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Original Article

Ceftazidime as an empiric therapy for neonatal sepsis

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Abstract

Background Sepsis is still the leading cause of death in neonates in developing countries. Proper administration of antibiotics is important for managing neonatal sepsis. The microorganisms that cause neonatal sepsis, as well as their sensitivity patterns, change over time and differ from one place to another. Since 2001, ceftazidime has been used as an empirical antibiotic for managing neonatal sepsis at Dr. Mohammad Hoesin Hospital, Palembang, South Sumatera, but its effectiveness is questionable.

Objective To evaluate the effectiveness of ceftazidime as an empiric therapy for neonatal sepsis.

Methods This study was pre-experimental, for one group, pre- and post-test, was conducted in 49 neonates with neonatal sepsis in the neonatal ward at Dr. Mohammad Hoesin Hospital, Palembang, South Sumatera, from April to September 2019. The effectiveness of ceftazidime was determined based on clinical and laboratory improvements 72 hours after ceftazidime administration.

Results Of 49 neonates, 28 experienced clinical and laboratory improvement, while 21 experienced improvement in only one parameter, either clinical or laboratory. Gram positive bacteria were found in 22/49 subjects.

Conclusion There is a significant difference on white blood cell count and CRP level between before and after ceftazidime administration but overall ceftazidime is no longer effective as empiric antibiotic therapy in neonatal sepsis. **[Paediatr Indones. 2021;61:198-204 ; DOI: 10.14238/pi61.4.2021.198-204**].

Keywords: *sepsis neonatorum; neonatal sepsis; ceftazidime; empirical*

Neonatal sepsis is still the leading cause of death in neonates, especially in developing countries. Sepsis in neonates often has non-specific signs and symptoms. Therefore, empiric antibiotic therapy should be chosen and immediately administered to the neonate with suspected sepsis, after having blood drawn for the culture and antimicrobial susceptibility testing. The empiric antibiotics used are generally broad-spectrum antibiotics.[1-3]

Ceftazidime has been used since year 2001 as an empiric antibiotic in the treatment of neonatal sepsis in the neonatal ward at Dr. Mohammad Hoesin Hospital, Palembang, South Sumatera. The use of ceftazidime based on the pattern of bacteria that cause neonatal sepsis and antimicrobial susceptibility conducted by Imran *et al.*[3] in 2001 and Indra *et al.*[4] in 2007. Ceftazidime also gave a good clinical response and a high recovery rate.

Since year 2018, 30% of babies with neonatal sepsis who received ceftazidime as empiric therapy had to be replaced with other antibiotics because they did not show a good clinical response. Therefore, this study aimed to assess the effectiveness of ceftazidime as an empiric antibiotic for neonatal sepsis in Dr. Mohammad Hoesin Hospital, Palembang, South Sumatera.

Methods

We conducted a pre-experimental, one group, pre- and post-test study from April to September 2019 in the neonatal ward at Dr. Mohammad Hoesin Hospital, Palembang, South Sumatera.

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Subjects were neonates with sepsis, treated with ceftazidime, and included by consecutive sampling. The inclusion criteria were neonatal sepsis patients with a gestation period of ≥ 37 weeks or a birth weight of ≥ 2,500 grams. The exclusion criteria were neonates who had previously received antibiotic treatment, and had major congenital abnormalities. Informed consent was obtained for all subjects. This study was approved by the Research Ethics Committee in Dr. Mohammad Hoesin Hospital, Palembang.

Criteria for neonatal sepsis were based on clinical sign, at least two abnormal laboratory results (white blood cell count <5,000 or >34,000 /mm^3; ESR > 15 mm /hour; IT ratio ≥ 0.2; CRP level > 10 mg/dL; positive or negative blood culture).

The minimum required sample size was 49 (α=0.05, β=0.2, π=0.5, ΔP=0.3, and 10% drop out). Sociodemographic data including identification of subjects, history of current disease, history of pregnancy and labor were collected from parents. Physical examination was carried out upon hospital admission, including body weight, activity, suction reflex, crying, heart rate, respiratory rate, rectal temperature, and organ systems (gastrointestinal, cardiovascular, and respiratory system). Blood specimen were collected by two trained nurses for peripheral blood examination (*Sysmex XN 1000/Sysmex XT 4000*), CRP (*ELISA from Nycocard*), and blood culture (*VITEK2*). The first blood test was performed before ceftazidime administration, and the peripheral blood test was repeated 72 hours after the first ceftazidime injection. The primary outcome of this study, the effectiveness of ceftazidime, was determined based on clinical and laboratory improvements 72 hours after ceftazidime administration. Follow up therapy was done every day for up to 3 days of treatment to assess the progress of therapy. Improvement was defined if overall clinical symptoms (as mentioned in Table 2) improved within 72 hours of treatment and peripheral blood laboratory tests (as mentioned in Table 3) results were within normal limits. No improvement was defined if after 72 hours of ceftazidime administration, there were no clinical improvement, abnormal laboratory results, and antibiotic replacement was performed. If the general condition worsened or there was no clinical improvement within 72 hours, antibiotic was adjusted by the doctor in charge, under the neonatologist supervision. The secondary outcome was the spectrum of bacteria causing neonatal sepsis and bacterial in-vitro sensitivity.

Data were recorded on a study form, then entered into a computer using *SPSS version 22.0*. A P value <0.05 was considered significant, with 95% confidence intervals. Categorical data were analyzed using the McNemar test. Data before and after empirical antibiotic treatment were assessed to determine the effectiveness of empirical therapy.

Results

Of 49 subjects, there were 28 males with an age ranged 0-27 days. The highest number of subjects was in the ≤ 3 days age group (23/49; 47%). The median age of subjects was 3 days, with an interquartile range of 1-15 days. Demographic characteristics are shown in **Table 1**.

All subjects received ceftazidime on hospital admission. Clinical sign and laboratory examinations were monitored for up to 72 hours of treatment. **Table 2** shows clinical sign before and after ceftazidime administration. The most common symptom was tachypnea. Some clinical signs significantly improved after administration of ceftazidime including hypoactivity, poor sucking reflex, hyperthermia, tachypnea, meteorism, and jaundice.

Laboratory examinations were done at the time of hospital admission and on the third day of treatment. Laboratory monitoring on the third day of therapy consisted of white blood cell count, IT ratio, micro-ESR, and CRP. **Table 3** shows the laboratory results before and after ceftazidime administration. Most subjects had normal white blood cell count and ESR. The most common markers of infection were increased CRP and IT ratio.

Laboratory results became normal in 40/49 (82%) subjects after empiric ceftazidime therapy. White blood cells count became normal in 14/49 (29%), micro-ESR in 7/49 (14%), IT ratio 23/49 (47%), and CRP in 28/49 (57%) subjects. In laboratory parameters, we found that mean white blood cells and CRP improved significantly (mean difference of WBCs 4.66; 95%CI 1.842 to 7.478; P=0.002 and mean difference of CRP 29.80; 95%CI 11.42 to 48.18; P=0.002, respectively).

In this study, the parameters of effectiveness

Table 1. Characteristics of neonatal sepsis patients

Characteristics	n = 49
Age, n (%)	
≤ 3 days	23 (47)
> 3 days - 7 days	10 (20)
> 7 days	16 (33)
Gender, n (%)	
Male	28 (57)
Female	21 (43)
Type of delivery, n (%)	
Normal delivery	27 (55)
Cesarean section	21 (43)
Vacuum/forceps	1 (2)
Pregnancy, n (%)	
Primigravida	28 (57)
Multigravida	21 (43)

of ceftazidime therapy were based on improvement in clinical signs and laboratory tests after 72 hours of treatment. **Table 4** shows that after ceftazidime administration, there was no improvement in clinical signs and laboratory tests in 57% and 43% of subjects, respectively.

Of the 49 subjects who underwent blood culture examinations, 29 of them showed the presence of bacterial growth. The most widely isolated bacteria were Gram-positive (22/49; 45%). Gram-negative bacterial isolates were found in 7/49 (14%) subjects, two of which were resistant to ceftazidime. Sensitivity test to ceftazidime was only performed in Gram-negative bacteria growth in culture media. Five out of 7 Gram-

Table 2. Clinical sign before and 72 hours after administration of ceftazidime

Clinical signs*	Before n=49	After n=49	P value#
Common symptoms of baby, n (%)			
Hypoactivity	19 (39)	10 (20)	0.016
Poor sucking reflex	16 (33)	4 (8)	0.002
Weak cry	11 (22)	6 (12)	0.063
Hypothermia	-	-	-
Hyperthermia	23 (47)	10 (20)	0.001
Sclerema	-	-	-
Central nervous system symptoms, n (%)			
Lethargy	5 (10)	3 (6)	0.625
Irritability	-	-	-
Seizures	5 (10)	3 (6)	0.625
Respiratory tract symptoms, n (%)			
Dyspnea	-	-	-
Tachypnea	27 (55)	15 (31)	0.002
Bradypnea	-	1 (2)	-
Apnea	-	-	-
Cyanosis	-	-	-
Gastrointestinal tract symptoms, n (%)			
Vomiting	6 (12)	4 (8)	0.5
Diarrhea	4 (8)	-	-
Meteorism	11 (22)	4 (8)	0.016
Hepatomegaly	-	-	-
Hematologic symptoms, n (%)			
Petechiae	3 (6)	1 (2)	0.5
Purpura	-	-	-
Other bleeding	-	-	-
Jaundice	7 (14)	-	0.016
Splenomegaly	-	-	-
Cardiovascular symptoms, n (%)			
Cyanosis	-	-	-
Tachycardia	4 (8)	1 (2)	0.25
Hypotension	-	-	-
Edema	-	-	-

Note: *In each subject may be found >1 clinical signs, #McNemar test

Table 3. Description of laboratory results before and after empirical therapy

Laboratory tests	Before n=49	After n=49	Mean (SD)	P value*
White blood cells count, n (%)			4.66 (9.81)	
< 5000/µL	10 (20)	2 (4)		0.002
5000-34,000/µL	32 (66)	46 (94)		
>34,000/µL	7 (14)	1 (2)		
IT ratio, n (%)				
< 0.2	13 (26)	36 (74)		0.001
≥ 0.2	36 (74)	13 (26)		
Micro ESR, n (%)				
≤ 15 mm/hour	36 (74)	43 (88)		0.118
>15 mm/hour	13 (26)	6 (12)		
Positive CRP, n (%)			29.80 (63.99)	
<10 mg/dL	7 (14)	35 (71)		0.002
≥10 mg/dL	42 (86)	14 (29)		

*McNemar test; micro ESR=micro erythrocyte sedimentation rate

Table 4. Effectiveness (response) of ceftazidime therapy based on clinical sign and laboratory test

Effectiveness	Clinical signs, n (%)	Laboratory tests, n (%)	Clinical + laboratory, n (%)
Improvement (effective)	28 (57)	40 (82)	28 (57)
No improvement (not effective)	21 (43)	9 (18)	21 (43)

negative bacteria found in culture media were sensitive to ceftazidime.

Gram-positive microorganisms were the most frequent causative microorganism for neonatal sepsis, including *Staphylococcus haemolyticus* in 9/29 (31%) and *Staphylococcus epidermidis* in 5/29 (17%) subjects. The Gram-negative microorganisms found where *Klebsiella pneumonie Ssp Pneumonia* in 3/29 (10%) and *Escherichia coli* in 4/29 (14%) subjects.

In subjects with positive cultures who were sensitive to ceftazidime, 2/5 subjects had an improved response after receiving ceftazidime and 3/5 subjects had no improved response. Positive culture subjects which showed resistance to ceftazidime were found in 2/7 subjects and all subjects had no improvement in therapeutic response. There were 20/49 (41%) subjects with sterile culture; 11/20 subjects experienced improvement and the remaining 9/20 subjects had no improvement, in either clinical sign or laboratory test. Bacterial pattern and sensitivity to ceftazidime are shown in **Table 5**.

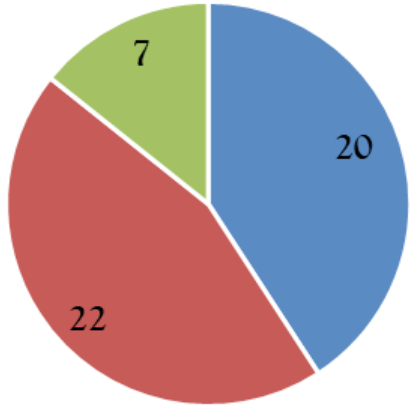

Figure 1. Pattern of microorganisms growth in blood cultures [green=Gram-negative, red=Gram-positive, blue=sterile]

Discussion

The majority of subjects were age > 72 hours, namely 26/49 (53%), with a median age of 3 days. Neonatal sepsis is classified into early onset (age ≤ 72 hours) and late onset (age> 72 hours). In this study, the majority of subjects were late onset sepsis. A previous study also found that the majority of neonatal sepsis was late onset neonatal sepsis, (192; 61.1%).[5]

We observed more male (28/49; 57%) than female

Figure 1. Pattern of microorganisms growth in blood

Table 5. Bacterial pattern and sensitivity to ceftazidime

Bacterial isolated	n	Sensitivity to ceftazidime			Improvement in clinical and laboratory	
		S	I	R	Yes	No
Positive culture	29	NA	NA	NA	17	12
Gram positive	22	NA	NA	NA	15	7
Staphylococcus haemolyticus	9	NA	NA	NA	7	2
Staphylococcus epidermidis	5	NA	NA	NA	3	2
Staphylococcus aureus	3	NA	NA	NA	1	2
Staphylococcus hominis	3	NA	NA	NA	3	0
Streptococcus pyogenes	2	NA	NA	NA	1	1
Gram negative	7	5	0	2	2	5
Kebsiella pneumoniae	3	1	0	2	1	2
Escherichia coli	4	4	0	0	1	3
Steril culture	20	NA	NA	NA	11	9

S=sensitive, I=intermediate, R=resistant, NA=not available (sensitivity to ceftazidim was not conducted)

with neonatal sepsis. A systematic review found that male gender was a risk factor for neonatal sepsis (OR 1.3; 95%CI 1.02 to 1.68),6 in accordance with our results. Male neonates are more sensitive to changes in perinatal to postnatal conditions and are more likely to be born prematurely with low birth weight, which increases the risk of neonatal sepsis.[6]

Most of subjects underwent normal delivery (27/49), followed by cesarean section (21/49). A previous study reported that neonates with a history of normal delivery were 2.29 times more risk of neonatal sepsis compared to cesarean section. This result related to normal delivery methods which unhygienic, unsafe, and inadequate place of delivery that predispose to sepsis.[7]

Most of subjects had general symptoms of hyperthermia (23/49; 47%), followed by hypoactivity in 19/49 (39%). A study found that the frequent clinical signs of neonatal sepsis were fever, tachypnea, breastfeeding intolerance and jaundice.[8]

The frequent symptoms were tachypnea in 27/49 (55%), meteorism in 11/49 (22%), and jaundice in 7/49 (14%) subjects. A study in Iran found that clinical and laboratory manifestations of neonatal sepsis was tachypnea in 49 (45.5%) subjects, followed by jaundice, vomiting, and reduced breastfeeding were 28 (25.5%), 26 (23.6%), and 23 (20.9%) subjects, respectively. However, in that study, fever and bloating were found in only 3.6% and 2.7% of subjects, respectively.9 General symptoms of neonatal sepsis are not specific, one or more common symptoms such as hypothermia or hyperthermia, lethargy, moaning, crying, lazy breastfeeding, changes in muscle tone, and poor perfusion, accompanied by specific symptoms involving various organ systems.[9-11]

The most common markers of infection found in this study were increase CRP and IT ratio. CRP value of ≥10 mg/dL was found in 42/49 (86%) subjects. A previous study showed that CRP had lower sensitivity (80.4%) compared to IT ratio, white blood cellS count, and platelets.[12] In contrast, another study showed that CRP cut-off > 4.09 ng/mL had a sensitivity of 95% and a specificity of 86% in diagnosing neonatal sepsis.[13]

Micro-ESR increased in 13/49 (26%) subjects. This result was higher than reported by Kafle *et al.*[14] who found increase micro-ESR in 29/250 neonates (12%), while West *et al.*[15] found that 406 neonates with sepsis, 251 (61.8%) subjects with increase micro-ESR (sensitivity of 75.7%) in the diagnosis of neonatal sepsis.

In our study, increasing of IT ratio was found in 36/49 (74%) subjects, while a study showed that in 53 neonates with suspicion of sepsis, IT ratio increased in 28 (52.8%) subjects. In their study, 23 subjects had positive blood cultures; IT ratio had a sensitivity of 88.46%.[16]

In this study, leukopenia (10/49; 20%) was more frequent than leukocytosis (7/49; 14%). A study in Guangzhou City reported that leukopenia was found in 35% of neonatal sepsis patients compared to leukocytosis in 4% of patients.[17] Leukopenia and increased IT ratio were associated with an increased risk of infection and inflammation.[13,17]

We observed, general symptoms improved in some subjects after 3 days of ceftazidime empiric therapy. The significantly improvement were hypoactive symptoms, weak suction reflex, and hyperthermia. A previous study showed that the majority of subjects

experienced improvement in general symptoms after 3 days of antibiotics, namely lethargy (90.7%), lazy breastfeeding (83%), moaning (37.3%), and hyperthermia (24%).[18] Furthermore, no significant difference in the improvement of clinical sign after administration of empiric antibiotics on the third and seventh day of treatment in cases of neonatal sepsis with negative cultures. The empirical antibiotics used were ciprofloxacin and netilmycin.18 In this study, several laboratory parameters were significantly improved after 3 days of empirical ceftazidime, namely, the mean number of white blood cells and CRP.

Two past studies reported on the effectiveness of ceftazidime therapy in combination with other antibiotics at our institution, with ceftazidime effectiveness of 88.5% in 2001 and 78.6% in 2007 in patients.[3,4] In this study, the effectiveness of empiric therapy with ceftazidime was 57%, with 28/49 (57%) subjects experienced clinical and laboratory improvement, while 21/49 (43%) experienced improvement in one parameter of the clinical or laboratory test criteria. Compared to the previous studies in 2001 and 2007, the effectiveness of ceftazidime therapy in the neonatology ward in our hospital was decreased. As such, it is necessary to consider whether ceftazidime should still be used as therapy or if we should find other more effective antibiotic alternatives.

In neonates with sepsis, more than 80% infants received antibiotic therapy even though blood culture results were negative, or antibiotics were started without waiting for blood culture results.19 In infants with sepsis, sterile blood culture results can occur due to low bacteria levels, inappropriate blood sampling in neonates, and causes of infection other than bacteria.[19]

In developing countries, Gram-positive bacteria cause about 70% of late-onset sepsis cases. The most common bacteria were coagulase-negative streptococci, followed by *Staphylococcus aureus, Enterococcus sp*, and *Staphylococcus aureus B haemolyticus*. Only about 18-20% of late-onset sepsis cases are caused by Gram-negative bacteria and 12% are caused by fungi. The most common microorganisms that cause early onset sepsis are Gram-negative, namely, *Klebsiella sp* and *Escherichia coli*.[20] In our study, blood culture showed that most microorganism was Gram-positive (22/29), accordance with the majority of subjects were late-onset neonatal sepsis. Gram-positive microorganisms cultured were *Staphylococcus haemolyticus* in 9/29 and *Staphylococcus epidermidis* in 5/29. The Gram-negative microorganisms were *Klebsiella pneumoniae Ssp* pneumoniae in 3/29 subjects and *Escherichia coli* in 4/29 subjects.

A previous study reported that the most microorganisms found in early onset sepsis were *Acinetobacter sp* (32.14%), *Staphylococcus aureus* (16%), *Escherichia coli* and *Enterobacter sp* (5.3%), *Citrobacter sp* and *Salmonella paratyphii* (3.5%). The microorganism found in late-onset sepsis were *Staphylococcus aureus* (19.6%), *Acinetobacter sp* (8.9%), coagulase-negative Streptococci (8.9%), *Klebsiella pneumonia* (5.3%), *Escherichia coli*, *Enterobacter sp*, and *Pseudomonas sp* (3.5%).[21]

In 29 subjects with positive blood culture results, only 7/29 were Gram-negative bacteria, and 5/7 were sensitive to ceftazidime. Based on culture isolated found in all neonatal sepsis patients in this study, there was a discrepancy between patterns of bacteria that cause sepsis and empiric antibiotic choice. In subjects with positive cultures who were sensitive to ceftazidime, only two had an improved response after receiving the therapy. In positive culture subjects with resistance to ceftazidime, there were 2/7 subjects and all subjects had no improvement in therapeutic response.

In conclusion, ceftazidime is no longer effective for use as empirical therapy in neonatal sepsis. Its effectiveness has decreased over time compared to 2001 and 2007 studies done in the same NICU setting at our institution. Further study is needed to find more effective antibiotic alternatives.

Conflict of interest

None declared.

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