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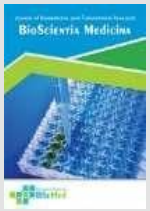

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The Relationship between Accurate Use of Antibiotics and Clinical Improvement of Sepsis in Neonates Using the Gyssens Method in the Perinatology Ward of Dr. M. Djamil General Hospital, Padang Indonesia

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A B S T R A C T

Background: Neonatal sepsis is a major cause of neonatal morbidity and mortality in developing countries. Inappropriate use of antibiotics causes an increase in antibiotic resistance, so the Gyssens method is needed, which is a qualitative method and is used to evaluate the use of antibiotics. This study aims to determine the relationship between the accuracy of the use of antibiotics using the Gyssens method on the clinical improvement of neonates in the Perinatology Ward of Dr. M. Djamil General Hospital Padang, Indonesia. **Methods:** This study used a cross-sectional conducted from January 2020 to December 2020. The study subjects were 67 neonates diagnosed with sepsis in the perinatology ward of Dr. M. Djamil General Hospital, Padang Indonesia. Data analysis was performed with SPSS for univariate and bivariate analysis. **Results:** Most neonatal sepsis occurs in male infants who have low birth weight. Most cultures do not grow. There was an improvement in clinical and hematological parameters to the administration of first-line, second-line, and culture-appropriate antibiotics according to the Gyssens method, but statistically not significant (p-value > 0.05). The rational use of antibiotics was 89.6%. **Conclusion:** There is a relationship between the accuracy of antibiotic use on clinical improvement and blood parameters of neonatal sepsis patients in the Perinatology ward of Dr. M. Djamil General Hospital based on the Gyssens method, but it is not statistically significant. The use of antibiotics based on the Gyssens method at Dr. M. Djamil General Hospital is quite good.

1. Introduction

Neonatal sepsis is a major cause of neonatal morbidity and mortality in developing countries and is often found in sub-Saharan Africa, South Asia, and Latin America, with a fatal case risk of 9.8% in the first month of life.[1] The worldwide population comprises approximately 28% of children and infants who are most susceptible to infectious diseases due to underdeveloped immune systems. Neonates, especially premature infants, are at higher risk of bacterial infection than term neonates due to immature physiological functions, leading to high morbidity and mortality. Worldwide morbidity is caused by sepsis consisting of various systemic infections in newborns, such as septic shock, meningitis, pneumonia, arthritis, osteomyelitis, and urinary tract infections. Empirical antibiotic therapy should be initiated immediately if sepsis is suspected, followed by culture and sensitivity studies.[2]

Antibiotics are the most commonly used drugs. Rational use of antibiotics is a process of planning, implementing, and monitoring that ensures the implementation of effective, safe, and economical antibiotic treatment.[1] Unnecessary or inappropriate use of antibiotics can lead to an increase in antibiotic

resistance and pathogenic microorganisms such as bacteria, parasites, viruses, and fungi leading to treatment failure as well as an increase in drug side effects and treatment costs.[3,4] In 2020, there were 719 neonates who were treated in the perinatology ward of Dr. M. Djamil General Hospital Padang, and there were 103 neonates diagnosed with sepsis, and all patients received antibiotic therapy. Antibiotics are the most commonly used drugs in the neonatal intensive care unit. Nearly all very low birth weight infants received antibiotics, and all other birth weight groups admitted to the neonatal intensive care unit were treated mostly with antibiotics. Most neonatal units have policies regarding the use of antibiotics.[5] When initiating antibiotics, the patient's clinical and laboratory findings should be considered, the spectrum of antibiotics initiated should not be wider or narrower than necessary, and unnecessary dual treatment should be avoided. The most commonly used antibiotic inappropriately is ceftriaxone, the second being ampicillin-sulbactam.[3]

Guidelines for the use of antibiotics are given according to the Gyssens method. The Gyssens method is a qualitative method that is used to evaluate the use of antibiotics from various things such as the exact indication, the right patient, the exact administration of the drug, the exact dose, the right method and duration of administration, and estimates of drug side effects that occur. Optimal use of antimicrobial drugs has implications for good evidence-based clinical practice, optimal use of available resources, and maximum efforts to avoid or delay antimicrobial resistance.[6-8] Gyssens method is needed because of the many irrational uses of antibiotics. This study aims to determine the relationship between the appropriateness of antibiotic administration and clinical improvement of neonatal patient sepsis in the Perinatology Ward of Dr. M. Djamil General Hospital Padang using the Gyssens method. This study is one of the pioneer studies in exploring the appropriateness of antibiotic administration at Dr. M. Djamil General Hospital, Padang, Indonesia.

2. Methods

The design of this study was an analytic observational study with a cross-sectional approach to determine the relationship between the appropriateness of antibiotic administration and clinical improvement of neonatal patient sepsis in the Perinatology Ward of Dr. M. Djamil General Hospital Padang using the Gyssens method. A total of 67 research subjects who were patients with neonatal sepsis took part in this study, where the research subjects met the inclusion criteria, namely: medical records of patients in the Children's Ward, neonatology sub-division class who received antibiotics for the period January – December 2020, infants with risk factors for neonatal sepsis. And having a diagnosis of sepsis in the medical record and given antibiotics for more than 5 days, the baby was born at Dr. M. Djamil General Hospital, Padang, Indonesia. This research has received ethical approval from the research ethics committee of Dr. M. Djamil General Hospital Padang Indonesia.

The research subjects collected secondary data from patient medical records in the form of sociodemographic data, assessed the quality of antibiotic use with the Gyssens category chart, assessed hematological parameters and clinical conditions of patients before and after being given antibiotics, both rational and irrational, and data analysis was carried out. Data analysis was carried out in stages, namely univariate and bivariate analysis, using SPSS version 25 software. Univariate analysis was carried out to see the description of the research variables. Categorical variables are presented in terms of frequency and percentage. Categorical variables in this study included gender, gestational age, fetal growth, age, length of treatment, type of antibiotic, duration of antibiotic use, route of administration, evaluation of antibiotic use based on the Gyssens method, and the results of growing cultures. In numerical variables, the data displayed in the form of central tendency is the mean value and standard deviation. Bivariate analysis was conducted to assess the relationship between data on the use of

antibiotics using the Gyssens method and the rationality of the use of antibiotics used in the treatment of neonatal sepsis. The results of Gyssens' evaluation were then used as the basis for conducting a bivariate test analysis to find the relationship between the rationality of treatment and patient recovery using Fisher's exact.

3. Results

Based on table 1, it was found that the gender of the research subjects was majority male (56.7%) compared to female (43.3%). The highest gestational age was a term (37-41 weeks) with 47.8%, followed by very preterm (29.9%), extremely preterm (13.4%), and moderate to late preterm (9%). Very low birth weight (5.9%), very low birth weight (17.9%), low birth weight (28.3%), and moderate birth weight (47.7%). The highest fetal growth was according to gestational age (83.6%), small for gestational age (11.9%), then large for gestational age (4.5%). The majority of neonates were aged 0-7 days (86.6%), 7-14 days (6%), followed by >21 days (4.5%), and 14-21 days (3%). Patients were most often hospitalized for >14 days (37.3%), 7-14 days (35.8%), then for 0-7 days (26.9%).

Table 1. Characteristics of research subjects

Category	n (%)
Gender	
Male	38 (56.7)
Female	29 (43.3)
Gestational Age	
Extremely Preterm (<28 weeks)	9 (13.4)
Very Preterm (28-<32 weeks)	20 (29.9)
Moderate to late preterm (32-<37 weeks)	6 (9.0)
A term (37-41 weeks)	32 (47.8)
Weight	
Extremely low birth weight	4 (5.9)
Very low birth weight	12 (17.9)
Low birth weight	19 (28.3)
Moderate birth weight	32 (47.7)
Fetal Growth	
Small for gestational age	8 (11.9)
Appropriate for gestational period	56 (83.6)
Large for gestational period	3 (4.5)
Age	
0-7 days	58 (86, 6)
7-14 days	4 (6.0)
14-21 days	2 (3.0)
> 21 days	3 (4.5)
Treatment Duration	
0-7 days	18 (26.9)
7-14 days	24 (35.8)
> 14 days	25 (37.3)

In table 2, as many as 64.2% of respondents had normal leukocyte levels, 26.9% had leukocytosis, and 9% had leukopenia. 44.8% of respondents had normal platelet levels, and 40.3% had thrombocytopenia. The majority of respondents experienced an increase in the IT ratio (64.2%) and PMN (70.1%). A total of 74.6% had no increase in temperature (afebrile), and 80.6% had normal heart rate and breathing (47.8%).

Table 2. Characteristics of hematological parameters and vital signs of study subjects

Category	n (%)	Mean
Leukocytes		
Leukocytosis	18 (26,9)	36,280
Leukopenia	6 (9)	2,450
Normal	43 (64,2)	7,890
Platelets		
Thrombocytosis	10 (14,9)	635,000
Thrombocytopenia	27 (40.3)	86,000
Normal	30 (44.8)	257,000
IT Ratio		
Increase	43 (64,2)	0.16
Normal	24 (35.8)	0.02
PMN		
Increase	47 (70,1)	74
Normal	20 (29.9)	46
Temperature		
Febrile	17 (25.4)	38.8
Afebrile	50 (74.6)	36.7
Heart rate		
Tachycardia	9 (13.4)	186
Bradycardia	4 (6)	106
Normal	54 (80.6)	145
Respiratory		
Tachypnea	(41.8)	82
Bradypnea	7 (10.4)	29
Normal	32 (47.8)	45

Table 3 shows the most commonly used antibiotics are ampicillin-sulbactam (100%), gentamicin (100%), cefoperazone sulbactam (37.3%), amikacin (37.3%), meropenem (25.3%), metronidazole (4.4%), ceftazidime (1.4%), and tigecycline (1.4%). Antibiotics were most often given with a duration of >14 days (40.3%).

Table 3. Characteristics of antibiotic use

Category	n (%)
Type of antibiotic	
Ampicillin sulbactam	67 (100)
Gentamicin	67 (100)
Cefoperazone Sulbactam	25 (37.3)
Amikacin	25 (37.3)
Meropenem	17 (25.3)
Metronidazole	3 (4)
Ceftazidime	1 (1.4)
Tigecycline	1 (1.4)
Duration	
1-7 days	18 (26.9)
7-14 days	22 (32.8)
> 14 days	27 (40.3)
Route	
Intravenous	67 (100)
Oral	0

In table 4, it was found that the evaluation of giving antibiotics to neonates at Dr. M Djamil General Hospital based on the Gyssens table was appropriate/rational, namely grade 0 (89.6%), then 6% of neonates entered grade IIIA (taking too long), and 4.5% entered into grade IVA (there are other antibiotics that are more effective).

Table 4. Evaluation of antibiotics based on the Gyssens method

Category		n (%)
0	: appropriate/rational use	60 (89.6)
I	: inappropriate timing	0
IIA	: inappropriate dose	0
IIB	: inappropriate interval	0
IIC	: inappropriate route of administration	0
IIIA	: inadequate administration too long	4 (6)
IIIB	: inadequate administration too short	0
IVA	: there are other antibiotics that are more effective	3 (4.5)
IVB	: there are other antibiotics that are less toxic	0
IVC	: there are other antibiotics that are cheaper	0
IVD	: there are other antibiotics that are more specific	0
V	: use of antibiotics without any indication	0
VI	: incomplete medical records for evaluation	0

In table 5, as many as 50% of patients with tachypnea who were given rational first-line antibiotics experienced improvement, and 40% did not develop repair. In the irrational use of antibiotics, as many as 10% of patients with tachypnea do not improve. Patients with bradypnea who were given rational antibiotics mostly did not improve (55.6%) compared to those who experienced improvement (22.2%), while with irrational antibiotics, 22.2% of patients experienced improvement. Patients with tachycardia who were given rational antibiotics improved by 22.2% but did not improve by 55.6%. While patients who were given antibiotics irrationally had an improvement value of 22.2%. 25% of patients with bradycardia who were given antibiotics rationally improved, and 50% did not improve, and 25% of patients with bradycardia who were given antibiotics rationally did not improve. 66.7% of patients with complaints of vomiting experienced a clinical improvement in the rational use of antibiotics, and only 25% did not experience improvement. 8.3% of patients with clinical symptoms of vomiting and being given antibiotics irrationally did not improve. As many as 58.8% of patients with temperature instability and given antibiotics rationally experienced improvement, while 35.3% of patients did not experience improvement. 5.9% of patients with temperature instability who were given antibiotics irrationally improved. Patients who experience seizures after being given antibiotics rationally have an improvement of 70%. Only 20% of patients with seizures after rational administration of antibiotics do not improve. A total of 83.3% of patients experiencing cyanosis after being given antibiotics rationally improved, and 4.2% did not improve, while 12.5% of patients who had seizures after being given antibiotics irrationally improved. There was a clinical improvement (tachypnea, bradypnea, tachycardia, vomiting, instability temperature, cyanosis, and temperature instability) with the administration of first-line antibiotics according to the Gyssen plot but statistically not significant with a p-value > 0.05.

Table 5. Appropriateness of giving first-line antibiotics, using the Gyssens method to neonates with sepsis associated with changes in clinical status

Clinical	Improvement	No improvement	P-value*
Tachypnea			
Rational	15 (50)	12 (40)	0.07
Irrational	0	3 (10)	
Bradypnea			
Rational	2 (22.2)	5 (55.6)	0.07
Irrational	2 (22.2)	0	
Tachycardia			
Rational	2 (22.2)	5 (55.6)	0.07
Irrational	2 (22.2)	0	
Bradycardia			
Rational	1 (25)	2 (50)	0.5
Irrational	0	1 (25)	
Vomiting			
Rational	8 (66.7)	3 (25)	0.52
Irrational	0	1 (8.3)	
Instability Temperature			
Rational	10 (58.8)	6 (35.3)	0.45
Irrational	1 (5.9)	0	
Seizure			
Rational	7 (70)	2 (20)	0.1
Irrational	0	1 (10)	
Cyanosis			
Rational	20 (83.3)	1 (4,2)	0.7
Irrational	3 (12,5)	0	

*Fisher exact test, p-value = 0.05

In table 6, it can be seen that the total leukocytes in patients with rational first-line antibiotics improved by 50 %. At the same time, 37.5% of patients did not experience leukocyte improvement. Total leukocytes on irrational administration did not improve as much as 12.5%. The total PMN in patients who were given antibiotics rationally did not improve as much as 44.7%, while the irrational administration did not improve as much as 10.6%. The I/T ratio on rational administration improved the majority (65%), and irrational administration of antibiotics caused 5% of patients to improve. Platelet counts in patients with rational administration of antibiotics did not improve by 60%, but irrational administration of antibiotics caused the platelet count to not improve by 14.3%. There was an improvement in hematological parameters (total leukocytes, total PMN, its ratio, and platelets) from the administration of first-line antibiotics according to the Gyssen path but statistically not significant, with a p-value > 0.05.

Table 6. Appropriateness of administration of first-line antibiotics by the Gyssens method in neonates with sepsis associated with abnormal changes in hematological parameters.

Hematological Parameters	**Improvement**	**No improvement**	**P value***
Total Leukocytes			
Rational	12 (50)	9 (37.5)	0.06
Irrational	0	3 (12.5)	
Total PMN			
Rational	20 (42.6)	21 (44.7)	0.14
Rational	1 (2.1)	5 (10.6)	
I**/T Ratio**			
Irrational	13 (65)	4 (20)	0.13
Rationale	1 (5)	2 (10)	
Platelet			
Rationale	9 (25.7)	21 (60)	0.16
Irrational	0	5 (14.3)	

*Fisher exact test, p-value = 0.05

In table 7, 53.8% of patients with tachypnea who were given second-line antibiotics rationally improved. In the irrational use of antibiotics, as many as 23.1% of patients with tachypnea experienced improvement. Patients with bradypnea who were given rational antibiotics did not improve as much as 67%, and 33% did not improve even though they were given irrational antibiotics. Patients with tachycardia who were given rational antibiotics had an improvement rate of 60%, while those who were given irrational antibiotics improved by 20%. While patients who were given antibiotics irrationally did not improve tachycardia by 10%. The rate of clinical improvement of bradycardia in patients given rational and irrational antibiotics was 33.3%. The majority of patients with vomiting who were given second-line antibiotics rationally experienced an improvement, namely 50%, while those who were given antibiotics irrationally experienced an improvement of 16.7%. As many as 60% of patients with temperature instability and given rational antibiotics experienced improvement, while 20% of patients did not improve. 20% of patients with temperature instability who were given antibiotics irrationally improved. Patients who experienced seizures after being given antibiotics rationally improved and did not improve by 33.3%. The majority of patients with cyanosis who were given rational antibiotics experienced improvement of as much as 66.7%. There was a clinical improvement with the administration of second-line, third-line, and culture-appropriate antibiotics according to the Gyssen plot but statistically not significant with a p-value > 0.05.

Table 7. Appropriateness of administration of second-line, third-line, and culture-appropriate antibiotics using the Gyssens method in neonates with sepsis associated with changes in clinical status

Clinical	Improvement	No improvement	P value*
Tachypnea			
Rationale	7 (53.8)	3 (23.1)	0.28
Irrational	3 (23.1)	0	
Bradypnea			
Rational	0	2 (67)	0.08
Irrational	1 (33)	0	
Tachycardia			
Rational	3 (60)	1 (20)	0.58
Irrational	1 (20)	0	
Bradycardia			
Rational	1 (33.3)	1 (33.3)	0.39
No rational	1 (33.33)	0	
Vomiting			
Rational	3 (50)	2 (33.33)	0.44
Irrational	1 (16.7)		
Instability Temperature			
Rational	3 (60)	1 (20)	0.58
No rational	1 (20)	0	
Seizures			
Rational	1 (33.3)	1 (33.3)	0.39
Irrational	1 (33.3)	0	
Cyanosis			
Rational	2 (66,7)	0	0.08
Irrational	0	1 (33.3)	

*Fisher exact test, p-value = 0.05

In table 8, it can be seen that the total leukocytes in patients receiving first-line antibiotics rationally had the same improvement and non-improvement rates. The same is 40%. At the same time, the total leukocytes on irrational administration did not improve as much as 20%. The total PMN in patients who were given antibiotics rationally did not improve as much as 43.5%, while in irrational administration, as much as 13% did not improve. The I/T ratio on rational administration improved the majority (65%), but irrational administration of antibiotics caused 10% of patients not to improve the I/T ratio. The number of platelets in patients with rational administration of antibiotics did not improve as much as 61.1%, but the irrational administration of antibiotics caused the platelet count to not improve as much as 13.9%. There was an improvement in hematological parameters (total leukocytes, total PMN, I/T ratio, and platelets) with the administration of second-line, third-line antibiotics and according to culture according to the Gyssen plot, but statistically not significant with a p-value > 0.05.

Table 8. Appropriateness of administration of second-line, third-line, and culture-appropriate antibiotics using the Gyssens method in neonates with sepsis was associated with changes in hematological parameters.

Hematological Parameters	**Improvement**	**No improvement**	**P value***
Total leukocytes			
Rational	4 (40)	4 (40)	0.2
Irrational	0	2 (20)	
Total PMN			
Rational	7 (30.5)	10 (43.5)	0, 71
Rational	3 (13)	3 (13)	
I/T Ratio			
Rational	13 (65)	4 (20)	0.13
Irrational	1 (5)	2 (10)	
Platelet			
Rational	9 (25)	22 (61.1)	0
Irrational	0	5 (13.9)	

*Fisher exact test, p-value = 0.05

4. Discussion

This study shows that there is no rationality relationship between the administration of first- and second-line antibiotics and in accordance with culture according to the Gyssens method with clinical improvement and hematological parameters (p-value >0.05). A study has conducted a study on the accuracy of giving antibiotics based on the Gyssens method with clinical improvement of patients with pneumonia, and there was no significant relationship between the accuracy of giving antibiotics based on the Gyssens line in community pneumonia with clinical improvement of patients.[9] Another study of antibiotics in the treatment of neonatal sepsis by the Gyssens method concluded that the rational use of antibiotics or not has nothing to do with a patient's faster or longer recovery.[10] Another study concluded that there was no significant difference (p>0.05) in the condition of patients leaving the ICU based on the rationale of antibiotic use, gender, age, and length of stay of septic patients.[11]

There are several risk factors that make not all neonates with sepsis who are given antibiotics, according to clinical, blood, and culture parameters, experience improvement where there are comorbid factors where most of the neonatal deaths in the NICU are caused by neonatal sepsis.[12] Deaths after sepsis are more common in boys and those with low birth weight. Estimates of gestational age of fewer than 37 weeks (prematurity) have shown a significant association with the risk of sepsis-related neonatal death, with a 4.6 times higher probability of death among neonates born before 37 weeks of gestation compared with neonates born after.[13] These results are consistent with studies conducted in Indonesia, Thailand, the city of Duhok in Iraq, central India, and southeastern Mexico and systematic reviews conducted in developing countries.[14] Premature and/or low birth weight neonates have a limited amount of immunoglobulin at birth and cannot produce an adequate quantitative and/or qualitative mounting response to infectious agents. The insufficient time a premature baby has in the womb reduces the transfer of immune globulins to the fetus. The deficiency of this immunoglobulin puts premature infants at a much higher risk for sepsis when compared to term infants. The total mortality and morbidity rates due to neonatal sepsis were estimated at 27.4% and 89.3%, respectively.[15-17] From the available data, it was found that the majority of patients had low birth weight and were preterm. Sepsis is very influential on mortality and morbidity rates in neonates. There was no significant

relationship between the accuracy of antibiotic administration based on the Gyssens method in neonatal sepsis with the clinical and hematological improvement of other patients because, in the Gyssens method, there were several assessment components that were not directly related to the clinical aspects of the patient, namely data completeness, drug prices, and especially those that related to the availability of various types of antibiotics with different spectrums and effectiveness where the purpose of the Gyssens method is to determine the right indication for antibiotic administration, the right patient, the right drug administration, the right dose, the right way and duration of administration, and to estimate the side effects of the drug that occur and to avoid or delay antimicrobial resistance because rational use of antibiotics in the NICU is critical to protect the population of neonates who are susceptible to infection.[18,19]

5. Conclusion

There is a relationship between the appropriateness of antibiotic use on clinical improvement and blood parameters of patients with neonatal sepsis in the Perinatology ward of Dr. M. Djamil General Hospital based on the gyssens method, but not statistically significant. The use of antibiotics based on the Gyssens method at Dr. M. Djamil General Hospital is quite good.

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