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Blood culture positivity for the diagnosis of neonatal sepsis: Is it always necessary

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Abstract
Neonatal sepsis is the third leading cause of neonatal mortality and an estimated 3 million newborns suffer from sepsis globally every year. Early diagnosis and treatment will go a long way in reducing the load. However, there is a lack of consensus on the definition and the accepted criteria for diagnosis of neonatal clinical sepsis in practice and research. The objective of this study was to assess the risk factors and laboratory parameters used in diagnosis of neonatal sepsis. A retrospective case control study was conducted among neonates admitted in the NICU. Blood parameters including total leukocyte count, immature/total neutrophil ratio, and C- reactive protein along with blood culture results were analyzed along with neonatal demographics and obstetric history. Although I/T ratio and CRP showed significant correlation with neonatal sepsis, positive blood culture results were found in 8.3% of the cases only. Hence the evaluation for presence of non-bacterial pathogens is an important consideration for a definition of neonatal sepsis and in particular, clinical sepsis.

Keywords: Neonate, sepsis, consensus, definition, blood culture

Introduction
Although the global epidemiological burden of sepsis is difficult to ascertain, the World Health Organization estimates that, there are 3 million newborns who suffer from sepsis globally every year [1]. Neonatal sepsis is the third leading cause of neonatal mortality, only behind prematurity and intrapartum-related complications. It is responsible for 13% of all neonatal mortality and 42% of deaths in first week of life [2, 3]. To bring down this burden, it is essential to improve the diagnosis of sepsis so that early treatment can be initiated and mortality and morbidity reduced. The World Health Organization is actively advocating new biomarkers of sepsis and early diagnosis is a priority for research and development[1]. However, in a country like India, resources are limited and routine use of novel markers may not be practical.

As per one definition neonatal sepsis refers to an infection involving the bloodstream in newborn infants less than 28 days old [4]. It is divided into two groups: early-onset sepsis (EOS) and late-onset sepsis (LOS). EOS refers to sepsis in neonates at or before 72 hours of life, and LOS is sepsis occurring after 72 hours of life [5]. However, there is a lack of consensus on the definite and accepted criteria for diagnosis of neonatal clinical sepsis in practice and research[5]. A positive blood culture has been historically considered "gold standard" for diagnosis of neonatal sepsis [6]. When blood and other sterile site culture are negative, but the infant manifests signs consistent with infection, they may be considered to have "clinical" sepsis [7]. Some studies suggest that a positive blood culture is not required to meet the consensus definition for sepsis in adults and children [8]. The main aim of this study was to study the risk factors and to study the commonly used parameters in diagnosis of neonatal sepsis.

Materials and methods
This retrospective case control study was conducted on the neonates admitted in the Neonatal Intensive Care Unit of Srinivas Institute of Medical Sciences and Research Centre, Mukka over a period of 2 years from January 2018 to December 2019.

A total of 96 cases were studied, of which 48 were considered cases and 48 as control. Cases were selected on the basis of clinical diagnosis upon admission into the NICU. Suspected clinical sepsis was considered if neonate had clinical features of perinatal risk factors i.e,

maternal pyrexia (within 1 week prenatal and /or 48 hrs postnatal), prolonged rupture of membranes (18 hours) and foulsmelling maternal discharge and/or maternal urinary tract infection diagnosed in the last month. Neonates having unexplained hypothermia or hyperthermia, lethargy, irritability, poor feeding or milk intolerance, respiratory dysfunction evidenced by apnea (>10 sec), tachypnea (>60 breaths/min), cardiovascular dysfunction such as tachycardia (>160 beats/min) or bradycardia (<100 beats/min), poor peripheral circulation, hypotension or circumoral cyanosis or pallor were also included. Neonates who were admitted to the NICU for safe confinement were selected as Controls.

Maternal and neonatal data was collected which included antenatal history, type of birth (vaginal/LSCS), reason for LSCS, term/preterm, neonatal age at admission, sex, birth weight and clinical features during the hospital stay. Laboratory data including hemoglobin, total leukocyte count, immature /total neutrophil, C-reactive protein and blood culture results were collected. Peripheral blood hemoglobin, total leukocyte count, were assessed on a 5-part hematology analyzer**.** Peripheral smear examination was done on EDTA anticoagulated blood to calculate the differential count and the immature-total neutrophil ratio (I/T Ratio). C- reactive protein test was done as per rapid slide latex agglutination method. Blood culture was done on brain heart infusion broth incubated at 37ºC for 7 days. Subcultures were done on blood agar and Mac Conkey's agar.

The data was tabulated on Microsoft Excel sheet and statistical analysis was done using the SPSS software. A P-value of < 0.05 was considered significant.

Results

The current study documents a total of 96 neonates with 48 clinically suspected neonatal sepsis (cases) and 48 neonates admitted in the NICU for safe confinement (controls). Majority of the neonates were below 7 days of age, representing 75% of cases and 79.1% of controls. Fig 1. shows distribution of cases according to gender.

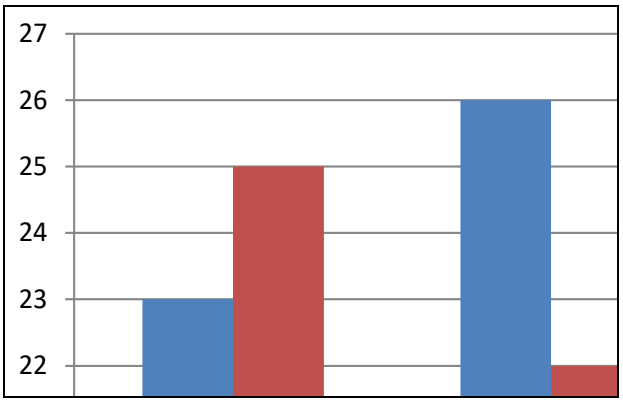

Fig 1: Distribution of cases according to gender of neonates

A higher proportion of neonates had birth weight more than 2500 gm, 77% among cases and 77% among controls. An insignificant difference was seen between the development of sepsis and birth weight (p=0.26). 83.4% of cases had total WBC count between 10,000 and 26000 cells/cumm of blood and 8.3% had total count more than 26000 cells/cumm of blood. 25% cases had low hemoglobin levels, < 14gm/dl, as compared to 16.65% neonates among the controls. A marginally higher percentage of cases i.e.,16.7% were preterm neonates, as compared to 12.5% of the controls. I/T ratio was significantly raised (≥0.2) in 16.7% of the cases and 2.1% of the control neonates. Kruskal Wallis H test showed a highly significant difference between cases and controls with respect to I/T ratio (p=0.028). CRP positivity was seen in 25% of neonates in case group while, none of the neonates in the control group showed a positive CRP. Kruskal Wallis H test showed a highly significant difference between cases and controls with respect to CRP level (p=0.00). 80% of the cases with negative CRP had an I/T ratio <0.2. Blood culture positivity was seen in 8.3% of the cases. Coagulase negative Staphylococcus was the predominant bacterial found in the blood culture, followed by Pseudomanas spp. Among the neonates in the case group, who had raised I/T ratio, 42.8% showed a positive blood culture. Blood culture positivity and a positive CRP was seen in 16.7% of the cases, while CRP positivity and negative blood culture was seen in 83.3% of the cases. 2 cases had history of maternal premature rupture of membranes before delivery and both the neonates were positive for Coagulase negative staphylococcus. Among the cases 12.5% of the neonates had history of Meconium aspiration.

Discussion

Neonatal sepsis is an important cause of mortality and morbidity encountered in the neonatal intensive care unit. According to the WHO the incidence is much higher in developing countries as compared to developed countries[1]. This is in part due to ignorance of the risk factors like deliveries without proper aseptic procedures, inadequate maintenance of hygiene and general non-availability of resources. Early diagnosis and treatment can prevent significant mortality and morbidity.

A definitive consensus regarding the parameters which define neonatal sepsis has not been reached. There is remarkable heterogeneity among studies regarding the case definition of neonatal sepsis [6]. Various laboratory parameters have been studied by many and gives varying results. The 'sepsis screen' which is commonly used for diagnosis includes total leukocyte count, absolute neutrophil count, immature/total neutrophil ratio, micro-ESR and C-reactive protein [7]. Although blood culture is historically considered gold stand in diagnosis of neonatal sepsis, there are various drawbacks including a waiting period of a minimum of 24 hours and a maximum of 7 days to obtain results for subcultures and antibiotic sensitivity. When blood and other sterile site cultures are negative, but the infant manifests signs consistent with infection they may be considered to have "clinical" sepsis[5]. However, clinical signs such as respiratory distress, hypotension, and temperature instability are non-specific for sepsis and occur at much higher rates among preterm infants than sepsis does. Unsurprisingly the majority of ill-appearing infants who are evaluated for sepsis are uninfected [10].

In this study we found I/T ratio ≥0.2 in 16.7% of the cases, considered to have clinical sepsis. In his study *Saied DA* found I/T ratio of ≥0.2 in 65.6% of the patients with 82.45 sensitivity, 81.3% specificity, 92.5% positive predictive value and 62.2% negative predictive value[11]. *Hornik et al* in

their multicentre study found progressively increasing odds of infection with I/T r atios >0.2, but concluded that it lacked adequate sensitivity and reliability to rule out sepsis [12]. We found positive CRP in 25% of the cases with clinically suspected sepsis and a highly significant difference between cases and controls with respect to CRP level (p=0.00). In their study *George L* and colleagues found that among the commonly used laboratory parameters, only values of CRP were significant in the diagnosis of neonatal sepsis (p-0.047) [13]. In our study 8.3% of the cases had blood culture positivity. *Hornik et al* reported that of 164,744 blood cultures obtained from 99,796 VLBW infants with suspected LOS, just 8.9% were positive [14]. In another study of 92 neonates ≥34 weeks with documented bacterial meningitis, 35(38%) had negative blood cultures [15]. Wynn explains in his study that the possibility of a non-bacterial (fungal, viral) cause of sepsis must also be considered as a microbial etiology for clinical sepsis. There is increasing evidence for novel viral pathogens associated with sepsis-like syndrome in preterm infants (e.g., echovirus, enterovirus, parechovirus, coxsackie, adenovirus, parainfluenza, rhinovirus, coronavirus) [16, 17]. A prospective cohort study of 100 infants with LOS showed presence of Respiratory virus in 85 of the cases and none of them had concurrent bacteremia, and the incidence of bacteremia was 15% [18]. These studies indicate that viral infections are contributing to some episodes of clinical deterioration that are associated with a negative blood culture.

Conclusion

Neonatal sepsis is one of the commonest diagnoses encountered in the neonatal intensive care unit. Globally there is no unified opinion over the definition and parameters of the disease. Although various studies have shown significance of one test over the other, a consensus opinion has not been reached. Historically positive blood culture for bacterial pathogens has been taken as gold standard, but studies have shown that it may not always be so. Our study shows that evaluation for the presence of non-bacterial pathogens is an important consideration for a definition of neonatal sepsis and in particular, clinical sepsis. More studies in this regard will be beneficial.

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