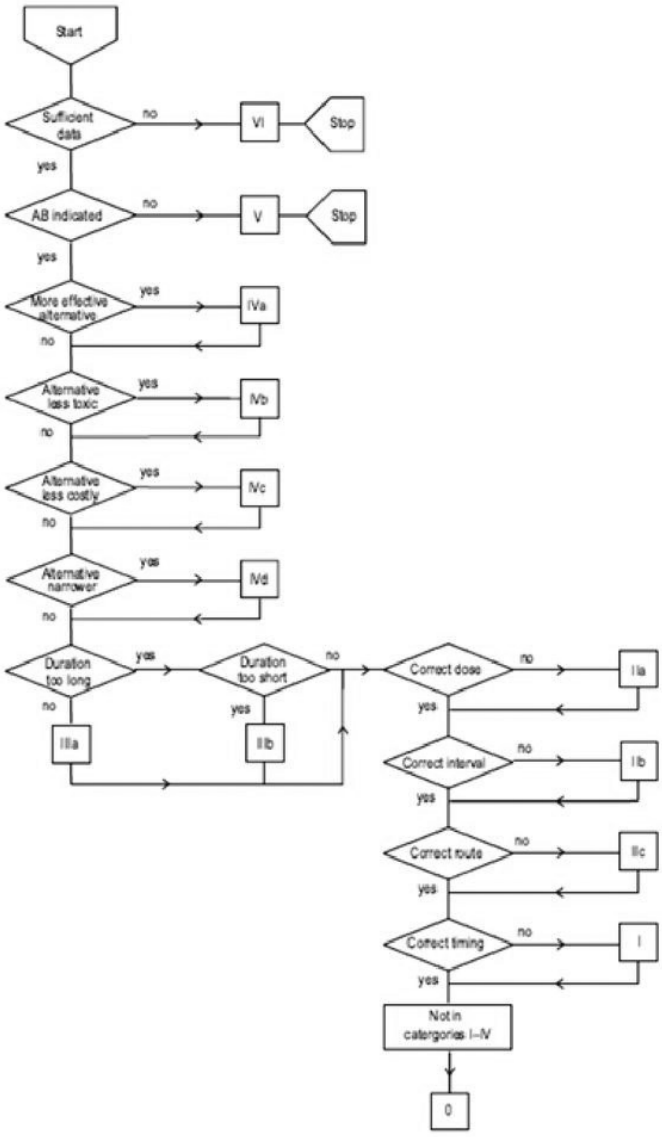

Figure 1. Gyssens method for the qualitative analysis of antibiotics.

Table 2. Profile of antibiotic types in the NICU.

No	Antibiotic Type	Route	Number of Uses	Percentage (%)	Category AWARE
1	Ampicillin	IV	38	32	Access
2	Ampicillin-sulbactam	IV	31	25	Access
3	Gentamicin	IV	24	20	Access
4	Meropenem	IV	19	16	Reserve
5	Erythromycin	PO	4	3	Access
6	Cefixime	PO	2	2	Watch
7	Cefotaxime	IV	1	1	Watch
8	Metronidazole	IV	1	1	Access
	Total		120	100	

Fig. 2 shows that sepsis was the most common disease type, affecting 43 patients (45%), followed by RDS in 26 (27%), and asphyxia in 18 (19%). The type of disease was correlated with the antibiotic used in the Gyssens analysis.

Evaluation of antibiotic use consisted of a quantitative analysis using the ATC/DDD method and a qualitative study using the Gyssens criteria to assess rationality. During the assessments, a total of 120 antibiotic uses were recorded from 63 patients. The quality of antibiotic use was assessed using the Gyssens method to evaluate the appropriateness of indication, dosage selection, route, interval, timing, and duration of use. The review process was conducted by a clinical supervising doctor (first reviewer) and a clinical pharmacist (second reviewer). The results of the quantitative analysis are presented in Table 3.

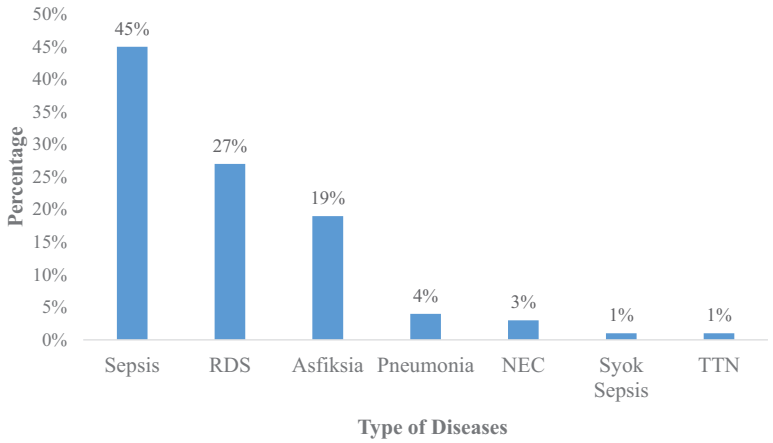

Figure 2. Types of diseases in the NICU. Note: One patient can have more than one diagnosis. [1]RDS: Respiratory Distress Syndrome [2] TTN: Transient Tachypnea Newborn.

Table 3. Quantitative analysis of antibiotic utilization in the NICU using the DDD/100 patient days method.

Antibiotic Type	ATC	Standard WHO DDD (grams)	Total Dose (grams)	Total (DDD)	DDD/100 patient days	AWARE Category
Ampicillin*	J01CR01	6	41.97	7	1.15	Access
Ampicillin-sulbactam	J01CA01	6	32.61	5.44	0.89	Access
Gentamicin	J01DH02	3	15.36	5.12	0.84	Reserve
Meropenem	J01GB03	0.24	1.10	4.61	0.76	Access
Erythromycin	J01DD08	0.4	0.04	2.69	0.44	Watch
Cefixime	J01FA01	1	0.71	0.71	0.12	Access
Cefotaxime	J01DD01	4	0.35	0.09	0.01	Watch
Metronidazole	J01XD01	1.5	0.098	0.07	0.01	Access

The Gyssens analysis showed that rational antibiotic use (category 0) was achieved in 110 antibiotic uses (91%). There were 2 cases (2%) characterized by a more effective antibiotic (category IV A), 2 cases (2%) where a more specific antibiotic with a narrower spectrum was available (category IV A), 4 cases (3%) with incorrect dosage (category IIA), and 2 cases (2%) where the antibiotic interval was incorrect (category IIB). In addition, the results showed that ampicillin-sulbactam had the highest DDD value. Aside from the quantitative analysis, a qualitative study was conducted using the Gyssens method, with 91% of antibiotic use falling into category 0, and these results are presented in Table 4. The clinical outcomes after treatment in the NICU and antibiotic administration showed that 62 patients (98%) were discharged alive, either recovered or able to continue outpatient treatment, while 1 (2%) was recorded dead.

Table 4. Qualitative analysis of antibiotics using the Gyssens method.

	GyssensCategory	Number of use	(%)
VI	Incomplete Medical Record Data	2	1.67%
V	No Indication of antibiotic uses	–	–
IV A	More Effective Alternative Antibiotics	2	1.67%
IV B	Less Toxic Alternative Antibiotics	–	–
IV C	Less Costly Alternative Antibiotics	–	–
IV D	Narrower spectrum Alternative Antibiotics	–	–
III A	Duration too long	–	–
III B	Duration too short	–	–
II A	Incorrect dose	4	3.33%
II B	Incorrect interval	2	1.67%
II C	Incorrect route	–	–
I	Incorrect timing	–	–
0	Rational use	110	91.66%

Discussion

The NICU patients were predominantly males, with a total of 39 (61%) and 24 females (39%). A similar study conducted at Sanglah Hospital in Bali recorded 75 males (54.1%) and 62 females (45.9%) (Suismaya and Artana 2020). The predominance of male neonates may be due to gender-related factors associated with the X chromosome. The gene associated with immunoglobulin synthesis is located on the X chromosome, and females, having two X chromosomes compared to one in males, possess stronger resistance to infections (Juwita et al. 2023). This was also supported by a study conducted in Australia, stating that the risk of neonatal sepsis was higher in males compared to female neonates. Male patients have a higher risk of infection and death compared to female neonates, specifically in cases of prematurity (Agnche et al. 2020). Moreover, most patients admitted to Airlangga University Hospital were early neonates aged 0 to 7 days, accounting for 62, with only one older than 7 days. As stated in a previous study, neonates aged 0–7 days are more vulnerable to nosocomial infections from the maternal genital tract (Zea-Vera and Ochoa 2015).

Based on the gestational age at birth, the patients were predominantly premature, with 38 (60%) born before 38 weeks of gestation. Meanwhile, the majority treated had a low birth weight, with < 2500 grams, totaling 34 (54%). These results were slightly different from those of Juwita et al. 2023 reporting that 48.21% of patients had low birth weight (BBLR). Neonates with birth weights less than 2500 grams are 1.42 times more likely to experience sepsis compared to those weighing 2500 grams or more. This increased risk may be attributed to several factors common among low-birth-weight infants, including prematurity, immature immune systems, lack of breastfeeding, lower glucose stores, and a higher risk of hypoglycemia (Belachew and Tewabe 2020).

In this study, the duration of hospitalization ranged from 4 to 26 days, with the majority staying in the 6 to 10-day range, totaling 39 patients (62%), and an average length of stay of 9.7 days. The varied duration of hospitalization can be attributed to factors such as gestational age of less than 37 weeks and low birth weight (Sahiledengle et al. 2020). This was supported by a study in the NICU of hospitals in India, where 50% neonatal patients hospitalized with sepsis stayed for 6 to 10 days. Additionally, neonates born between 28 and 36 weeks of gestation stayed in the hospital for 6 to 30 days (Kanimozhi et al. 2019).

Antibiotics are frequently used by neonatal patients in the NICU include ampicillin at 32% and ampicillin-sulbactam at 25% as empirical treatment. Ampicillin-sulbactam can be an alternative to ampicillin due to the similar spectrum of activity and a longer half-life (Gallagher and Macdougall 2022). The use of single antibiotic ampicillin was lower than in studies conducted in India, where it was used in 21.73% of cases (Subash and Shanmugarpriyan 2015). Ampicillin is effective against serious infections caused by anaerobes, enterococci, as well as beta-lactamase-negative gram-positive cocci and gram-negative bacilli, namely *E. coli* and *Salmonella* sp. yet has a higher resistancy risk due to beta-lactamase enzymes produced by some bacteria (Katzung et al. 2021a, b). It is a bactericidal antibiotic that penetrates the bacteria's cell wall and is active against gram-negative bacteria resistant to Penicillin G. Furthermore, in studies conducted on neonates with gestational age less than 34 weeks and postnatal age less than 7 days, the half-life, clearance, and distribution volume of ampicillin were found to be 5 hours, 0.055 l/hour/kg, and 0.4 l/kg, respectively. As neonates mature, the half-life decreases and clearance increases, but the distribution volume remains unaffected (Pacifi 2017). Therefore, age and organ maturity of neonates influence the frequency of ampicillin administration.

Patients admitted to the NICU at Airlangga University Hospital and receiving antibiotic treatment mainly were diagnosed with sepsis, totaling 45%. Neonatal sepsis is the third leading cause of death among neonates, accounting for 13% in the first week of life (Zea-Vera and Ochoa 2015). A study in the NICU in Ethiopia showed that neonatal sepsis patients reached 46.7%, namely 158 out of 338 (Agnche et al. 2020). Another study conducted at a general hospital in Bangladesh found that 5.8% of neonatal patients had sepsis, namely 10 out of 173 (Nyma et al. 2020). Meanwhile, approximately 22% of patients were diagnosed with neonatal sepsis in a study conducted at Dr. Soetomo Hospital in 2019 (Utomo et al. 2021).

Sepsis remains a leading cause of morbidity and mortality in neonates worldwide. A study conducted in India in 2016 reported positive culture-confirmed sepsis in 9.5 per 1000 births. Infants at higher risk of sepsis include premature, very low birth weight, males who require additional respiratory support, pregnancies less than 37 weeks, and those with premature rupture of membranes (Jain 2021). Sepsis may be caused by bacteria that colonize the mother's genitourinary tract, leading to contamination of the amniotic fluid, placenta, cervical mucus, and vaginal canal. The bacteria associated include *Streptococcus*, *L. monocytogenes*, *E. faecalis*, *Enterobacter faecium*, streptococci, *α-hemolytic* streptococci, staphylococci, *S. pneumoniae*, and *H. influenzae*. Gram-negative bacteria, particularly *E. coli* and *Klebsiella*, dominate as causes of sepsis (Geyesus et al. 2017). In Southeast Asian studies, positive cultures identified gram-negative bacteria, with *Klebsiella pneumoniae* accounting for 90.4% of cases (Salsabila et al. 2022). This was consistent with a study at Airlangga University Hospital, where neonatal sepsis frequently occurred due to contaminated amniotic fluid, birth canal transmission, and maternal infections such as urinary tract infections (UTI).

According to the management of sepsis in neonates, empiric antibiotic treatment typically includes ampicillin combined with gentamicin when the causative organism is unknown, providing coverage against both gram-positive and negative bacteria (Bradley et al. 2023). Ampicillin is administered at 25–50 mg/kg every 12 hours, while gentamicin is given at 4–5 mg/kg/day. The duration of treatment can range from 3 to 9 days (Shann 2017; NeoFax 2023). Ampicillin-sulbactam is recommended as a first-line treatment at Airlangga University Hospital (Airlangga University Hospital Antibiotic Policy (PPAB RSUA) 2022).

A qualitative study using the Gyssens method assessed the appropriateness of antibiotic use based on indication, selection (effectiveness, toxicity, cost, spectrum), duration, dose, interval, route, and timing of administration. Among the 63 patients with 120 antibiotic administrations, the analysis showed the following categories: 2% in VI (incomplete patient data), 2% in IVa (more effective alternative antibiotic is available), 3% in IIa (inappropriate antibiotic dosing), 2% in IIb (inappropriate antibiotic dosing interval), and 91% in 0 (appropriate and judicious antibiotic use). The proportion of category 0 was higher compared to another study conducted in the NICU of Banjarnegara Hospital at 85.66% but slightly lower than in Banyumas Hospital at 94% (Nastiti et al. 2022; Juwita et al. 2023).

In category VI, there were two patients (2%) with incomplete medical record data due to missing pages, preventing further analysis. Category IVa included two patients (2%) where a more effective alternative antibiotic could have been used. This result was consistent with a study by Hendiyani et al. 2021 on neonatal patients at

Purwakarta Hospital, which also used Gyssens analysis and found three patients (4.3%) in category IVa. There was one patient in category IVa who prescribed cefixime, a newly introduced medication. The patient was diagnosed with Transient Tachypnea of the Newborn (TTN), a temporary respiratory disorder caused by lung adaptation issues. When not promptly addressed, TTN can lead to severe respiratory complications (IDAI 2018). According to guidelines, affected patients with additional risk factors for infection may receive empiric antibiotic treatment. The first-line empiric antibiotic choice is intravenous ampicillin and gentamicin (IDAI 2018; Airlangga University Hospital Antibiotic Policy 2022).

In category IIa, there were four antibiotics with inappropriate dosing, accounting for 3%. This value was lower than the evaluation of antibiotic use in a type B hospital in Bandung, which found nine cases (3.91%) of inappropriate gentamicin dosing (Sartika and Amalia 2023). Another study in Purwakarta Hospital identified 39 patients receiving inappropriate antibiotic doses. Incorrect dosing, whether excessive or insufficient, often results from rounding off doses based on the neonatal patient's weight, leading to higher or lower doses than intended (Hendiyani et al. 2021). Inappropriate dosing prolongs the healing process, increasing the length of stay in the pediatric intensive care unit (PICU) and contributing to antibiotic resistance (Mathur et al. 2018; Sundariningrum et al. 2020). In this study, inappropriate dosing occurred from using ampicillin-sulbactam in three patients, as referenced in the literature, including Neofax Micromedex 2020 and Frank Shann 2017. According to Le et al. 2022, ampicillin doses ranging from 100 mg/kg to high levels of 300 mg/kg were administered to neonates with early-onset sepsis. The results showed that 30% of newborns in the moderate group and 85% of those receiving high-dose regimens still had drug concentrations above the neurotoxicity threshold after 48 hours. Therefore, the safety profile of high doses ranging from 100–300 mg/kg requires further testing or monitoring. In this study, antibiotic dosages were generally high compared to the literature due to rounding off.

Inappropriate antibiotic interval use was found in two cases in category IIb. According to the studies, most patients receiving meropenem treatment did not receive the correct intervals. Mesoponem is distributed in the extracellular fluid and excreted through glomerular filtration, affecting the disposition in cases of body fluid changes and developing renal function. It has a larger volume of distribution and lower clearance in premature neonates, even higher than in adults, requiring dose regimen adjustments. Doses of 10 and 20 mg/kg given as a 30-minute infusion and an 8-hour interval may be more appropriate for organisms with higher minimum inhibitory concentrations (MICs) (van den Anker et al. 2009). Another study mentioned that 20 mg/kg of meropenem doses could be administered every 12 hours for neonates aged less than 7 days and every 8 hours for those aged more than 7 days (Pacifi 2016).

Based on the drug consumption data, defined daily dose (DDD) only provides an approximate estimate of gross consumption and does not accurately reflect actual drug use (WHO 2022a). Quantitative analysis of antibiotics was conducted as a form of pharmaceutical care activity (PGA) evaluation. The analysis was performed by calculating DDD/100 patient-day units. In this study, 8 types of antibiotic use were identified with a total of 4.22 DDD/100 patient days. The results showed that the highest antibiotic used was ampicillin-sulbactam, with a DDD value of 1.15 DDD/100 patient days, followed by ampicillin at 0.89 and meropenem at 0.84. These results were lower than those of NICU patients at Purwakarta Hospital, with a total DDD value of 12.9 DDD/100 patient days. Similarly, ampicillin-sulbactam had the highest value at 3.25 DDD/100 patient days, which was higher than the results at Airlangga University Hospital (Hendiyani et al. 2021). Differences in the values could be influenced by the number of inpatient days in Purwakarta, totaling 338, with the longest stay being 23 days for 1 patient. Meanwhile, in this study, the total inpatient days were 610, with the longest stay being 26 days for 1 patient. Another study conducted in the NICU at Dr. Soetomo Hospital in 2019 by Aprisa reported that gentamicin had the highest DDD value at 3.58 DDD/100 patient days. This implies that out of 100 patients, 4 used 0.24 g of gentamicin daily, resulting in a total value of 10.93 DDD/100 patient-days.

The outcome of treatment showed that 62 patients (98%) were discharged alive, and 1 (2%) passed away. According to medical records, patients declared alive and recovered were eligible for outpatient care once signs and symptoms of the disease subsided. Supporting examinations indicated improvement, with the infants in good condition and normal body temperature, respiratory rate, and pulse rate.

The limitation of this study was the reliance on retrospective data, which might pose issues regarding data completeness in medical records. Therefore, regular prospective evaluations are necessary. Constant monitoring and evaluation are essential to enhance prudent antimicrobial use through interprofessional collaboration.

Conclusion and recommendations

In conclusion, the quantitative analysis using the DDD per 100 patient-days method showed that the top three antibiotics most widely used were ampicillin-sulbactam, ampicillin (classified as access), and meropenem (classified as reserve). Meanwhile, the qualitative study using the Gyssens method showed that antibiotic use was categorized as rational in 91% of cases, with inappropriate dose (category II A) observed in 3%, inappropriate interval (category II B) in 2%, more effective alternative antibiotic (category IV A) in 2%, and incomplete medical record data (category VI) in 2% of cases. These findings underscore the importance of collaboration between neonatologists as prescribers and clinical pharmacists in monitoring, evaluating, and managing antibiotic use so as to increase the prudent and rational use of antibiotics in neonatal patients.

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