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Original article

Association between Duration of Early Empiric Antibiotics and Necrotizing Entercolitis and Late-onset Sepsis in Preterm Infants

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Abstract

Background: Early empiric antibiotic exposure (EEAE) is a common practice in neonatal intensive care units (NICUs) to prevent infections in preterm infants. However, concerns have arisen regarding its potential association with adverse outcomes, including necrotizing enterocolitis (NEC) and late-onset sepsis (LOS). **This study aims to** evaluate the relationship between EEAE and the incidence of NEC and LOS in preterm infants. **Methods:** A comparative cross-sectional study was conducted involving 48 preterm neonates admitted to the NICU from January to August 2024. Participants were divided into two groups based on the duration of EEAE; Group I: those receiving prolonged antibiotics (>7days) and Group II: those receiving short-term antibiotics (<7days). Clinical data were collected, and the incidence of NEC and LOS was recorded for both groups. **Results**: Among the 48 neonates, 11 (22.9%) developed NEC, with a significantly higher incidence in Group I (9/24, 37.5%) compared to Group II (2/24, 8.33%) (p=0.01). Additionally, 25 (52%) neonates experienced LOS, with a notable increase in Group I (17/24, 70.8%) versus Group II (8/24, 33.3%) (p=0.00). The average duration of early empiric antibiotic exposure was 10.5 days in Group I and 4.3 days in Group II, highlighting a direct correlation between prolonged exposure and the incidence of these complications. **Conclusion:** Prolonged early empiric antibiotic exposure is significantly associated with an increased risk of both NEC and LOS in preterm infants. These results underscore the importance of careful antibiotic stewardship in this vulnerable population to mitigate the risk of severe complications.

Keywords: Necrotizing Enterocolitis; Late-onset Sepsis; Preterm Infants; Early Empiric Antibiotic Exposure.

Introduction

Neonatal sepsis remains a significant cause of morbidity and mortality in neonatal intensive care units (NICUs), with preterm infants often facing low thresholds for empiric antibiotic initiation due to the high risk associated with delayed treatment of early-onset sepsis (EOS) (1, 2). Consequently, over 75% of very low birth weight (VLBW, <1500 g) infants are empirically treated with antibiotics (3).Necrotizing enterocolitis (NEC), a common gastrointestinal disorder in newborns, also contributes to high morbidity and neurodevelopmental impairments in preterm survivors (4).

Empirical antibiotic therapy is usually discontinued if blood cultures are negative after 48–72 hours, yet often extended due to the low sensitivity of blood cultures and fear of undertreating sepsis (5). Adverse effects of early antibiotic exposure include antibiotic resistance, gut dysbiosis, and increased risks of long-term metabolic and autoimmune disorders (6, 7).

In very low birth weight (VLBW) infants, prolonged antibiotic exposure has been associated with an increased risk of adverse events, such as NEC and late-onset sepsis (LOS) (8). However, recent observational studies and animal models suggest that antibiotics may mitigate NEC risk by reducing bacterial colonization and lowering the intestinal bacterial load (9, 10). Effective biomarkers for early NEC detection should align with disease pathogenesis, focusing on epithelial damage, muscle injury, inflammation, and pathogen invasion. Fatty-acid-binding proteins (FABP), small cytoplasmic proteins with high organ sensitivity, are among these promising markers (11).

Intestinal fatty acid-binding protein (I-FABP) makes up about 2% of the cytoplasmic proteins in mature enterocytes and is released into the bloodstream when intestinal epithelial cells are damaged, as it passes through the glomerular filter with a renal excretion rate of 28% and a half-life of 1 minute (12). Plasma levels of I-FABP can thus indicate the extent of gut wall injury, serving as a noninvasive marker for assessing gut integrity and inflammation in infants suspected to have NEC. I-FABP in plasma (I-FABP) has shown promise as an early NEC diagnostic biomarker, with elevated levels found in patients with NEC, sepsis, and even in healthy individuals after abdominal trauma or alcohol intake (13).

The purpose of this study is to explore the extent of early empiric antibiotic exposure in preterm infant and the association between the duration of early empiric antibiotic exposure with necrotizing enterocolitis and late onset sepsis within different early empiric antibiotic exposure groups.

Patients and methods

Study design

This comparative cross sectional study included 48 neonates admitted in NICU at Benha University Hospital, during the period from January till August

2024. The study was done after being approved by the Research Ethics Committee, Faculty of Medicine-Benha University (Approval Code: MD 1-1-2023). An informed consent was obtained from the parents of the infants. Parents received an explanation of the purpose of the study and had a secret code number.

Inclusion criteria were preterm neonates of both sexes with gestational age of 34 weeks or less who were 2.5 kg or less and were exposed to early empiric antibiotics.

Exclusion criteria were neonates with culture-proven EOS, neonates who pass away within the first week of life regardless of the cause, neonates undergoing major surgeries and neonates with major congenital anomalies, including gastrointestinal issues like anal or intestinal atresia and Hirschsprung's disease.

Grouping: The patients were divided into two groups: **Group I:** 24 patients with prolonged early empiric antibiotic exposure (more than one week). **Group II:** 24 patients with short term early empiric antibiotic exposure (less than one week).

Evaluation

All the studied neonates underwent a comprehensive assessment including:

Perinatal and obstetric history, which covered the gestational age, birth weight, gender, and delivery mod, were evaluated.

Thorough clinical examination comprising full general and systemic evaluation, assessment of invasive ventilation needs at 48–72 hours of life, type of enteral feeding and duration of parenteral feeding.

Laboratory investigations including routine tests as complete blood count (CBC), C-reactive protein (CRP) and blood culture taken after 3 days of life in addition to clinical suspicion (fever, poor activity, poor perfusion and feeding intolerance) for diagnosing LOS. Additionally, we measured the plasma levels of intestinal fatty acid-binding protein (I-FABP) using ELISA to diagnose NEC.

Two milliliters of venous blood were collected under aseptic conditions and placed in an EDTA vaccutainer (violet cap), mixed gently for 10–20 minutes, and then centrifuged at 2000 rpm for 20 minutes. The supernatant was removed, and the separated plasma was used to assay i-FABP. For our groups, blood samples were taken at two time points: within the first 24 hours of birth, and after the start of feeding, generally around 6–10 postnatal days.

Statistical analysis

Data management and statistical analysis were done using SPSS version 26 (IBM, Armonk, New York, United States). Qualitative data were presented as numbers and percentages, while quantitative data were displayed as means, standard deviations and ranges for parametric distributions. For comparisons between two groups with qualitative data, the Chi-square test was used, or Fisher's

exact test when the expected count in any cell was less than 5. Comparisons between two independent groups with quantitative, parametric data were conducted using the Independent t-test. A 95% confidence interval and a 5% margin of error were set, with significance levels as follows: $p > 0.05$ as non-significant (NS), $p < 0.05$ as significant (S), and $p < 0.001$ as highly significant (HS).

Results

There is no statistically significant differences between the groups in the following measured variables: Gestational age was similar in both groups, with means of 30.88 ± 1.90 weeks for Group I and 31.29 ± 1.97 weeks for Group II ($p = 0.459$). Birth weight showed no significant difference, with means of 1.98 ± 0.36 kg in Group I and 1.85 ± 0.34 kg in Group II ($p = 0.223$). The proportion of small-for-gestational-age (SGA) infants was comparable between the groups (25.0% in Group I and 37.5% in Group II, $p = 0.350$). Gender distribution, delivery mode, and singleton status did not differ significantly, with slightly more females and singleton births in Group II but not to a statistically significant degree. Overall, the groups were well-matched on these baseline characteristics, as indicated by the non-significant p-values across all variables.

Statistically significant differences were found between Group I and Group II in the need for invasive ventilation and inotropic medication at 48–72 hours of life. In contrast, there was no significant difference regarding the type of enteral feeding between the two groups. Additionally, significant differences were noted in the incidence of NEC, as well as a highly significant difference in the occurrence of late-onset sepsis between the groups. **Table 1**

There was highly statistically significant increment in Group I compared to Group II regarding the duration of EEAE and plasma levels of i-FABP at the time of diagnosis and at the first 24 hours and in the highest C-reactive protein (CRP) levels within the first 72 hours of life. However, no significant differences were observed in the age of onset of NEC or LOS. Group I also showed highly significant increments in i-FABP levels at the time of diagnosis and the first 24 hours. **Table 2**

There was a statistically significant positive correlation between plasma levels of i-FABP at the time of diagnosis and the duration of EEAE. Additionally, negative correlations were observed between I-FABP levels at the time of diagnosis and both gestational age and birth weight, although these correlations were not statistically significant. Similarly, there was a positive correlation between I-FABP levels at the time of diagnosis and the age of onset for NEC and LOS, but these were also non-significant. At the first 24 hours, a statistically significant positive correlation was again found between I-FABP levels and EEAE duration, with negative correlations present for gestational age and birth weight, though not statistically significant. Positive correlations were also noted between I-FABP levels at the

first 24 hours and the ages of NEC and LOS onset, but these did not reach statistical significance. **Table 3**

Table 1: Comparison between Group I and Group II regarding invasive ventilation and inotropic medication at 48–72 h of life, enteral feeding type, NEC and late-onset sepsis

Variables		Group I		Group II		Test value	P-value	Sig.
		No.	%	No.	%			
Invasive ventilation at 48–72 h of life	**No**	9	37.5%	17	70.8%	5.371*	0.020	S
	Yes	15	62.5%	7	29.2%			
Inotropic medication at 48–72 h of life	**No**	2	8.3%	8	33.3%	4.547*	0.033	S
	Yes	22	91.7%	16	66.7%			
Exclusive Human milk		19	79.2%	18	75.0%	0.227*	0.892	NS
Formula milk only		2	8.3%	3	12.5%			
Combination		3	12.5%	3	12.5%			
NEC	**No**	15	62.5%	22	91.7%	5.779*	0.016	S
	Yes	9	37.5%	2	8.3%			
Surgical NEC		6	66.7%	1	50.0%			
Late-onset sepsis	**No**	7	29.2%	16	66.7%	6.762*	0.009	HS
	Yes	17	70.8%	8	33.3%			
CoNS LOS		10	58.8%	5	62.5%			
All non- CoNS pathogens		7	41.2%	3	37.5%			
Gram-negative LOS		4	57.1%	1	33.3%			
Gram-positive LOS		3	42.9%	2	66.7%			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS), *: Chi-square test, •: Independent t-test, NEC: Necrotizing enterocolitis, CoNS: coagulase-negative staphylococcus, LOS: late-onset sepsis.

Table 2: Comparison between Group I and Group II regarding EEAE duration, highest CRP within the first 72 h of life, age of NEC onset, age of LOS onset and plasma level of intestinal fatty acid binding protein

Variables		Group I	Group II	Test value	P-value	Sig.
		No. = 24	No. = 24			
EEAE duration (days)	**Mean ± SD**	7.38 ± 1.66	2.50 ± 1.14	-11.837•	0.000	HS
	Range	5 – 10	1 – 5			
Highest CRP within first 72 h of life	**≥10 mg/L**	8 (33.3%)	2 (8.3%)	4.547*	0.033	S
	< 10 mg/L	16 (66.7%)	22 (91.7%)			
Age of NEC onset (Days)	**Mean ± SD**	13.92 ± 5.27	13.08 ± 5.23	0.550•	0.585	NS
	Range	6 – 24	6 – 25			
Age of LOS onset (Days)	**Mean ± SD**	12.79 ± 3.56	10.96 ± 3.09	1.902•	0.064	NS
	Range	7 – 20	6 – 15			
Plasma i-FABP at time of diagnosis (6-10 d's postnatal) (ng\ml)	**Mean ± SD**	20.71 ± 3.17	2.85 ± 0.34	27.448•	0.000	HS
	Range	15 – 27	2.4 – 3.5			
Plasma i-FABP at 1st 24 h's (ng\ml)	**Mean ± SD**	6.91 ± 1.03	1.92 ± 0.15	23.451•	0.000	HS
	Range	5 – 9	1.5 – 2.1			
Test value		-20.982	-12.302	-	-	-
P-value		0.000	0.000	-	-	-
Sig.		HS	HS	-	-	-

EEAE: Early empirical antibiotic exposure, CRP: C reactive protein, LOS: Late onset sepsis, NEC: Necrotizing enterocolitis, P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS), *: Chi-square test, •: Independent t-test.

Table 3: Correlation between plasma level of intestinal fatty acid-binding protein at the time of diagnosis (ng/ml) and plasma level of intestinal fatty acid binding protein at 1st 24 hour (ng/ml) with gestational age, birth weight, parental feeding, EEAE duration, age of NEC onset and age of LOS onset

Variables	Plasma level of intestinal fatty acid binding protein			
	At the time of diagnosis (ng\ml)		At 1st 24 hour (ng\ml)	
	R	P-value	R	P-value
Gestational age (weeks)	-0.053	0.718	-0.217	0.138
Birth weight (gm)	0.125	0.399	0.122	0.408
EEAE duration (days)	0.726**	0.000	0.714**	0.000
Age of NEC onset (days)	0.153	0.300	0.028	0.851
Age of LOS onset (days)	0.233	0.111	0.369	0.075

EEAE: Early empirical antibiotic exposure, LOS: Late onset sepsis, NEC: Necrotizing enterocolitis.

Discussion

In the current study, there was no statistically significant difference in the occurrence of small for gestational age (SGA) or cesarean deliveries between the study groups. Additionally, the recent NEOMUNE study, which included 2831 very low birth weight (VLBW) infants, found a disproportionately high number of infants born SGA and/or delivered by cesarean section in the group without early empiric antibiotic exposure (EEAE), both recognized as risk factors for necrotizing enterocolitis (NEC) ***Ree et al.,2014*** (14)

In our study, there was no significant difference in gestational age between Group I and Group II***. Dierikx et al., 2022*** conducted a multicenter cohort study examining EEAE in preterm infants with low GA <28 weeks and its relationship with the duration of EEAE, NEC, and LOS and found that infants with prolonged EEAE had lower gestational ages. The effects of antibiotics and potentially induced microbial dysbiosis were related to the development of NEC and LOS (5). This present study indicated no significant difference in birth weight between Group I and Group II. ***Zhu et al., 2023*** reported that LBW is associated with increased early antibiotic therapy (EAT) use and prolonged EAT (15).

In our study, there was a significant increase in invasive ventilation and inotropic medication use in Group I compared to Group II. ***Zhu et al., 2023*** reported that longer mechanical ventilation is associated with increased EAT use and prolonged EAT (15). also, ***Dierikx et al., 2022*** noted that infants with prolonged EEAE were more frequently intubated and received inotropic medication (5).

Our study revealed no significant difference between Group I and Group II regarding enteral feeding type. ***Zhu et al., 2023*** suggest that EEAE may lead to an increased duration to reach full enteral feeding and a higher risk of feeding intolerance among very preterm infants (VPIs) (15).

The present study showed a highly significant increase in EEAE duration among Group I compared to Group II. ***Dierikx et al., 2022*** observed that

most preterm infants are empirically exposed to antibiotics immediately after birth, with about one-quarter continuing antibiotic treatment beyond one week despite negative cultures but clinically not stable cases (5).

Our study showed a significant increase in the highest CRP levels within the first 72 hours of life in Group I compared to Group II. This finding aligns with a study published by ***Dierikx et al., 2022*** which reported that infants with prolonged EEAE exhibited higher CRP values during this period (5).

The present study indicated no significant differences between Group I and Group II regarding the age of onset of LOS and NEC. In Group I, a large proportion had NEC, while a large proportion in Group II did not. There was a statistically significant difference between the two groups concerning NEC. Similarly, the NEOMUNE study involving VLBW infants find significant differences in NEC incidence between short and prolonged antibiotic exposure groups; also, it reported a lower incidence of NEC following any early antibiotic exposure compared to non-exposed infants ***Ree et al.,2014*** (١٤). In contrast, ***Greenberg et al., 2019*** study on extremely and incredibly low birth weight (400-1000 gm) and GA 22-28 weeks reported an increased incidence of NEC and death following prolonged antibiotic exposure compared to short term antibiotic exposure.

The present study found a significant difference between Group I and Group II regarding the incidence of LOS, with a higher proportion in Group I. ***El Manouni et al,٢٠١٩*** suggested a potential protective role of EEAE against LOS, indicating that antibiotic exposure was linked to reduced odds of developing gram-positive LOS, regardless of the type and duration of antibiotics (16). However, this contradicts the findings of ***Dierikx et al., 2022*** who reported that infants with prolonged EEAE had higher adjusted odds of developing LOS (5).

Our study indicated a notable difference in the incidence of LOS between both groups, with a higher occurrence in Group I. The proportions of coagulase-negative staphylococcus (CoNS) and non-CoNS pathogens were similar across both groups, and there was no significant difference regarding gram negative and positive LOS. ***Becker et al.,2014*** suggested that exposure to cephalosporins might lower the risk of CoNS invasion from the skin or gut into the bloodstream (17). Additionally, ***Russell et al .,2012,*** concerning the increasing resistance of CoNS, prompt a rise in the optimal trough vancomycin concentration needed to maintain an effective therapeutic range against these pathogens (18).

The present study demonstrated significantly elevated levels of i-FABP in Group I compared to Group II at both the time of diagnosis and after 24 hours, indicating a substantial increase over time in both groups. This finding highlights the clinical importance of monitoring i-FABP levels for diagnosing conditions like NEC.

Supporting these results, ***Al-banna et al., 2020*** reported a significant rise in plasma i-FABP levels in the patients group within the first 24 hours compared to the control group. The measurements taken around the time of diagnosis further confirmed higher mean i-FABP concentration in the patients group compared to earlier values, reinforcing the potential diagnostic value of i-FABP in NEC (13).

The present study showed non-significant negative correlation between the plasma level of I-FABP at diagnosis and gestational age, nor any significant positive correlation with the age of onset of LOS. ***Al-banna et al., 2020*** discussed the diagnostic and prognostic properties of I-FABP, highlighting its effectiveness in identifying NEC. They indicated specific cutoff values for i-FABP at different time points that provide high sensitivity and specificity, helping to minimize the risk of misdiagnosis. By conducting serial measurements of i-FABP, the likelihood of false-negative results can be reduced (13). This aligns with the findings of ***Gregory et al., 2014*** study which noted that elevated i-FABP levels shortly before NEC can serve as a predictive marker (20).

Yet our study has some limitations include a relatively small sample size, which may affect the generalizability of the findings, the study's observational design limits the ability to establish causal relationships between early empiric antibiotic exposure, i-FABP levels, and the development of gastrointestinal complications. Furthermore, the reliance on i-FABP as a biomarker for detecting NEC and LOS may have limitations related to its specificity and sensitivity, particularly in the context of other gastrointestinal conditions. Lastly, long-term outcomes of the infants were not assessed, which could provide additional insights into the implications of early antibiotic exposure on overall health and development.

Conclusion

The duration of EEAE is linked to the incidence of NEC and LOS. Elevated levels of i-FABP in preterm infants suggest its potential as a valuable biomarker for detecting these complications. These findings underscore the importance of monitoring early empiric antibiotic exposure in preterm infants, as it may impact gastrointestinal and infectious complications. Additionally, plasma i-FABP levels can reflect intestinal epithelial cell damage and serve as a non-invasive test for assessing gut wall integrity and inflammation in infants suspected for NEC, highlighting its value for early diagnosis. Moreover, each additional day of antibiotic exposure is correlated with adverse outcomes, including increased rates of NEC and LOS.

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