

## Original Research Article

# An observational study on clinical and bacteriological profile of new-borns with early onset sepsis

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**Received:** 25 August 2020

**Accepted:** 01 September 2020

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### ABSTRACT

**Background:** Neonatal sepsis related mortality is preventable with timely recognition, rational antimicrobial therapy and aggressive supportive care. The objective of this study was to study the maternal and neonatal risk factors in new-borns with early onset sepsis and to ascertain commonest pathogen responsible.

**Methods:** This study was done in the neonatal intensive care unit tertiary care hospital, Thrissur. Data collected after clinical examination and from the records of new-borns diagnosed with early onset sepsis were analyzed. All neonates suspected to have sepsis had a septic screen to corroborate the diagnosis. Blood culture was performed in all cases of suspected sepsis prior to starting antibiotics. The risk factors for sepsis, both maternal and neonatal were analysed. Their clinical features and bacteriological profile were studied. Data analysis was done using their mean±standard deviation (SD), percentage analysis, chi-square test or Fischer's test.

**Results:** Fifty newborns with diagnosed early onset sepsis (EOS) were studied. Results suggest that maternal screening is prudent, interventions like vaginal examination were causative of sepsis than meconium stained liquor or prolonged rupture of membranes. A coincidental finding suggests that sepsis is more common in males and term babies. Blood culture showed predominant pathogen to be *Klebsiella*.

**Conclusions:** Among the maternal factors, increased frequency of vaginal examination was most prevalent in the study group. Prematurity and asphyxia were not strong pre-runners for sepsis. EOS cases presenting with respiratory distress were 50%. Fever and tachycardia were the next common clinical features. The cases yielded blood culture positive were 20% and *Klebsiella pneumonia* (40%) was the commonest organism isolated.

**Keywords:** Sepsis, Early onset sepsis, New-born, Risk factor

### INTRODUCTION

Neonatal sepsis is a clinical syndrome of bacteremia (probable or proven) characterized by systemic manifestations of infection in the first month of life. Neonatal sepsis encompasses systemic infections of the newborn including septicemia, meningitis, pneumonia, arthritis, osteomyelitis and urinary tract infection of the newborn. Treatment in time is effective against the causative pathogen and safe for the newborn. Neonatal deaths claim about 4 million lives each year globally.<sup>1</sup> About 0.75 million neonates die every year in India, the

highest for any country in the world. The neonatal mortality rate (NMR) declined from 52 per 1000 live births in 1990 to 28 per 1000 live births in 2013, but the rate of decline has been slow and lags behind that of infant and under-five child mortality rates.<sup>2</sup> Sepsis is at present one of the leading causes of morbidity and mortality in the neonatal population.<sup>3</sup>

Neonatal sepsis can be categorized into two types, depending up on the onset of symptoms.<sup>4</sup> Early onset sepsis (EOS) presents within the first 72 hours of life and in severe cases, the neonate may be symptomatic at birth.

Infants with EOS usually present with respiratory distress and pneumonia. It is usually caused by organisms prevalent in the maternal genital tract. Late onset sepsis (LOS) usually presents after 72 hours of age. The source of infection in LOS is either nosocomial (hospital-acquired) or community-acquired and neonates usually present with septicemia, pneumonia or meningitis.<sup>5</sup> The pattern of organisms causing sepsis also differs from place to place and can change in the same place over a period of time. The rational use of antimicrobials is of paramount importance in this population and structured antimicrobial stewardship interventions should be in place.<sup>6</sup>

The present study was carried out to determine the current incidence of early onset sepsis, identify maternal risk factors and any associated neonatal factors and also the clinico-bacteriological profile of EOS in the neonatal unit of a tertiary care center. As studies pertaining to this topic done in Kerala are limited, this study has its relevance and is a humble step hoping to shed more light into the subject. The aim was to determine the clinical and bacteriological profile of newborns diagnosed with early onset sepsis who are admitted to the neonatal intensive care (NICU). The objectives were to study the prevalence of maternal and neonatal risk factors in newborns diagnosed as early onset sepsis and also the bacteriological profile of early onset sepsis.

**METHODS**

The study was a hospital-based observation study conducted in the NICU of tertiary care hospital in Thrissur, Kerala. The study population included newborns who are diagnosed with early onset sepsis (EOS) when sepsis screen was positive with or without positive blood culture or when blood culture was positive alone. The data collection period was from July 2015 to December 2015 (6 months). The inclusion criteria included all newborns diagnosed with EOS newborns with a positive sepsis screen and or positive blood culture. Newborns referred to here on first day of life and meeting the criteria were also included. The exclusion criteria included newborns born with major congenital anomalies and those referred to our neonatal unit after twenty-four hours of life. All neonates suspected to have sepsis had septic screening to corroborate the diagnosis (Table 1). The various components of the septic screen included total leukocyte count (TLC), absolute neutrophil count (ANC), immature to total (IT) neutrophil ratio, micro-erythrocyte sedimentation rate and C reactive protein (CRP). If two (or more) parameters were abnormal, it was considered as a positive screen. If the screen is negative but clinical suspicion persisted, it was repeated within 12 hours. If the screen was still negative, sepsis was excluded with reasonable certainty.

Blood culture is the gold standard for diagnosis of septicemia and was performed in all cases of suspected sepsis prior to starting antibiotics. A positive blood culture with sensitivity of the isolated organism is the best guide

to antimicrobial therapy. In EOS, lumbar puncture is indicated in the presence of a positive blood culture or if the clinical picture is consistent with septicemia. EOS was diagnosed when sepsis screen was positive with or without positive blood culture or when blood culture was positive alone.

**Statistical methods**

The study was conducted in NICU of Jubilee Mission Medical College situated in Thrissur city. This hospital receives referred cases from all over Thrissur and Palakkad district. The target populations were newborns admitted in our NICU with early onset sepsis. Data was acquired after examining and from the reports of newborns detected with early onset sepsis meeting the inclusion criteria, who are admitted during the data collecting period. Data collected was analyzed using their mean±standard deviation (SD), percentage analysis, chi-square test or fisher’s test.

**Table 1: A practical sepsis screen.**

Components	Abnormal value
<b>Total leukocyte count</b>	<5000 /mm <sup>3</sup>
<b>Absolute neutrophil count</b>	Low counts as per Manroe chart for term and Mouzinho’s chart for VLBW infants
<b>Immature / total neutrophil</b>	>0.2
<b>Micro-ESR</b>	>15 mm in 1 <sup>st</sup> hour
<b>C reactive protein (CRP)</b>	>1 mg/dl

VLBW: very low birth weight.

**RESULTS**

Fifty cases of diagnosed EOS were studied. Babies of mothers in the age group 20-25 years formed the majority out of the EOS cases and that too primi mothers. Consanguinity was present only in a few cases. ABO incompatibility (14%) was found to be more than Rhesus (Rh) incompatibility (2%) in these cases. Only few mothers had Gestational diabetes mellitus (GDM) (8%) and Pregnancy-induced hypertension (PIH) (12%). Among these cases, 30% of mothers had febrile illness. Urinary Tract Infection (UTI) and maternal pyrexia accounted for 40% of cases each and lower respiratory infection the rest. The cases that had received antibiotic prophylaxis, mostly ampicillin was 68%. Duration of rupture of membranes in majority 44% of cases is less than 6 hours. More than 24 hours lasted only in 2 cases. Fifty eight percent of cases had history of more than 3 per vaginal examination during their first stage of labor. (Table 2) In none of those cases duration of labor was more than 24 hours. 14% of cases showed meconium stained liquor. No cases with foul smelling liquor were there. Only 6% cases showed abnormal Doppler parameters in antenatal scans. Fifty-two percent of babies were born by caesarian section, 40% by vaginal route and 8% by vacuum. Among babies born by LSCS, most common

indication was non progression of labor and next common were previous caesarian section and fetal distress.

Out of total 50 cases 76% were inborn and 28% were preterm. Surprisingly 70% were males. 18% of babies had perinatal depression (1-minute, appearance, pulse, grimace, activity, and respiration (APGAR) <7) and severe perinatal depression (1 minute, APGAR <4) only in 2%. Out of total 50 cases, 18% of babies needed prolonged inpatient treatment, while 68% required less than a week. Non-specific features also differed variably in cases. Out of total 50 cases, 48% babies presented with fever, while 28% had lethargy and 22% had weak cry. Out of total 50 cases, 20% babies had refusal to suck, and 8% hypotonia but none had depressed neonatal reflexes. Most of the babies had tachycardia (44%) rather than bradycardia (14%).

Twenty two percent were low birth weight but only 10% were Small for gestational age (SGA). Out of the study population, 50% of babies had respiratory distress, where 8% of them only required oxygen support by oxygen through hood. Twenty babies required continuous positive airway pressure (CPAP) support while 7 cases needed mechanical ventilation. One case presented with pulmonary hemorrhage. 6% of babies had hypoglycemia while 32% had metabolic acidosis.

Seizures are the most frequently seen neurological manifestation in EOS, in about 50% cases. Then high-pitched cry and irritability are the next common manifestations.

Two cases of necrotizing enterocolitis (NEC) were present. No manifestations of renal, dermatological, hematological or hepatic were present. Out of the study population, 70% of cases had hemoglobin levels between 15 and 20. Twenty cases of EOS cases had elevated WBC counts (>15,000) and only one case below 5000. Seventy two percent of EOS cases had IT ratio more than 0.2, which is supportive of sepsis (Table 3). Low absolute neutrophil count (ANC) was found in 32% of EOS cases. Majority of cases normal platelet counts in the initial sepsis screen.

Almost all cases showed elevated C-reactive protein (CRP) levels. Out of the study subjects, 84% of the cases showed levels between 1 and 5 mg/dl. Twenty percent of EOS cases showed positive blood culture (table 4). Most common pathogen isolated is *Klebsiella pneumonia* (40%) (Table 5). Cerebrospinal fluid (CSF) study was done in 30 newborns with EOS and only one came positive. None of the cases had any growth in CSF culture. Maternal screening found to be positive 62% of EOS cases. In 5 cases cervical smear culture showed growth. In 3 cases neurosonogram was found to be abnormal. Abnormal echo findings in two cases. In 4 cases electroencephalogram (EEG) was found to be abnormal, out of 7 cases.

**Table 2: Distribution of study population in relation to history of more than 3 per vaginal examination.**

History of more than 3 per vaginal examination in mother	Number of new-born	%
No	21	42.0
Yes	29	58.0
<b>Total</b>	<b>50</b>	<b>100.0</b>

**Table 3: Distribution of study population in relation to their immature to total neutrophil ratio (IT ratio) values.**

IT ratio > 0.2	Number of new born	%
No	14	28.0
Yes	36	72.0
<b>Total</b>	<b>50</b>	<b>100.0</b>

**Table 4: Distribution of study population in relation to their blood culture.**

Blood culture	Number of new-born	%
No growth	40	80.0
Growth	10	20.0
<b>Total</b>	<b>50</b>	<b>100.0</b>

**Table 5: Distribution of study population in relation to the organism isolated in their blood culture.**

Pathogen	Number of new-borns
<i>Klebsiella</i>	4
<i>Enterobacter cloacae</i>	2
<i>E. coli</i>	1
<i>Enterococcus faecalis</i>	1
<i>Methicillin-resistant coagulase-negative Staphylococci (MRCONS)</i>	1
<i>Streptococcus agalactiae</i>	1

**DISCUSSION**

Neonatal sepsis is one of the major causes of morbidity and mortality in the newborn. EOS, with an onset during the first 72 hours of life is caused by organisms prevalent in the maternal genital tract or in the labor room and maternity operation theatre. It can occur due to ascending infection following rupture of membranes or during the passage of the baby through infected birth canal.<sup>7</sup>

EOS was more seen in babies born to primi mothers especially in the 20-25 years of age groups. In the National Institute of Child Health and Human Development Neonatal Research Network, 14% to 28% of women delivering preterm infants at 22 through 28 weeks' gestation exhibited signs compatible with chorioamnionitis.<sup>8</sup> The major risk factors for chorioamnionitis

include low parity, spontaneous labour, longer length of labour and membrane rupture, multiple digital vaginal examinations (especially with ruptured membranes), meconium-stained amniotic fluid, internal foetal or uterine monitoring, and presence of genital tract microorganisms (example: *Mycoplasma hominis*).<sup>9</sup> 30% of our cases had history of febrile illness in last two weeks of pregnancy. In women with preterm labor and intact membranes, the rate of microbial invasion of the amniotic cavity is 39%, and if there is Preterm premature rupture of membranes (PPROM), the rate may be as high as 75%.<sup>10</sup>

Prematurity and rupture of membranes of more than 18 hours before delivery were significant risk factors reported by Oddie et al.<sup>11</sup> Maternal risk factors for sepsis were present in our cases, but only history of frequent vaginal examination was correlating with EOS cases. Duration of rupture of membranes was short, antibiotic prophylaxis given in most cases and no significant prolongation of labour in our cases. So, we could conclude that these factors were not contributing. Moreover, we did not observe any increased risk of EOS in babies born through meconium stained amniotic fluid. Soman et al observed an association of asphyxia with neonatal sepsis which is different from our scenario.<sup>12</sup> Present study showed only 18% of cases with history of perinatal depression.

UTI and maternal pyrexia were leading causes. Bhutta and Yusuf reported a significant association of EOS with maternal UTI and pyrexia in their case control study of risk factors.<sup>13</sup> Sepsis is more likely to develop in male infants was found in several population-based studies, particularly with gram negative organisms for reasons that are not clear.<sup>14</sup> Surprisingly 70% cases in our study are male infants.

Preterm birth/low birth weight is the risk factor most closely associated with early-onset sepsis.<sup>15</sup> The increased risk of early-onset sepsis in preterm infants is also related to complications of labor and delivery and immaturity of innate and adaptive immunity.<sup>16</sup>

A prospective study concerning neonatal sepsis was carried out in Christian Medical College, Ludhiana over a period of 15 months from October 2000 to December 2001.<sup>17</sup> Among 1743 live births during the study period, a total of 69 episodes of sepsis occurred in 65 neonates, the incidence being 37.2/1000 live births. EOS occurred in 36 neonates, with an incidence of 20.7 per 1000 live births constituting 55.4% of an overall neonatal sepsis. Among a total of 136 neonates, with an underlying potential maternal risk factor for sepsis 20.6% developed EOS, while in those without these risk factors EOS occurred in only 8 (0.5%) ( $p=0.0000$ ). Among the various high risk group of infants such as very low birth weight babies, preterms and SGA babies, the incidence of sepsis was negligible if maternal risk factors were absent (0.46% to 4.3%) but in those in whom risk factors were present this varied from 30.5% to 37.5%. One fifth of mothers with PROM and 30% with foul smelling liquor had infants with

EOS, the odds ratio being 25.5 and 22.08 respectively ( $p<0.001$ ) compared to those without these risk factors. Preterm infants constituted 39.7% of EOS in the report by Tallur et al which is comparable with our (28%) study population.<sup>18</sup> In our study 22 percent were low birth weight and only 10% were SGA babies.

Results suggest maternal screening is necessary, as it correlated with more cases, as mother was symptomatic only in one third of the cases. Interventions like increased frequency of vaginal examination were more contributive to sepsis than meconium stained liquor or prolonged rupture of membranes. No relation has been found between duration of labour and EOS. Although given in almost all cases, Antibiotic prophylaxis was found to be not that effective. Surprisingly sepsis is more commonly found in term babies and boys, with no statistically significant difference. Although Prematurity and asphyxia were strong pre-runners for sepsis, our study could not find any correlation.

All neonates suspected to have sepsis should have a septic screen to corroborate the diagnosis.<sup>19,20</sup> The ANC varies considerably in the immediate neonatal period and the normal reference ranges are available from Manroe's charts.<sup>21</sup> The lower limit for normal ANC begins at 1800/cumm at birth, rises to 7200/cumm at 12 hours of age and then declines and persists at 1800/cumm after 72 hours of age. For very low birth weight infants, the reference ranges are available from Mouzinho's charts.<sup>22</sup> The IT ratio is 0.16 at birth and declines to a peak value of 0.12 after 72 hours of age. Presence of two abnormal parameters in a screen is associated with a sensitivity of 93-100%, specificity of 83%, positive and negative predictive values of 27% and 100% respectively in detecting sepsis. Hence, if two (or more) parameters are abnormal, it should be considered as a positive screen. If the screen is negative but clinical suspicion persists, it should be repeated within 12 hours. If the screen is still negative, sepsis can be excluded with reasonable certainty. Acute phase reactant like CRP was positive in all cases. Next factor being IT ratio was high ( $>0.2$ ) in 72% cases. These two factors were more suggestive of sepsis than ANC, platelet count and micro ESR. 20% of cases yielded blood culture positive.

Many of the pathogens recovered from amniotic fluid in women with preterm labor or PPRM (example: *Ureaplasma* species or *Mycoplasma* species) are strongly associated with placental inflammation. Both *Ureaplasma urealyticum* and *Mycoplasma hominis* can be recovered from the bloodstream of infants whose birth weight is less than 1500 g, and are associated with neonatal inflammatory response syndrome.<sup>23</sup> Report from National Neonatal Perinatal Database (NNPD) 2000 reveals *Klebsiella pneumoniae* and *S. aureus* to be the most frequent causative organisms in India.<sup>24</sup>

In our study sepsis screen, almost all cases showed CRP elevation. Though total WBC counts were not suggestive,

low ANC (32%) and high IT ratio (72%) were predominantly seen. Maternal screening was positive in 62% of cases, though only 30% were symptomatic in the peripartum period. Maternal cervical culture though yielded results in four cases, they were not correlating with septicemic pathogens of new-borns. The culture positivity rate in the current study was 20%. Most common pathogen isolated is *Klebsiella pneumonia* (40%). Blood culture showed predominant pathogen to be *Klebsiella*, which agrees with general consensus. *Enterobacter cloacae* is the next common.

The usual presentation of EOS is with respiratory distress and pneumonia within 72 hours of age according to the NNPD 2000 report. Similarly, 50% of our cases presented with respiratory distress, out of which 20 cases required CPAP support and a few mechanical ventilation too. Of nonspecific clinical features, fever (48%) and tachycardia (44%) were predominant. Seizure was the most common among central nervous system (CNS) symptoms, next being high pitched cry and irritability. But only one case of meningitis was present. In a retrospective study by Cordero and Ayers, the average duration of treatment in 695 infants (<1000 g) with negative blood cultures was 5±3 days.<sup>25</sup> Cotten et al have suggested an association with prolonged administration of antimicrobial agents (>5 days) in infants with suspected early-onset sepsis (and negative blood cultures) with death and necrotizing enterocolitis.<sup>26</sup>

Kuruvilla et al carried out a study in Christian Medical College, Vellore with an aim to study the pattern of sepsis in their neonatal unit and assess the influence of maternal factors on early onset sepsis (EOS).<sup>27</sup> It was a prospective survey conducted from 1995-1996. Thirty (24%) had EOS (≤48 hours) and 95 (76%) had LOS (≥48 hours). Sepsis occurred in 9.8 per 1000 livebirths and 4.4% of all nursery admissions. *E. coli* and *E. fecalis* were the predominant organisms causing EOS, while *Klebsiella* and *E. fecalis* were the predominant organisms in LOS. This was in consensus with our study.

Low birth weight, small for gestation age and preterm babies are very vulnerable to sepsis because of compromised immunity in the form of deficit immunoglobulin, complement and phagocytic capacity and also due to iatrogenic factors like excessive handling results in breaks in skin and mucosa barriers. It is unique that it is associated with varied organisms and varied sensitivity pattern in different times of the year. Sepsis related mortality is largely preventable with prevention of sepsis itself, timely recognition, rational antimicrobial therapy and aggressive supportive care. Hence, it is essential that we know the organism profile and sensitivity pattern for the appropriate management of the neonatal sepsis.

## CONCLUSION

Neonatal factors such as prematurity, asphyxia or very low birth weight were found to have not significantly

contributing to causation of EOS. But maternal risk factors were predominant in their history. So, we should be more watchful for maternal risk factors and follow up those babies in order to intervene at the earliest. In addition, knowledge of the likely causative organisms and their sensitivity patterns would also contribute towards a more rational and appropriate use of antibiotics, thus minimizing the emergence of multidrug resistant bacteria in neonatal unit. A large multi centric study for a longer duration would ideally bring out role of maternal and neonatal factors in the etiopathogenesis of EOS and bacteriological profile of the same with much assuring statistical significance.

## ACKNOWLEDGEMENTS

Authors would like to thank Dr. Johny Vincent, Professor of Paediatrics, for his support during the course of this research. We express our sincere gratitude to faculty members of Jubilee Center for Medical Research for editing this article. We express our sincere gratitude to Dr. Sankara Sarma P, professor, AMCHSS, SCTIMST, Trivandrum and Mr. Tom Thomas, Biostatistician, Jubilee Mission Medical college and Research Institute, Thrissur for the statistical help.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Tharu MG, Santhakumar R, Manoj VC. An observational study on clinical and bacteriological profile of new-borns with early onset sepsis. *Int J Contemp Pediatr* 2020;7:1962-7.