

## Original Research Article

# Forecasting the possibility of neonatal early onset sepsis based on perinatal risk factors

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### ABSTRACT

**Background:** Neonatal sepsis remains a leading cause of neonatal mortality and morbidity, diagnosis of which remains difficult due to variable presentations. With the increasing threat of antimicrobial resistance, it is important to identify perinatal risk factors which are associated with higher incidence of definite sepsis, to initiate empirical antibiotics, while awaiting blood culture reports.

**Methods:** This was hospital based cross-sectional study done in SVPPGIP, Cuttack, Odisha during January 2019 to April 2019, enrolling all neonates  $\geq 37$  weeks gestation and aged less than 72 hours, with suspected early onset sepsis. Neonates with TORCH infections, congenital anomalies, syndromic baby or with surgical conditions were excluded. After obtaining informed consent, blood culture was sent for all and their perinatal risk factors noted. Blood culture positive newborns were considered to have definite sepsis. Data was analysed with Chi-square test and percentages, using SPSS 18.

**Results:** Among the 200 cases, incidence of definite sepsis was 26%. The most common risk factor was low birth weight and birth asphyxia. Majority (67%) had single or lesser risk factor and number of risk factors was significantly associated with definite sepsis. A significant association was seen between blood culture positivity with low birth weight ( $p=0.003$ ), foul smelling liquor ( $p=0.025$ ), birth asphyxia ( $p=0.018$ ) and premature rupture of membranes ( $p=0.016$ ). The combination of maternal fever and unclean vaginal examination was also significantly associated with the same.

**Conclusions:** Protocols for initiating empiric antibiotics need to be formulated, taking into account the significant risk factors, in resource limited settings, to avoid resource and time wastage.

**Keywords:** Neonatal sepsis, Perinatal risk factors

### INTRODUCTION

In the modern times, neonatology seems to be victim of two simultaneously occurring phenomena. On one hand, neonatal sepsis remains to be one of the major killers, contributing to more than 1 million babies annually.<sup>1</sup> On the other hand, is the emerging threat of antimicrobial resistance, which is bound to occur by misuse of these antibiotics empirically, given to all neonates. This poses a challenge to the physician, regarding who to treat and when to treat with these drugs.<sup>2</sup>

Worsening the situation is the unclear and varied presentations of early onset sepsis present, which leads to most newborns being admitted under the tag of suspected early onset sepsis.<sup>3</sup> A clear consensus case definition is still lacking especially in Low and Middle Income countries.<sup>4,5</sup> Though blood culture remains the gold standard in diagnosing septicaemia, and should be performed on all suspected cases before commencing treatment, the reality remains that there is considerable constraints in the availability of such facilities in developing countries, especially in the peripheries.<sup>6</sup>

Added to this, is the long-time taken for culture reports to arrive, which could lead to disastrous consequences if treatment is delayed.

A perinatal risk factor based approach would not only be cost-effective, but also highly effective in deciding the neonates most likely to develop early onset sepsis, so that both resources and manpower can be allocated accordingly. It is recommended that in resource-limited settings with a high neonatal mortality rate, such as in India, a combination of risk factors and clinical signs should guide intrapartum and neonatal management.<sup>7</sup>

In order to strike a balance between the initiation of empirical treatment, in order to prevent the fatal consequences to the newborn suspected to have early-onset sepsis, with the ill-effects of antibiotic misuse in a child who doesn't require it, it is essential to study the risk factors associated with early onset sepsis. By knowing the relative importance of the risk factors, new antibiotic guidelines can be formulated especially in resource-poor areas of the country. There is paucity of recent data regarding the same. Thus, this study has been designed to assess the current perinatal risk factors that are associated with early onset sepsis in term neonates, and identify those with higher possibility of definite sepsis.

## METHODS

A hospital based cross-sectional study was conducted during the period January 2019 to April 2019 among the neonates of SVPPGIP, Cuttack, a tertiary care hospital in Odisha.

### Inclusion and exclusion criteria

All the neonates admitted in SVPPGIP, Cuttack with suspected early onset sepsis with gestational age  $\geq 37$  weeks and age within 72 hours. Neonates with TORCH infections, congenital anomalies, syndromic baby or with surgical conditions have been excluded from the study.

All the eligible neonates were registered in the study after obtaining informed consent from the patient attendants. Blood culture (BACTEC) was taken from all the babies, prior to administration of antibiotics. Samples were collected with all aseptic precaution, from a peripheral veni-puncture site. 1 ml - 3ml sample of blood was added to a paediatric BacT/ALERT blood culture bottle. Bacteria thus isolated were identified, and antimicrobial susceptibility testing was done using Vitek 2 compact system.

In the event of suspicion of meningitis or urinary tract infection, those neonates were also subjected to cerebrospinal fluid culture and urine culture. Cerebrospinal fluid was obtained by lumbar puncture, under aseptic precautions. Urine Cultures were taken under all aseptic precautions by catheterization.

Those neonates which showed growth on blood culture were considered to have definite sepsis

Their antenatal history was recorded, either from antenatal records, pregnancy cards, referral letters or history by ASHA workers or mothers themselves, in this order of preference. The perinatal risk factors considered in our study were seven- Low birth weight, prolonged labour, premature rupture of membranes, foul smelling liquor, maternal fever, unclean vaginal examination and perinatal asphyxia. The definitions of these risk factors have been listed in Table 1.<sup>8</sup>

**Table 1: Definition of perinatal risk factors.**<sup>17,25</sup>

Prolonged rupture of membranes (PROM)	Interval between rupture of membranes and birth of baby; > 18 hours.
History of Maternal Fever (MF)	Fever in mother > 38°C before delivery with evidence of bacterial infection in the mother in haemogram or culture. Exclusion of malaria by peripheral blood film examination.
Low birth weight Prematurity (LBW)	<2500g, > 37 weeks
Foul smelling liquor (FSL)	Abnormal smell of liquor as perceived by attending obstetrician or neonatologist. Frankly purulent liquor.
Prolonged labour (PL)	Sum of I and II stage of labour 2 24 h
Birth asphyxia (BA)	Apgar score at 5 minut <6 and/or requirement of IPPR for resuscitation or endotracheal intubation
Unclean vaginal examination (UVE)	Vaginal examination performed: <ul style="list-style-type: none"> <li>• Without gloves</li> <li>• With unsterile gloves</li> <li>• Any vaginal examination performed by an untrained birth attendant.</li> </ul>

### Data analysis

All the data was collected and compiled systematically. Data was evaluated with SPSS version 18.0 and analysed with Chi-square test and percentages, with p value <0.05 being considered significant.

## RESULTS

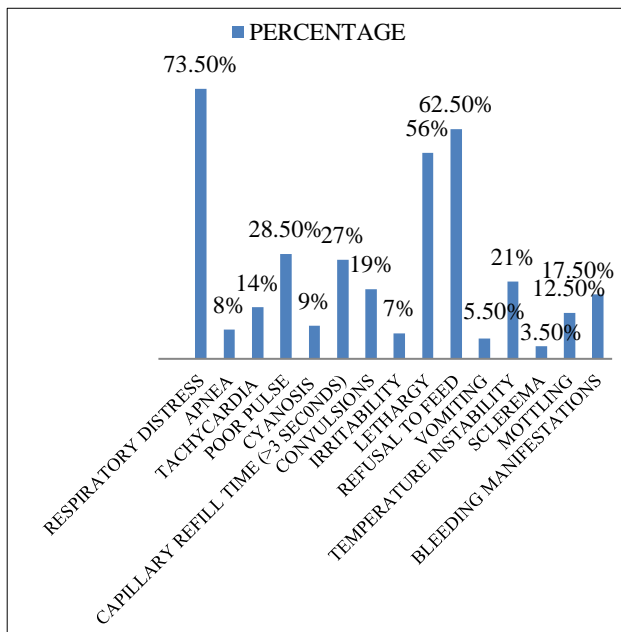
Among the 200 neonates that were enrolled in the study with suspected early onset sepsis, 63% were male with male: female ratio being 2.2. 56% were low birth weight and 57.5% born out of normal vaginal delivery (Table 2).

Most newborns presented with respiratory distress (73.5%) followed by refusal to feed (62.5%) and lethargy

(56%). Features of shock namely tachycardia, poor pulses and delayed capillary refill time was observed in 14%, 28.5% and 27% respectively. Temperature instability was noted in 21% of the cases and convulsions in 19% (Figure 1).

**Table 2: Characteristics of study population.**

Age at admission		Number of cases (n=200)
<12hrs		10 (5%)
12 - 24 hrs		3 (1.5%)
25 - 48 hrs		120 (60%)
>48hrs		67 (33.5%)
Sex	Male	126 (63%)
	Female	74 (37%)
Birth weight	<2.5kg	88 (44%)
	≥2.5kg	112 (56%)
Mode of delivery	NVD	115 (57.5%)
	LSCS	85 (42.5%)



\*percentages may not add up to 100 as many babies may have more than 1 clinical feature.

**Figure 1: Clinical features of study population.**

The incidence of blood culture positivity in our study population was 26% (52 out of 200), 2 out of 40 had cerebrospinal fluid culture positive i.e. 5%, both of which had growth in blood culture. 1 out of 10 (1%) had urine culture positive, which was also blood culture positive.

A total of seven risk perinatal risk factors were considered in our study namely Low birth weight, maternal fever near delivery, foul smelling liquor, premature rupture of membranes, prolonged labour, unclean vaginal examinations and perinatal asphyxia. The most common risk factor was low birth weight followed by birth asphyxia (Table 3).

**Table 3: Incidence of perinatal risk factor in relation to early onset sepsis.**

Risk factor	Total no. of cases	Definite sepsis	p value
Low Birth Weight	88 (44%)	32	0.003
Maternal fever	2 (1%)	1	0.43
Foul smelling liquor	19 (9.5%)	9	0.025
Premature rupture of membranes	48 (24%)	17	0.016
Unclean vaginal examination	30 (15%)	4	0.086
Prolonged labour	10 (5%)	5	0.075
Birth asphyxia	49 (24.5%)	19	0.018

p-value <0.05 is significant

\*One baby may have more than 1 risk factor, hence percentages may not add up.

Of the 200 cases, 134 (67%) had less than or equal to 1 risk factor, 46(23%) had two risk factors whereas rest 10% had more than or equal to three risk factors. A significant association was noted between the number of risk factors with definite sepsis, measured in terms of blood culture positivity, with p-value being 0.01 (Table 4).

**Table 4: Incidence of early onset sepsis in relation to number of perinatal risk factors presented at the time of admission.**

No. of risk factor	No. of cases	Definite sepsis	p value
≤1	134	26	0.01
2	46	13	
≥3	20	13	
Total	200	52	

p-value <0.05 is significant

On assessing the perinatal risk factors individually, a significant association was seen between blood culture positivity with low birth weight (p-value =0.003), foul smelling liquor (p-value = 0.025), birth asphyxia (p-value= 0.018) and premature rupture of membranes (p-value= 0.016).

Only 3.3% of the cases with combination of maternal fever with unclean vaginal examinations showed growth on blood culture, where as it was 10% in those with both maternal fever and prolonged labour. Blood culture was further, positive in 40% of the neonates who had unclean vaginal examinations with prolonged labour.

A significant association was also noted with the combination of maternal fever and unclean vaginal examinations, p- value being 0.009. No association could

however be established with other possible combinations (maternal fever and prolonged labour; unclean vaginal examination and prolonged labour with p-value 0.39 and 0.12 respectively). The combinations with the individually risk factors were not assessed as it is evident that their combinations would be significant as a corollary.

## DISCUSSION

A total of 200 newborns were admitted with suspected early onset sepsis in the study, and all of them subjected to blood culture, prior to administration of antibiotics. Their antenatal history was recorded, either from antenatal records, pregnancy cards, referral letters or history by ASHA workers.

The neonates with suspected early onset sepsis had presented with various clinical features, of which respiratory distress was seen in 73.5% and poor sucking 62.5%, making them the most common presenting symptoms. They were followed by lethargy present in 56%. The findings in our study were in agreement with those in studies done by Waseem et al, Ganguly et al and Basu et al, where respiratory distress, feeding difficulty and lethargy were leading in list of presenting complaints.<sup>9-11</sup> Respiratory distress was identified the most common clinical feature in early onset sepsis in a recent study by Bhishma et al, where it formed 79.7% of the population, comparable to our study.<sup>12</sup> Other clinical features worth mentioning included tachycardia (14%), poor pulses (28.5%), delayed capillary refill time (27%), convulsions (19%) and temperature instability (21%).

The incidence of blood culture positivity in our study population was 26% (52 out of 200). This was in accordance with the studies done by Joshi et al, NNPD 2002-03 and Vandana, where the incidence of blood culture positivity was 25%, 28.6% and 22% respectively.<sup>13-15</sup>

About 40 babies had symptoms suggestive of meningitis and lumbar puncture was done. 5% of them were cerebrospinal fluid culture positive, comparable to NNPD 2002-03 and the study done by Baltimore R. S. 10 neonates also were suspected to have urosepsis and urine cultures of 1% were positive, similar to the study done by Mamta et al, where it was 2%.<sup>14,16,17</sup> The babies, in our study, whose urine and cerebrospinal fluid cultures were positive, had growth on blood culture as well.

Analysis of risk factors that were present in the neonates in the study revealed that majority of them (67%) had either one or lesser risk factors. 23% had two perinatal risk factors. Three or above three risk factors were seen in 10% of the study population. This was in contrast to the studies done by Meenu et al and Vamsi et al, where 15% and 34% of the babies had single or lesser risk factors.<sup>8,18</sup> In the study by Meenu et al, nearly 85% had two or more risk factors, whereas this contributed only 33% in our

study.<sup>8</sup> The difference could be attributed to the fact that in the other two studies the data was obtained from obstetricians, unlike in our study, which obtained from records and mothers themselves.

A significant association was established between the diagnosis of definite sepsis, or those babies who showed growth on blood culture, with the number of perinatal risk factors present (p value= 0.01). Greater the number of risk factors, greater was the chance that the neonate would have definite sepsis.

If we consider each individual risk factor by itself, leading in the list was low birth weight (44%), followed by birth asphyxia (24.5%). In various studies done by Meenu et al and Mamta et al, low birth weight was seen to be the most common risk factor with incidence being around 60%.<sup>8,17</sup> Birth asphyxia was also identified a prime risk factor in studies done by Meenu et al, Mamta et al and Agarwal et al, similar to our study.

The incidence of premature rupture of membranes was found to be 24%, which is comparable to 29.2% observed by Hossain et al. Foul smelling liquor was present in 9.5% of the babies, which was similar to the results in study by Meenu et al (13%) and Shah et al (7%).<sup>8,20</sup> Unclean vaginal examination and prolonged labour constituted 15% and 5% respectively, which was in line with DeNIS study.<sup>21</sup>

In the light of the increasing difficulty segregating true sepsis from their close mimics, especially in resource-limited areas, and at the same time prevent the neonates without sepsis from unnecessarily being exposed to antibiotics and its hazards, it is imperative to establish an association between individual risk factors and definite sepsis. If one could be aware of the likelihood of sepsis, given a risk factor, anticipation would become easier and various thresholds could be set for initiating empiric antibiotic therapy, awaiting final reports. Thus, an attempt was made to find the same.

Four of the perinatal risk factors namely low birth weight, birth asphyxia, foul smelling liquor and premature rupture of membranes were found to be significantly associated with blood culture positive sepsis, with p-values being 0.003, 0.018, 0.025 and 0.016 respectively.

In the study by Shah et al, low birth weight was considered to be significant risk factor, similar to our study (p-value<0.01).<sup>20</sup> Similarly, a meta-analysis in India yielded a significant association with low-birth weight.<sup>22</sup> Other studies by Oddie et al and Murthy et al also found premature rupture of membranes to be significant, which was similar to our study.<sup>22,23</sup>

Previous studies done by Betty et al, and Shah et al, also observed foul smelling liquor to significantly associated with neonatal sepsis, like in our study.<sup>24,20</sup> Authors also considered the combination of the remaining risk factors,

excluding the four which were individually significant, as their combination with any other risk factor would also naturally come significant.

Only 3.3% of the cases with combination of maternal fever with unclean vaginal examinations showed growth on blood culture, whereas it was as high as 50% in study by Meenu et al.<sup>8</sup> Furthermore, 10% of the babies in our study with both maternal fever and prolonged labour had definite sepsis, in contrast to 44% in the other study. However, the incidence was higher in our study, when comparing the same in babies with combination of unclean vaginal examinations with prolonged labour (40% in our study vs 27% in Meenu et al).<sup>8</sup> Moreover, a significant association was noted with the combination of maternal fever and unclean vaginal examinations, p-value being 0.009.

It can, thus, be inferred that the relative importance of the four perinatal risk factors- low birth weight, premature rupture of membranes, birth asphyxia and foul smelling liquor, is higher than the other risk factors (maternal fever, prolonged labour and unclean vaginal examinations). This is important to note, as the presence of these risk factors, singly or in combination should alert the physician to keep a low threshold and commence the baby on empirical antibiotics, in view of the impending disaster that might follow. Likewise, the presence of multiple risk factors should also prompt the physician for extra vigilance and urgent referral to higher centres, anticipating definite sepsis and its consequent complications, more so if the combination happens to be of maternal fever and unclean vaginal examinations. Maintaining a strict record of the perinatal risk factors, formulating and implementing new protocols not only pave way to a more systematic approach, with early suspicion for definite sepsis, but at the same time, will help in allotting resources and manpower to those babies who need it most.

## CONCLUSION

Keeping in mind the challenges faced by physicians in the context of early onset neonatal sepsis, be it in identifying sepsis or combating it in time or to avoid treating those babies who do not require it, new and updated antibiotic policies in management and anticipation of early onset of sepsis must be formulated. The perinatal risk factors identified in the study, should be taken into consideration, and those neonates vulnerable should be carefully monitored and commenced on aggressive treatment. This is of special importance in developing countries like ours, where financial and health resources are limited as compared to the huge population.

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