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Research Article

Clinical and Biomarker Predictors of Neonatal Sepsis - An Observational Study in a Tertiary Care Centre

Abhishek Dubey[1], Pratibha V Kale[2]

[1]Junior Resident, [2]Professor, Department of Paediatrics, Dr. Panjabrao Deshmukh Memorial Medical College, Amravati, Maharashtra, India.

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Corresponding Author:
Abhishek Dubey, Department of Paediatrics, Dr. Panjabrao Deshmukh Memorial Medical College, Amravati, Maharashtra, India.
E-mail Id:
abhidubeyair264@gmail.com
Orcid Id:
https://orcid.org/0000-0001-5022-684X
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A B S T R A C T

Objectives: Assessing the early clinical features for the early diagnosis of neonatal sepsis in a tertiary care centre from central India.

Method: This is an observational, cross-sectional study done between December 2019 and June 2021. Neonates from a tertiary care centre of central India with clinical features of probable sepsis were included in the study. Clinical and laboratory data were collected and analysed. Association was sought between various clinical features and complications with culture-proven neonatal sepsis.

Results: Sixty-five neonates were included, of which 44 (67.7%) were preterm and 21 (32.3%) were full-term. The most common presenting features of early as well as late-onset sepsis were respiratory distress, lethargy, and refusal to feed. Majority of neonates had EOS (60, 92.3%) compared to LOS (19, 29.2%). 14 neonates who were initially treated for EOS were readmitted as LOS. Out of the total 79 blood culture samples sent, only 29 (36.7%) were positive. In both EOS and LOS, Klebsiella pneumoniae (10, 34.5%) was found to be the most commonly isolated organism. Next in frequency were MRSA (6, 20.7%) and Streptococcus pyogenes (3, 10.3%). Respiratory failure (47, 72.3%) was the most common complication, followed by persistent hyperbilirubinemia (42, 64.6%) and hypoperfusion (14, 21.5%).

Conclusions: High suspicion should be kept for neonatal sepsis especially when neonates present with features like respiratory distress, refusal to feed, lethargy, weak/ high pitched cry, thermal imbalance, irritability etc. These features can be implemented at the primary health care level to start early treatment and make quick referrals.

Keywords: Neonatal Sepsis, Late-Onset Sepsis, Early-Onset Sepsis

Introduction

Neonatal sepsis can be defined as a systemic infection of viral, bacterial, or fungal origin which is usually accompanied by clinical manifestations and haemodynamic changes resulting in substantial morbidity and mortality.[1]

As per the WHO global report on epidemiology and burden

of sepsis, neonatal sepsis accounted for approximately 1.3 to 3.9 million cases with 400,000-700,000 deaths worldwide annually. Hospital-acquired infections lead to 4% to 56% of all neonatal mortality in hospital-born infants.[2]

The highest neonatal sepsis incidence is seen in underdeveloped and developing countries, which is 40 times more than that in developed countries.[3] In the National Family Health Survey (NFHS-5) of India, neonatal mortality rate was found to be 15.8 per 1000 live births, amounting to a large proportion of infant mortality rate.[4]

Neonates present with subtle clinical manifestations; thus, it becomes important to recognise even the slightest variations in respiratory status, temperature instability or feeding issues, which could be the first signs of a life-threatening infection.[5] Timely identification may help in the early administration of appropriate therapy. One can discontinue therapy if the investigations turn out to be negative and further antibiotic therapy is not indicated.[6] Early diagnosis along with effective clinical management initiated in a timely manner can help in the prevention of approximately 84% of neonatal mortality caused by infections.[2]

This study was aimed at assessing the early predictive clinical features of neonatal sepsis along with its complications found in neonates admitted in the Neonatal Intensive Care Unit (NICU) with probable sepsis.

Material and Method

This observational, cross-sectional study was carried out in a tertiary care centre in central India, after obtaining the required approval from the institutional review board and the institutional ethical committee (IEC).

The study was conducted from December 2019 to June 2021, over a duration of 18 months. Among all the neonates admitted in NICU during this period (Universal Sample), those who fulfilled the inclusion and exclusion criteria and whose parents consented for participation in the study, were enrolled. The sample size was 65.

Inclusion Criteria were: Neonates presenting with signs and symptoms of probable sepsis [thermal dysregulation (temperature < 34.4˚C & > 38˚C), respiratory distress (respiratory rate > 60/min, subcostal retractions and grunting), decreased activity, feeding difficulties, unexplained jaundice, or hypoglycaemia (< 45 mg/dL)]. Neonates who presented with known inborn errors of metabolism (IEM) or congenital anomaly and whose parents were unwilling to give consent for participation were excluded from the study.

A semi-structured case record form was used to record the details about clinical vignette. The neonates who presented with signs and symptoms of probable sepsis were investigated with CRP. Only limited sepsis screen parameters could be performed due to a lack of resources. Those neonates whose CRP was > 5 mg/L were diagnosed as probable sepsis and further categorised as either early-onset sepsis (EOS) or late-onset sepsis (LOS).

Statistical Analysis

Data were entered in MS-excel. The categorical variables were expressed in proportion and Chi-square test was utilised to compare dichotomous variables. A descriptive analysis was done to characterise the participant population by socio-demographic data. Statistically significant p value was defined as 0.05 or less.

Result

Out of 84 [35 in 2020 and 49 in 2021 (till completion of study)] neonates, 65 were included in the study. The baseline population profile of the enrolled neonates is as shown in Table 1.

Table 1.Baseline Population Characteristics

Variables	Population Characteristics (n = 65)	
	N	%
Gender		
Male	28	43.1
Female	37	56.9
Onset of sepsis		
EOS	60	75.9
LOS	19	24
Gestational age (Mean in weeks)	34.3	
Preterm	44	67.7
Term	21	32.3
Birth weight in kg (mean)	1.82	
ELBW	1	1.5
VLBW	24	36.9
LBW	26	40
Normal (> 2.5 kg)	14	21.5
Mode of delivery		
NVD	28	43
LSCS	36	55.4
Assisted	1	1.5
APGAR score (1 min)		
≤ 6	23	35.4
≥ 7	42	64.6
APGAR score (5 min)		
≤ 6	5	7.7

≥ 7	60	92.3
PROM > 18 hours	12	18.5
Maternal fever	7	10.8
Initial bag & mask resuscitations	13	20
Mechanical ventilation	11	16.9
Maternal age in years (mean)	27.4	
Gravid status of mother		
Multigravida	32	49.2
Primigravida	33	50.8

Seven neonate's mothers had history of fever (Pearson Chi-square value = 0.633, df = 1; p value = 0.426). Sixty (92.3%) neonates had EOS, among whom 34 (56.7%) were females and 26 (43.3%) males. Fourteen neonates who were initially treated for EOS were readmitted as LOS. A total of 19 neonates had LOS, with a higher proportion of females than males (13:6).

Clinical presentation of the enrolled neonates is as shown in Figure 1. Out of 65 neonates, 49 (75.4%) had respiratory distress, 24 (36.9%) had vomiting and loose motions, 23 (35.4%) had irritability, 8 (12.3%) had persistent cyanosis, 3 (4.6%) had temperature instability, 48 (73.8%) had refusal to feed, 50 (76.9%) had lethargy, 18 (27.7%) had abdominal distension, 33 (50.8%) had weak/ high pitched cry, and 44 (67.7 %) had prolonged jaundice.

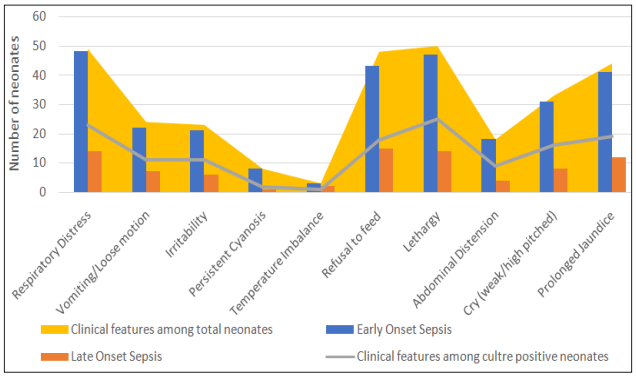

Figure 1.Clinical Features in Neonates with Probable Sepsis

Figure 2 shows the culture profile of isolates in our study. Out of the 29 culture isolates, Klebsiella pneumoniae (10, 34.5%) was the most frequent occurring organism followed by MRSA (6, 20.7%) and Streptococcus pyogenes (3, 10.3%). In the EOS and LOS, the most common organism was klebsiella pneumonia.

The most common complication was respiratory failure (47, 72.3%) followed by persistent hyperbilirubinemia (42, 64.6%), and hypoperfusion (14, 21.5%) (Figure 3).

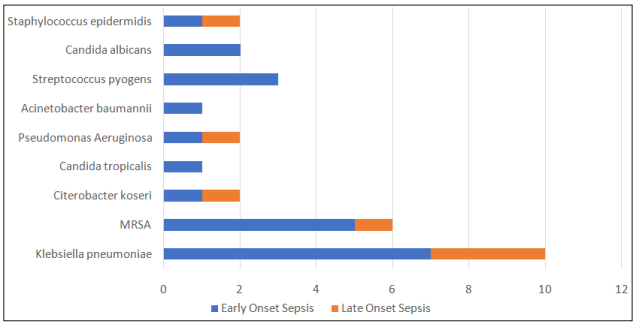

Figure 2.Blood Culture Isolates in Early-Onset Sepsisand Late-Onset Sepsis

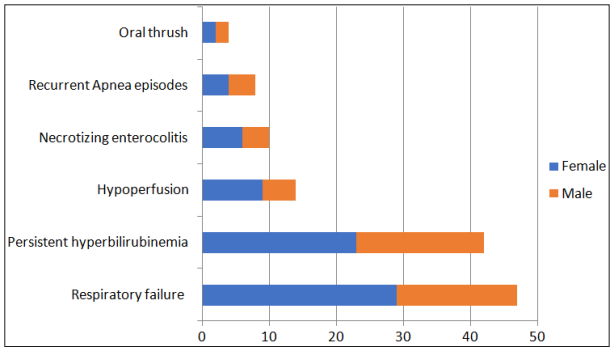

Figure 3.Distribution of Common Complications in Probable Sepsis Neonates

Discussion

Majority of the neonates in our study were preterm as observed by other researchers including Verma et al. and Pokhrel et al. with 58.15% and 68.1% preterm neonates respectively.[7,8] This is possibly because Low Birth Weight (LBW) and preterm newborns are at an increased risk of infection as a consequence of their immature innate immunity along with decreased immunoglobins received trans-placentally in addition to other factors like total parenteral nutrition, invasive procedures, and prolonged hospital stay.

All patients were enrolled after applying precise clinical criteria for suspected sepsis. Out of the enrolled 65 neonates, 14 neonates who were initially treated for EOS were readmitted as LOS. Majority were found to have early-onset sepsis. This is consistent with the results obtained by other researchers though the number was higher in our study.[7-9]

However, on the contrary, Giannoni E et al. observed in their study that only 20% of cases were EOS, with 62% having hospital-acquired LOS, and 18% having community-acquired LOS.[10] This may be due to better hygiene and universal precautions observed during the peripartum period in other centres across the world.

In our study, we observed lethargy (50, 76.9%) and respiratory distress (49, 75.4%) being the most common clinical features. Similar observations were noted by

Jatsho et al. Arowosegbe et al. and Chaudhari et al. in their studies.[11-13] Jatsho et al. observed that respiratory distress, fever, feeding intolerance, and jaundice were the commonly occurring clinical features[11] while in the study of Chaudhari et al., the common features were refusal to feed (77.4%) and lethargy (67.9%).[13]

An important indicator of sick newborn infants is refusal to feed and merits due consideration for a CNS (brain or spine) or peripheral nervous system disorder, infection, intestinal obstruction, inborn error of metabolism, and other abnormalities.[14] Clinical appearance of lethargy along with biochemical derangements like acidosis, hyperammonemia, or hypoglycaemia after the second day should indicate an infection or an inborn error of metabolism.[14]

Similar observations have been noted by Verma et al. in their study with respiratory distress, vomiting, hypothermia, and abdominal distension being the common presenting features in early-onset sepsis while lethargy, refusal to feed, and fever in late-onset sepsis.[7]

Castellanos et al. observed thermal gradient alterations to have a high diagnostic yield for late-onset sepsis (LOS). High sensitivity and specificity were noted when a more than 2˚C rise in thermal gradient that could not be normalised in 3 hours, was used to diagnose late-onset neonatal sepsis.[15] Rotaru et al. reported that hypoglycaemia/ hypothermia are associated with sepsis followed by respiratory failure and other confounding factors.[16]

In our study, out of 65 neonates, only 7 neonates' mothers were having h/o maternal fever. This was consistent with the study of Towers et al., who observed that newborns of mothers with a clinical diagnosis of chorioamnionitis or those suffering from intrapartum fever had a low risk of neonatal sepsis.[17]

In our study, blood culture was positive only in 29 (36.7%) samples out of 79 samples of suspected neonates of probable sepsis. Similar observations have been noticed by Goswami S et al. who observed 34% culture positivity in their study.[18] Similarly, Pokhrel B et al. in their study observed that only 20.5% of neonates had positive blood culture.[8] The blood culture positivity rate is low and is affected by several factors including small, inoculated blood volume, bacteremia level, antimicrobial exposure and laboratory handling among the few. Hence, although a positive blood culture establishes the diagnosis, it cannot rule out infection. Also, blood culture has high specificity but relatively poorer sensitivity and negative predictive accuracy.[18] It is also time-consuming and takes little part in influencing the decision to initiate treatment.[18] It is not available universally and is also expensive.

We found similar culture positivity rates among our EOS and LOS patients. Al-Shamahy HA et al. also observed that EOS showed higher positive culture results (61.7%) than LOS (32%).[19]

Klebsiella and Staphylococcus were the most common isolates observed in this study. This profile was similar to that observed by Pokhrel-, Jatsho- and Dalal et al.[8,11,20] Gram-negative organisms are the predominant isolates, especially in South-East Asia as compared to the western world where GBS is predominant.[14,21]

The biggest limitations of our study were small sample size, limited availability of septic screen investigations, and poor culture positivity, as the desired association couldn't be sought between various clinical features and complications with culture-proven neonatal sepsis. Some neonates may be missed from inclusion in the study due to negative CRP value or absence of the above-mentioned clinical features.

Conclusion

Neonatal sepsis causes significant morbidity and mortality in the neonatal period, especially in low-income countries, and poses a diagnostic challenge. Neonatal sepsis is sometimes diagnosed with difficulty; hence a high index of suspicion helps in arriving at early diagnosis as well as management of sepsis. The present study shows that early clinical features including respiratory distress, refusal to feed, lethargy, weak/ high pitched cry, thermal imbalance, irritability etc. can be used as a clinical marker for suspecting both early and late-onset sepsis. These features can be implemented at the primary health care level to start early treatment and make quick referrals. This could prevent complications and improve the outcome of the disease.

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