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Neonatal Bacterial Meningitis among Term Neonates with Early Onset Sepsis: Prevalence, Clinical Features and Outcomes at a Tertiary Care Center in Thailand: a Retrospective Study over a 7-Year Period (2013-2019)

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ABSTRACT

OBJECTIVE: To determine the prevalence and clinical features associated with early onset neonatal bacterial meningitis (EONBM) in term infants with early onset neonatal sepsis (EOS).

METHODS: This was a retrospective descriptive study of term neonates with EONBM (defined as diagnosis of proven meningitis within 72 hours of age) at Vajira Hospital during 2013–2019. Data from medical records including demographic data, cerebrospinal fluid (CSF) analysis, microbiological results, and neonatal outcomes were reviewed.

RESULTS: There were 1,203 term neonates with EOS. Of these, 18 neonates were diagnosed with EONBM, which corresponded to a prevalence of 15.0 cases per 1000 term neonates with EOS. A total of 409 (34.0%) neonates with EOS underwent lumbar puncture (LP) within 72 hours of age, of which 4.4% had EONBM. Of the 18 neonates with EONBM, 1 (5.6%), 2 (11.1%), and 15 (83.3%) neonates had positive CSF Gram stain, latex agglutination test, and CSF white blood cell > 20 cells/millimeter^3 (mm^3), respectively. All neonates with EONBM had negative blood and CSF culture. Median gestational age and birthweight were 39.0 (interquatile range [IQR] 37.0–39.0) weeks and 3.3 (IQR 2.9–3.4) kg, respectively. Apnea (adjusted odds ratio [aOR] 57.2; 95% confidence interval [CI] 7.1–460.9), history of maternal chorioamnionitis (aOR 13.66; 95% CI 2.08–89.59), and absolute neutrophil count ≥ 18,000 cells/mm^3 (aOR 7.05; 95% CI 2.13–23.30) showed a significant association with EONBM.

CONCLUSION: The prevalence of EONBM in this cohort of term neonates with EOS was relatively low. The current literature does not provide the definite elucidation of risk factors associated with EONBM. A promptly performed LP remains a challenge in neonates with clinical or laboratory indices suggestive of EOS.

KEYWORDS: bacterial meningitis, early onset neonatal sepsis, lumbar puncture, term neonates

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INTRODUCTION

Bacterial meningitis is one of the leading causes of neonatal morbidity and mortality[1-2]. The incidence of neonatal bacterial meningitis varies among regions depending on maternal risk factors, gestational age (GA), and clinical setting. Developed countries have a lower incidence of neonatal bacterial meningitis (0.3 per 1000 live births)[3] compared to developing countries (as high as 0.8 per 1000 live births)[4]. In Thailand, the prevalence of culture proven neonatal meningitis cases was 0.37 per 1000 live births in single university hospital[5]. The prevalence of neonatal meningitis exhibited limitation in Thailand.

Early clinical manifestations of meningitis are typically non-specific (such as temperature instability, lethargy, apnea, respiratory distress, bradycardia, or tachycardia) and are difficult to differentiate from those of early onset neonatal sepsis (EOS)[6]. More specific neurological signs, such as bulging anterior fontanelle and seizures, are late manifestations of meningitis; therefore, cerebrospinal fluid (CSF) analysis via lumbar puncture (LP) plays an important role in the diagnosis of neonatal bacterial meningitis[7].

According to the guidelines of the American Academy of Pediatrics (AAP)[8] and National Institute of Health and Care Excellence (NICE)[9], the indications for LP in EOS include infants with culture-positive bacteremia, infants who do not show improvement with initial antimicrobial therapy, or infants whose clinical course or laboratory indices are suggestive of sepsis. Due to undetermined clinical course of sepsis in neonates, the decision to promptly perform LP greatly depends on institutional policy and the discretion of the attending physician[10]. Better characterization of the epidemiology and clinical course of early onset neonatal bacterial meningitis (EONBM) is a key imperative for early and appropriate investigations and diagnosis.

METHODS

A retrospective descriptive study was conducted at the neonatal care units at the Vajira Hospital, a teaching university hospital and tertiary care center in Thailand (COA 092/2563). The inclusion criterion was term newborns (GA ≥ 37 weeks) who were born at Vajira Hospital during January 1st, 2013–December 31st, 2019 and were diagnosed with EOS according to international classification of disease (ICD) 10 (P360–365, P369) and subsequently diagnosed with EONBM. EOS is defined as infection in bloodstream occurring within the first 3 days of life[11]. Culture-confirmed EOS defined as positive blood culture within 72 hours[11].

Culture-negative EOS defined as ≥ 2 clinical signs of sepsis (temperature instability, irritability, lethargy, feeding difficulties, capillary refill > 2 seconds, apnea, tachycardia or tachypnea), abnomal laboratory finding (c-reactive protein [CRP] > 10 milligram/liter (mg/L), white blood cell (WBC) ≤ 5,000 cells/millimeter^3 (mm^3), physician assigned ICD-10 diagnosis P369 and complete course of antibiotics (at least 7 days) was administered[12-15].

EONBM is defined as proven meningitis in infants who had positive CSF culture, or gram stain results, or latex agglutination test, or CSF WBC > 20 cells/mm^3 without CSF red blood cell (RBC) > 500 cells/mm^3 [16]. Exclusion criterion was infants in whom LP was performed due to other conditions apart from suspicion of neonatal sepsis and meningitis. Infants with incomplete and missing data was excluded. Data pertaining to demographic data, CSF analysis, microbiological results, and neonatal outcomes were retrived from medical records. The data of infants who underwent LP according to ICD 9 with 8,232 were collected.

Using a previously report prevalence of early onset neonatal bacterial sepsis and meningitis of 9.2%[17], we calculate the sample size required to estimate proportion with an error 0.046 and an alpha 0.05. The sample size required for estimating the prevalence of EONBM was 152 cases.

Descriptive statistics were analyzed by using Statistical Package for social science (SPSS) software version 22.0 (SPSS Inc., Chicago, IL., USA). Categorical data are presented with numbers and percentages, and continuous data are presented with the median and interquartile range (IQR). The maternal and neonatal characteristics and neonatal outcomes between infants with EONBM and without non-EONBM were compared using Chi-square, Fisher's exact test, Student's t-test, or Mann-Whitney U Test. The factors significantly associated with EONBM were identified. Variables with a p-value less than 0.05 in univariate analysis were entered into a multivariate logistic regression model. A p-value less than 0.05 was considered statistically significant.

RESULTS

The total of 15,959 neonataes born during the study period. A total of 1,203 term neonates with EOS were identified during the study reference period. Of these, 18 neonates were diagnosed with EONBM, which corresponded to a prevalence of 15.0 cases per 1000 term neonates with EOS. A total of 409 (34.0%) neonates with EOS had undergone LP within 72 hours of age and 4.4% of these had EONBM (figure 1).

Out of 18 infants with EONBM, 1 (5.6%) infant had positive CSF gram stain results identified as Gram-negative rod, 2 (11.1%) infants had positive latex agglutination test (one was identified as *Haemophilus influenzae* and the other one was identified as *Streptococcus* group B *with Streptococcus pneumoniae*). Fifteen (83.3%) infants had CSF WBC > 20 cell/mm^3. However, all infants with EONBM had negative blood and CSF culture.

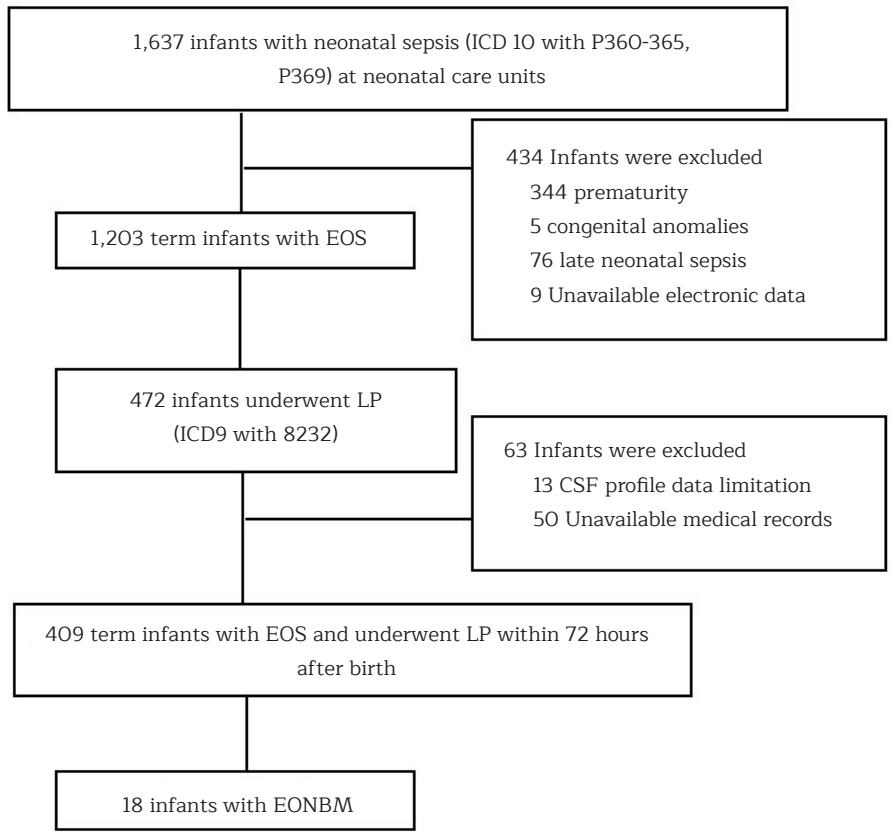

Figure 1 Flowchart demonstrating selection of study. Lumbar puncture, Early onsetneonatal sepsis, Early onset neonatal bacterial meningitis

Maternal and neonatal characteristics of term infants with EOS compared between those with and without EONBM are shown in Table 1. Among infants who had EONBM, the proportion of infants with maternal history of chorioamnionitis (11.1% versus (vs) 1.8%, p = 0.055) and prolonged premature rupture of membrane > 18 hours (16.7% vs 17.9%, p = 0.186) was higher than that among infants without EONBM. None of the mothers of infants with EONBM underwent adequate intrapartum antibiotic prophylaxis (IAP). The median GA and birthweight (BW) of infants in the EONBM group were 39.0 (IQR 37.0–39.0) weeks and 3.3 (IQR 2.9–3.4) kilograms, respectively. The most common clinical signs were respiratory distress (9/18 infants, 50.0%), feeding intolerance (7/18 infants, 38.9%), apnea (2/18 infants, 11.0%), and hyperthermia (2/18 infants, 11.0%). The proportion of infants who developed apnea in the EONBM group was significantly greater than that in non-EONBM group (11.1% vs 1.0%, p = 0.025). None of the neonates with EONBM required respiratory support.

Table 1 Maternal and neonatal characteristics and clinical features with early onset neonatal bacterial meningitis (EONBM) compared with non-EONBM. (n = 409)

Characteristics	EONBM (n = 18)	Non-EONBM (n = 391)	P-value
Maternal data			
Antenatal care	18 (100.0)	356 (92.0)	0.328
Primigravida	8 (44.4)	189 (48.5)	0.739
Chorioamnionitis	2 (11.1)	7 (1.8)	0.055
PROM > 18 hours	3 (16.7)	31 (7.9)	0.186
Vaginal delivery	11 (61.1)	234 (60.0)	0.834
Adequate IAP	0 (0)	21 (5.4)	0.148
Birth before arrival	1 (5.6)	5 (1.3)	0.238
Neonatal data			
GA (weeks)	39.0 (37.0-39.0)	38.0 (38.0-39.0)	0.511
Birth weight (kg)	3.3 (2.9-3.4)	3.0 (2.7-3.3)	0.223
Male gender	11 (61.1)	164 (41.9)	0.110
Small for gestational age	0 (0)	14 (3.6)	0.778
Apgar scores at 5 minutes < 7	1 (5.6)	3 (0.8)	0.166
Clinical features*			
Respiratory distress	9 (50.0)	140 (36.0)	0.316
Feeding intolerance	7 (38.9)	219 (56.3)	0.155
Apnea	2 (11.1)	4 (1.0)	0.025
Hyperthermia	2 (11.1)	45 (11.6)	> 0.999
Hypothermia	0 (0)	13 (3.3)	> 0.999
Seizure	0 (0)	3 (0.8)	> 0.999
Lethargy	0 (0)	21 (5.4)	0.613
Shock	0 (0)	2 (0.5)	> 0.999
Late onset sepsis	0 (0)	20 (5.1)	> 0.999

Abbreviations: EONBM, early onset neonatal bacterial meningitis; GA, gestational age; IAP, intrapartum antibiotic prophylaxis; kg, kilogram; n, number; PROM, premature rupture of membrane
Data reported as number and percentage or median and interquartile range (IQR).
* Some infants had ≥ 1 clinical features .

Laboratory indices of term infants with EOS compared between those with and without EONBM are shown in Table 2. The proportion of infants with absolute neutrophil count (ANC) ≥ 18,000 cells/mm^3 in the EONBM group was significantly greater than that in the non-EONBM group (61.1% vs 30.0%, p = 0.005). In EONBM group, all infants with history of chorioamnionitis (2/2 infants, 100%) and 5 of 11 infants with ANC ≥ 18,000 cells/mm^3 (5/11, 45%) had respiratory distress, respectively. The neonatal outcomes of term infants with EOS compared between those with and without EONBM are shown in Table 3.

The results showing factors associated with EONBM in term infants with EOS are shown in Table 4. By multivariable regression, apnea (adjusted odds ratio [aOR] 57.2; 95% confidence interval [CI]: 7.1–460.9), history of maternal chorioamnionitis (aOR 13.7; 95% CI: 2.1–89.6), and ANC ≥ 18,000 cells/mm3 (aOR 7.1; 95% CI 2.1–23.3) were significantly associated with EONBM.

Table 2 Laboratory data of infants with EONBM compared with non-EONBM (n=409)

Laboratory data	EONBM (n = 18)	Non-EONBM (n = 391)	P-value
ANC ≥ 18,000 cell/mm^3	11 (61.1)	117 (30.0)	0.005
Platelet ≥ 150,000 cell/mm^3	18 (100)	35 (88.9)	0.238
Positive hemoculture	0 (0)	4 (1.0)	> 0.999
CSF WBC > 20 cell/mm^3	15 (83.3)	72 (19.5)	< 0.001
CSF RBC < 500 cell/mm^3	17 (94.4)	193 (52.3)	< 0.001
CSF protein > 100 mg/dL	4 (22.2)	165 (45.2)	0.086
CSF glucose < 30 mg/dL	0 (0)	1 (0.3)	> 0.999
CSF glucose ratio < 0.6	2 (11.1)	9 (2.5)	0.090

Abbreviations: ANC, absolute neutrophils count; CSF, cerebrospinal fluid; EONBM, early onset neonatal bacterial meningitis; mg/dL, milligrams per decilitre; mm, millimeter; n, number; RBC, red blood cell; WBC, white blood cell
Data reported as number and percentage.
*Calculated from 14 infants with EONBM (excluded 4 cases because of no laboratory results).

Table 3 Neonatal outcomes of infants with early onset neonatal bacterial meningitis (EONBM) compared with non-EONBM (n = 409)

Neonatal outcomes	EONBM (n = 18)	Non-EONBM (n = 391)	P-value
Antibiotic duration (days)	10.0 (7.0-14.0)	7.0 (7.0-10.0)	0.006
Oxygen supplement	7 (38.9)	98 (25.1)	0.189
Respiratory support	0 (0)	9 (2.3)	> 0.999
Length of stay (days)	10.5 (7.0-14.0)	9.0 (8.0-11.0)	0.253
Cost (bath)	17,416.0 (14,809.0-22, 509.0)	16,083.0 (13,496.0-20, 102.0)	0.286

Abbreviations: EONBM, early onset neonatal bacterial meningitis; n, number
Data reported as number and percentage or median and interquartile range (IQR).

Table 4 Factors associated with EONBM in term infants with EOS

Factors	Univariate OR (95%CI)	P-value	Multivariate aOR (95%CI)	P-value
Low birth weight	Factors	0.209	3.0 (0.7-12.2)	0.126
PROM ≥ 18 hours		0.683	0.99 (0.2-4.9)	0.990
Chorioamnionitis		0.006	57.2 (7.1-460.9)	< 0.001
Apnea		0.022	13.7 (2.1-89.6)	0.006
ANC ≥ 18,000 cell/mm^3		0.009	7.1 (2.1-23.3)	0.001

Abbreviations: ANC, absolute neutrophil count; CI: confidence interval, EONBM, early onset neonatal bacterial meningitis; EOS, early onset neonatal sepsis; OR, odds ratio; PROM, premature rupture of membrane

Analysis adjusted for all factors in the table.

DISCUSSION

In this study, we investigated the prevalence and clinical features of early bacterial meningitis in term neonates with proven and clinical EOS within 72 hours of age at our center over a period spanning 7 years (2013–2019). The prevalence rate was relatively low. Moreover, this study highlights the favorable outcomes of meticulous implementation of AAP 2012 guidelines for management of neonates with suspected or proven early onset bacterial sepsis[8] and Centers of Disease Control and Prevention (CDC) about prevention of perinatal group B streptococcal disease 2010 guidelines[18]. These guidelines have been followed as a standard practice at our hospital for almost a decade prior to a newly published AAP guidelines in 2020[19].

In a prospective surveillance study conducted in Australia and New Zealand (1992–2002), the incidence of EONBM was 92 cases per 1000 infants with only proven EOS. This was despite more strict diagnostic criteria of EONBM, which included clinical presentation consistent with meningitis and either a positive CSF culture or a positive blood culture in association with a total CSF WBC > 100 cells/mm^3 [17]. Similar to our study, a study conducted in Iran found a low incidence of early bacterial meningitis in neonates younger than 3 days (12.8 cases per 1000 neonates with suspected sepsis)[20]. Our study helps characterize the epidemiology and clinical features of early meningitis in term infants with EOS. The difference among previous[17,20] studies is that the study population comprised of term/preterm infants who are known to have an increased risk of sepsis and meningitis and infants with just suspected sepsis[20].

The differences in the reported prevalence rates of early bacterial meningitis in neonates with EOS are likely attributable to use of different CSF parameters for diagnosis of bacterial meningitis and differences with respect to the study population (term and/or preterm infants), definition of EOS (proven or presumed or suspected sepsis), and age at diagnosis of meningitis.

With respect to the criteria for diagnosis of neonatal meningitis, we included all reliable methods that aid in the diagnosis of bacterial meningitis, i.e., positive CSF culture, CSF Gram stain, polymerase chain reaction (PCR) detected organisms, or CSF WBC > 20 cells/mm^3 [16]. In order to improve the accuracy of CSF pleocytosis for diagnosis of neonatal bacterial meningitis, we excluded traumatic tapping, which is defined as CSF RBC > 500 cells/mm^3, prior to the use of CSF WBC > 20 cells/mm^3. A similar approach was used in an epidemiological study of neonatal meningitis in Morocco[21] and a multicenter retrospective cohort study in China[22].

Because traumatic LP attempts are common in newborns and can affect the interpretation of CSF WBC count, several methods have been used to adjust CSF WBC counts based on CSF and peripheral RBC counts. However, these techniques

do not improve the diagnostic utility and can result in loss of sensitivity with marginal gain in specificity[23].

Similar to our study, The Neonatal Research Network (NRN) showed that EOS cases are caused by organism other than group B *streptococcus* (GBS) or *Escheirchia coli* (E coli), other *Streptococcal species* (12.8%) and *Haemophilus species* (3.8%) are commonly identified[24].

Meningitis is commonly associated with neurological manifestations including seizures, bulging fontanelle, irritability, abnormal consciousness, and dystonia[6,23,25]. However, none of the infants with EONBM in our cohort showed neurological symptoms. This may be attributable to subtle clinical presentation in the early stage of meningitis.

Respiratory distress in newborns is one of the most common signs of EOS and sometimes is the reason for early LP as part of sepsis screening. Eldadah et al. [26] investigated 203 infants (GA ranging from 23–40 weeks) with respiratory distress who underwent LP within the first 24 hours after birth and found that none of them had meningitis. Weiss et al. [27] studied 1,495 preterm infants (GA: 27–36 weeks) with respiratory distress in whom LP were performed as part of sepsis evaluation; only 4 (0.3%) infants were found to have had true meningitis. In the study by Xu et al[22], none of the full-term neonates who were clinically diagnosed as early onset meningitis presented with symptoms of respiratory distress. This is consistent with our study in which respiratory distress was not a differentiating clinical feature between EONBM and non-EONBM groups, and thus was not found to be a risk factor for meningitis. Therefore, the results of previous study and our study suggest that performing an early LP can be delayed in infants with isolated respiratory symptoms[28].

In the 2012 AAP[8] and NICE[9] guidelines, one of the challenging indications for LP is infants whose clinical course or laboratory indices are suggestive of sepsis. For almost the past decade, the decision to promptly perform LP varies from one center to another, and from one physician to another[10].

Of note, after implementation of the current guidelines[8,9,17] which have partially altered the clinical and laboratory features of EOS over time, symptoms of apnea or maternal history of chorioamnionitis or ANC ≥ 18,000 cells/mm^3 in term infants with EOS showed a significant association with increased incidence of EONBM. Krebs et al.[29] reported clinical signs of meningitis in infants with BW < 2,500 grams found that apnea (20.6%). Overall JC[30] reported predisposing factors significantly associated with meningitis were complications during labor and delivery, maternal peripartum infection, and chorioamnionitis. In contrast, Garage et al.[31] reported a low predictive value of peripheral WBC count for late preterm/term neonatal meningitis (defined as only culture-proven meningitis). The difference from previous study[31] is that EONBM was defined as CSF pleocytosis apart from positive CSF culture. Our aim was to include infants who were pretreated with antibiotics before performing an LP. Consistently, Nigrovic et al[32]. reported infants pretreated had lower rates of positive CSF culture than nonpre-treated infants (84 vs 58%). The general practice in our hospital was to perform an LP on clinically stable infants with suspected EONBM, antibiotic treatment is usually started before performing LP. Similar to the ANC ≥ 18,000 cells/mm^3 in term infants with EOS that showed a significant association with increased incidence of EONBM, Ajayi et al[33]. reported that term infants with sepsis (N = 196) in maternal chorioamnionitis showed the ANC 17,800 ± 6,000 cells/mm^3 in timepoint 2.

For this reason, clinical presentations such as respiratory distress should be considered in conjunction with a laboratory parameter (such as ANC) or maternal risk factors (such as chorioamnionitis) while considering early LP in infants with suspected EONBM. Our study showed that a total of 39% (472/1,203) infants

with EOS had undergone LP within 72 hours of age. The LP is an invasive procedure, the indications for LP in the current guidelines of AAP[8] and NICE[9] is not recommend that an LP should be performed in all infants with EOS or was one as part of the septic work up in EOS. Respiratory distress is the one of most common clinical presentation of EOS, however, it is difficult to differentiate between infectious (EOS, meningitis) and non-infectious course (transient tachypnea of the newborn) in the early clinical course. Clinical judgment is required in deciding when to perform an LP[34]. This might be the result of selection bias or information bias.

Some limitations of our study should be considered. Firstly, this may have potentially introduced an information or misclassification bias. The diagnosis of EONBM was mostly not based on gold standard diagnosis for meningitis from microbiology. The result may be better if the database from microbiology was choosen. The information of all cases with positive hemoculture who underwent LP was incomplete. Secondly, this was a retrospective study with possibility of incomplete data or inappropriate ICD coding. Thirdly, this was study was conducted at a single academic tertiary care center, which may limit the generalizability of our findings to other general healthcare settings. The interpretation of the factors associated with EONBM was cautious because of the small of cases and wide confidence interval.

CONCLUSION

This study found a relatively low prevalence of EONBM in term neonates with EOS. The decision to promptly perform lumbar puncture is still a subjective decision. Understanding of the epidemiology, clinical course, and related laboratory indices of EONBM can help inform more precise investigations for diagnosis of EONBM.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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DATA AVALABILITY STATEMENT

All of the data generated and analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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