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Original Article

Paediatrics Section

Clinico-bacteriological Study of Sepsis in VLBW Neonates in Tertiary Care NICU in Central India: A Descriptive Observational Study

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ABSTRACT

Introduction: Low Birth Weight (LBW) is one of the most serious challenges in maternal and child health in developing countries. Neonatal sepsis is responsible for about 30-50% of the total neonatal deaths in developing countries. Given the high prevalence of Very Low Birth Weight (VLBW) neonates and the increasing incidence of sepsis in this population, there is a need to study the clinical and bacteriological profile of sepsis.

Aim: To study the clinico-bacteriological profile of neonatal sepsis in VLBW neonates (Birth weight <1500 gm) in a tertiary care NICU in central India.

Materials and Methods: The descriptive observational study was conducted among VLBW neonates with clinically suspected sepsis admitted to the NICU of Indira Gandhi Government Medical College and Mayo Hospital in Nagpur, Maharashtra, India, from November 2019 to October 2021. All 160 VLBW neonates with clinically suspected sepsis and positive sepsis screen consisting of four parameters {Absolute Neutrophil Count (ANC), Total Leucocyte Count (TLC), Immature/Total Neutrophil Ratio (I/T Ratio), C-Reactive Protein (CRP)+} and whose mothers provided informed consent were included in the study within 24 hours of admission. Details such as demographic data, maternal risk factors and type of delivery, clinical signs of sepsis presentation, any Central Nervous System (CNS) signs, day of onset of sepsis, sepsis screen parameters (CRP, TLC, ANC, I/T Ratio), blood culture, and Cerebro-spinal Fluid (CSF) examination findings were studied. Continuous variables were evaluated using the student t-test, and categorical variables were evaluated using the chi-square test.

Results: There were 96 (60%) males and 64 (40%) females. In the sepsis screen parameters, the majority of the neonates were CRP positive 148 (92.3%) followed by TLC positive among 119 (74.38%) neonates. Lethargy was the most common clinical presentation among 147 (91.88%) neonates followed by difficulty in feeding among 121 (75.63%) neonates. Blood culture was positive among 61 (38.13%) neonates, and *Escherichia coli* was the most common organism isolated among 21 (34.43%) neonates.

Conclusion: The most common clinical presentation of neonatal sepsis was lethargy followed by difficulty in feeding. In the present study, the most common organism isolated was *E.coli*.

Keywords: Blood culture, Lethargy, Sepsis screen, Very low birth weight

INTRODUCTION

Low Birth Weight (LBW) is one of the most serious challenges in Maternal and Child Health in developing countries. The lower the birth weight, the lower the survival chances [1]. The World Health Organisation (WHO) defines LBW as birth weight less than 2500 gm [2] and Very Low Birth Weight (VLBW) as birth weight less than 1500 gm. The WHO estimates that globally about 25 million LBW babies are born each year, constituting 17 percent of all live births, with nearly 95 percent of them in developing countries [2]. In India, VLBW babies constitute 4% to 7% of live births [3]. The World Health Organisation estimates that of the four million neonatal deaths worldwide each year, over 35% are due to infection in the neonatal period; this translates to approximately two deaths per minute [2].

Neonatal mortality from sepsis has remained around 20% for nearly three decades [4]. Neonatal sepsis is responsible for about 30-50% of the total neonatal deaths in developing countries [5]. In India, according to the national neonatal peri-natal database, the incidence of neonatal sepsis was 30 per thousand live births, and it was found to be one of the commonest causes of neonatal mortality, contributing to 19% of all neonatal deaths [6]. Studies have already proven that there is an increased risk of sepsis in VLBW neonates. It is well established that the incidence of sepsis is inversely proportional to birth weight and Gestational Age (GA) [7]. There is a decreased risk of Early Onset Neonatal Sepsis (EONS) in infants who are Small for Gestational Age (SGA) but at higher risk for Late Onset Neonatal Sepsis (LONS) than their appropriately grown GA-matched peers [8]. EONS is typically caused by colonisers of the maternal genito-urinary tract, leading to contamination of the amniotic fluid, placenta, cervix, or vaginal canal [9]. The principal causes of early neonatal sepsis are bacteria such as *Streptococcus* such as *S. pneumoniae*, group D *Streptococci*, α-haemolytic *Streptococci*, *L. monocytogenes*, *E. faecalis, E. faecium, Staphylococci,* and *H. influenzae* type B [9]. Late-onset sepsis is predominantly caused by *Staphylococci* species and *E. coli* and is frequently related to LBW of infants.

The use of intravascular catheters, endotracheal intubation, assisted ventilation, surgery, contact with the hand of colonised personnel, and contact with contaminated equipment are the main risk factors for the LONS [10]. The problem of neonatal sepsis is also complicated by its changing bacteriological profile. Several studies have documented that the sepsis fatality rate is highest for gram-negative and fungal infections [11-13]. Thus, a rational protocol for sepsis management must be based on continuously updated knowledge of the prevalent organisms causing neonatal sepsis. In view of the high prevalence (18%) of VLBW neonates in our institute and the increasing incidence

of sepsis in them, the present study was undertaken to determine the clinical and bacteriological profile of sepsis in VLBW neonates admitted in the NICU in a tertiary care hospital in Central India.

MATERIALS AND METHODS

The present descriptive observational study was conducted in the NICU of Indira Gandhi Government Medical College and Mayo Hospital, Nagpur, Maharashtra, India, from November 2019 to October 2021 after obtaining approval from the Institutional Ethics Committee (approval no. 589-90/2019). Written informed consent was obtained from all the parents.

Inclusion criteria: All VLBW (<1500 gm) neonates with clinically suspected sepsis and a positive sepsis screen admitted to the NICU of the study hospital were included in the study.

Exclusion criteria: All VLBW neonates with clinically suspected sepsis but a negative sepsis screen, and neonates whose parents did not give consent, were excluded from the study.

A sepsis screen was considered positive if more than or equal to two points for the parameters were present as shown in [Table/Fig-1] [14]. If the onset of symptoms is within 72 hours of life, they are classified as EONS, and if the onset of symptoms is after 72 hours of life, they are classified as LONS [14,15].

Parameters	Points
Absolute Neutrophil Count (ANC) <1750/mm^3	1 point
Total white blood cell count (TLC) <7500/mm^3 or >40,000/mm^3	1 point
Immature/Total Neutrophil ratio (I/T) more than or equal to 0.20	1 point
Immature/total neutrophil ratio more than or equal to 0.40	2 points
C-Reactive protein (CRP)+(more than or equal to 1 mg/dL)	1 point
CRP+(more than or equal to 5 mg/dL)	2 points

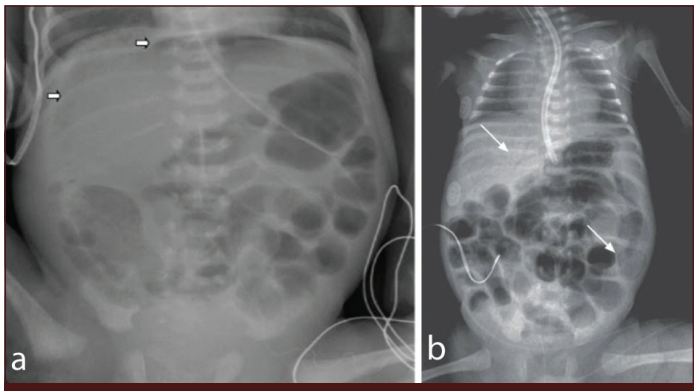
[Table/Fig-1]: Sepsis screen parameters.

A total of 188 neonates with clinically suspected sepsis were admitted to the tertiary care NICU in central India during the study period. Among these 188 neonates, only 160 neonates whose sepsis screen was positive were included in the study.

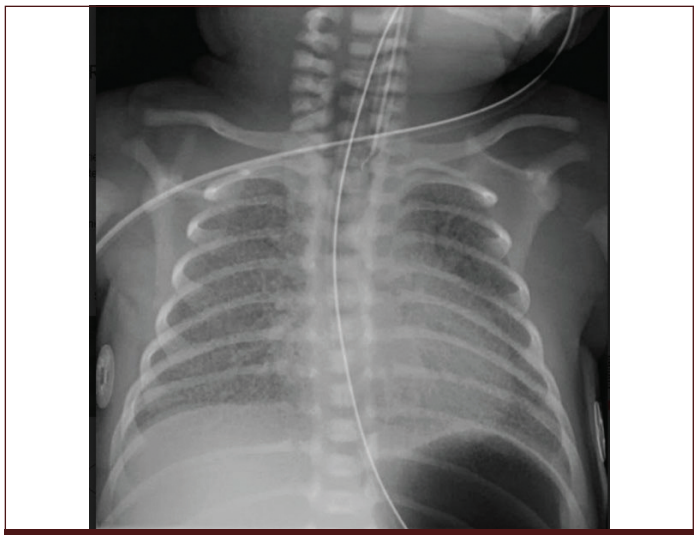
Procedure

After obtaining written informed consent from the parents, cases were enrolled in the study within 24 hours of admission. Basic information of each neonate such as name, age, sex, date of admission, registration number, address, and contact details were obtained. Mothers of enrolled cases were interviewed about antenatal history, obstetric history, and any history of high-risk pregnancy. Detailed natal history of enrolled cases was collected, including mode of delivery, birth weight, whether the baby cried immediately after birth, and details of any required resuscitation. The GA was assessed using the New Ballard Score [12]. GA <37 weeks indicated preterm neonates, and ≥37 weeks indicated full-term neonates [12].

Presenting clinical features of the enrolled babies such as decreased acceptance of feed, lethargy, fever or hypothermia, bleeding manifestations, convulsions, fast breathing, abdominal distension, vomiting, etc., were noted. Anthropometric classification was used to categorise neonates into SGA/AGA/IUGR. A neonate with a birth weight for GA less than the 10th percentile for GA was considered SGA/IUGR [12]. A thorough physical examination of each neonate, including general examination, systemic examination, and head-to-toe examination, was conducted. Laboratory investigations such as CBC, CRP, and CSF culture (in suspected meningitis cases) were performed. Blood culture was conducted using Trypticase soy broth incubated overnight, followed by repeated sub-cultures for five days to study the bacteriological profile. Radiological investigations such as X-ray were performed in suspected cases of necrotizing enterocolitis and respiratory distress/apnea, as shown in [Table/Fig-2a,b,3], respectively. All the data were collected in a pre-determined case proforma.



[Table/Fig-2]: Necrotising enterocolitis. a) X-ray of a preterm neonate, in the supine position with b): In the above image, upper arrow points to portal air, vertical rays, indicating generalised distension of intestinal loops and the lower arrow points to a ring of intramural gas, which and pneumatosis (arrows) in segments of the large and small bowel is indicative of pneumatosis intestinalis.



[Table/Fig-3]: Respiratory distress. X-ray of a preterm neonate showing widespread granular opacification through both the lungs with extensive air space consolidation.

STATISTICAL ANALYSIS

The collected data was then entered into Microsoft excel and analysed using the Statistical Package for the Social Sciences (SPSS) version 10.0. Categorical variables were presented as frequency and percentage.

RESULTS

This study was conducted among 160 VLBW neonates with clinically suspected sepsis who tested positive on the sepsis screen and were admitted to the tertiary care NICU in central India. In the present study, the majority, 96 (60%) of the neonates, were males, and 64 (40%) were females. About 97 (60.63%) neonates were delivered via normal vaginal delivery, while 63 (39.37%) were delivered through LSCS. Preterm birth was present in 141 (88.12%) neonates, and 116 (72.5%) neonates had a birth weight of 1201-1500 gm. LONS was present in 84 (52.5%) neonates, while EONS was present in 76 (47.5%) neonates [Table/Fig-4].

Characteristics	Frequency (N=160)	Percentage
Gender		
Male	96	60.0
Female	64	40.0
Residence		
Rural	99	61.87
Urban	61	38.12
Type of delivery		
Normal vaginal delivery	97	60.63
LSCS	63	39.37
Cried immediately after birth	152	95.0
Didn't cry immediately after birth	08	5.0
Gestational Age (GA)		
Pre-term (<37 weeks)	141	88.12
Full-term (≥37 weeks)	19	11.87
Birthweight (gm)		
1000-1200	44	27.5
1201-1500	116	72.5
Appropriateness of Gestational Age (GA)		
SGA	78	48.75
AGA	82	51.25
Age of onset of sepsis		
EOS	76	47.5
LOS	84	52.5

[Table/Fig-4]: Characteristics of the VLBW neonates with clinically suspected sepsis with sepsis screen positive.
EONS: Early onset neonatal sepsis; LONS: Late onset neonatal sepsis; LSCS: Lower segment cesarean section

Among the maternal risk factors, maternal anaemia was the most common risk factor, present in 99 (62%) cases, followed by PIH in 26 (16.25%) cases. Among the neonatal risk factors, prematurity was present in 107 (66.88%) cases, and birth asphyxia was present in 08 (5%) cases as shown in [Table/Fig-5].

Risk factors	Number (n)	Percentage (%)
Maternal risk factors	**(N=160)**	**Percentage**
Maternal anaemia	99	62
PIH*	26	16.25
Abruptio placenta	7	4.38
Cardiovascular disease in mother	3	1.88
Febrile illness in mother during pregnancy	18	11.25
Foul smelling liquor	25	15.63
Meconium-stained liquor	21	13.13
Prolong rupture of membranes (>18 hrs)	21	13.13
More than 3 P/V* examinations	25	15.63
Prolonged and difficult delivery with instrumentation	10	6.25
Neonatal risk factors		
Birth asphyxia	8	5
Prematurity	107	66.88

[Table/Fig-5]: Maternal and neonatal risk factors among study subjects.
*PIH: Pregnancy induced hypertension; P/V: Per vaginum examination

In the present study, CRP was positive in the majority, 148 (92.3%) of the neonates, followed by TLC being positive in 119 (74.38%) neonates [Table/Fig-6].

Parameters	Points	Positive (n)	Percentage
Absolute Neutrophil Count (ANC) <1750/mm^3	1 point	78	48.75
Total white blood cell Count (TLC) <7500/mm^3 or >40,000/mm^3	1 point	119	74,38
Immature/Total neutrophil ratio (I/T) more than or equal to 0.20	1 point	31	45.63
Immature/Total neutrophil ratio more than or equal to 0.40	2 points	42	26.25
C-Reactive Protein (CRP)+(more than or equal to 1 mg/dL)	1 point	62	38.75
CRP+(more than or equal to 5 mg/dL)	2 points	86	53.75

[Table/Fig-6]: Sepsis screen parameters among neonates.

Most of the neonates, 147 (91.88%), presented with a complaint of lethargy, followed by feeding intolerance among 121 (75.63%) neonates. The cardiovascular system and coagulation system were also involved, showing clinical manifestations like mottling and gastrointestinal bleeding in 54 (33.75%) and 50 (31.25%) neonates, respectively [Table/Fig-7].

Clinical presentation	Frequency (N=160)	%
CVS		
Delayed CRT	42	26.25
Mottling	54	33.75
Hypothermia	32	20
Pallor	36	22.5
Poor pulsations (shock)	22	13.75
GI		
Feed intolerance/vomiting	86	53.75
Feeding difficulty	121	75.63
Abdominal distension	46	28.75
Passage of blood/mucus per rectum	18	11.25
Decreased bowel sounds	26	16.25
Diarrhoea	11	6.9
RS		
Tachypnoea with respiratory distress	68	42.5
Apnea	24	15
cyanosis	8	5
DIC		
Ecchymoses	22	13.75
Pulmonary haemorrhage	8	5
Gastric bleed	50	31.25
CNS		
Convulsion	19	11.88
Staring look	12	7.5
Bulging AF	11	6.88
High pitched cry/excessive cry	15	9.38
Lethargy	147	91.88
Others		
Periumbilical redness or discharge	12	7.5
Multiple pustules	8	5
Oral thrush	7	4.38
Failure to gain weight	6	3.75
Sclerema	15	9.38

Eye discharge	14	8.75
Joint involvement: redness/swelling of joints with restriction of movements	10	6.25

[Table/Fig-7]: Clinical presentation of neonatal sepsis.
*CVS: Cardiovascular system; CRT: Capillary refilling time; GI: Gastrointestinal system; RS: Respiratory system; DIC: Disseminated intravascular coagulation; CNS: Central nervous system; AF: Anterior fontanell

Blood culture was positive in 61 (38.12%) neonates. *E.coli* was the most common organism, present in 21 (34.43%) neonates, followed by *Klebsiella* in 13 (21.31%) neonates. In the present study, *Acinetobacter* was the least common organism. Non-fermenters including *Burkholderia* and *Legionella* were cultured in 3 (4.91%) and 5 (8.20%) cases, respectively [Table/Fig-8].

Isolated organisms	Frequency (N=61)	%
E. coli	21	34.43
Klebsiella	13	21.31
Non-fermenters *burkholderia*	3	4.91
Non fermenter *legionella*	5	8.20
Candida	07	11.4
Staphylococcus aureus	06	9.84
Pseudomonas	05	8.19
Acinetobacter	01	1.64

[Table/Fig-8]: Bacteriological profile of VLBW neonates with clinically suspected sepsis with sepsis screen positive.

DISCUSSION

The present study was conducted among 160 VLBW neonates with a positive sepsis screen who were admitted to a NICU in a tertiary care hospital in Central India to study the clinico-bacteriological profile of neonatal sepsis. Among them, 60% were males and 40% were females, which is comparable to the study by Tallur SS et al., and Kuruvilla KA et al., which also showed a higher incidence of sepsis in males (63.63%) and (68.3%) respectively. Conversely, a higher incidence of sepsis in females (53.9%) was noted by Hornik CP [14,16,17]. The majority (87.13%) of the babies in the present study group belonged to the preterm group. Similar to this study findings, a higher incidence of sepsis in premature babies has also been noted by Jatsho J et al., and Ahmed NU et al., [18,19].

In this study, 60.63% of the babies were born through vaginal delivery, and 39.37% were delivered by LSCS. This was also observed in a study conducted by Kuruvilla KA et al., where 73.3% were born through vaginal delivery and 26.7% were born through LSCS [16]. Prematurity/LBW was the most common risk factor, present in 66.88% of all cases, which is comparable to that of Geme JW et al., (78%) [20]. Tallur SS et al., and Roy I et al., also reported a high incidence of prematurity/LBW in their series [14,21]. EOS was present among 47.5% of neonates, and LOS was present among 52.5% of neonates in this study. In a study by Varsha et al., the incidence of EOS was 74.6%, and LOS was 25.3% [22].

Lethargy and Respiratory distress were the two most common presenting features in our study and were present in >90% of cases. Ahmed NU et al., also reported a high incidence of respiratory distress (46.7%) in their study [19]. Conversely, in a study done by Hornik CP [17], feeding difficulty (92.3%) was the most common presentation. In the present study, Blood culture was positive in only 38.13% of cases. In studies by Roy I et al., and Tallur SS et al., blood culture positivity was 47.5% and 64.8%, respectively [14,21].

In this study group of 61 cases of neonatal sepsis, *E.coli* (13.13%) was the most common organism isolated in both the EONS and LONS groups. *E.coli* was reported as the most common pathogen (23.5%) of neonates by Kuruvilla KA et al., in their study [16]. While Tallur SS et al., found it to be the least common cause of neonatal sepsis (2.93%) in their study [14]. We did not find any cases of Group B Streptococcus (GBS) sepsis in our study, which was also the case in the study by Tallur SS et al., [14]. This is in sharp contrast to the trend in western developed countries where it is a major agent of early-onset neonatal septicaemia [18].

Limitation(s)

Since the study was a single-centered observational study, the findings cannot be generalised to other study settings.

CONCLUSION(S)

The most common clinical presentation was lethargy, followed by feeding difficulty, and *E.coli* was the most common organism isolated among neonates with sepsis. Considering the common risk factors for sepsis such as prematurity, maternal anemia, and PIH, and common clinical features like lethargy, tachypnea, refusal to feed, and delayed CRT were present in the overwhelming majority of cases, it is suggested that a scoring system which takes into consideration risk factors, clinical features, and sepsis screen should be formulated. This would be a more reliable tool for the early presumptive diagnosis of sepsis.

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