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# Role of Sepsis Screening in Early Diagnosis of Neonatal Sepsis

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**Abstract**
**Introduction:** *Neonatal sepsis, a clinical syndrome of bacteremia with systemic signs and symptoms of infection in the first 4 weeks of life is a major cause of morbidity and mortality in newborn. Early diagnosis is critical, as sepsis can progress more rapidly in neonates than in adults. An attempt was made to establish correlation between early neonatal sepsis screening & blood culture in neonates presenting with features of sepsis. The aim of this study is to assess the usefulness of sepsis screen in early diagnosis of neonatal septicemia.*
**Materials and Methods:** *The study was done in SGT Medical College and Hospital, Gurugram from January 2016 to January 2017. Statistical correlation between early indicators of sepsis screen & blood culture (considered as gold standard) was established in clinically suspicious cases of neonatal sepsis.*
**Results***: Out of 100 cases studied, 38 were culture positive. Markers like CRP (77.8%) and ratio of immature cells versus total neutrophils (I/T ratio) (73%) showed highest sensitivity. CRP (66.7%), band forms and I/T ratio (61.5%) showed highest specificity. Positive predictive value was highest for CRP (68.2%) followed by I/T ratio (63.8%) and corrected total leukocyte count (56.2%).*
**Conclusion***: Serum CRP is the most sensitive marker of sepsis. Use of peripheral smear study and CRP can be implicated effectively as a sepsis screen for early diagnosis of neonatal sepsis. The combination of parameters yielded better results than single tests and proved to be an invaluable tool for early diagnosis of neonatal sepsis.*
**Keywords***: Blood culture; CRP, I/T ratio; Band forms; Neonatal sepsis; Sepsis screening*.

## Introduction

Neonatal sepsis is defined as systemic inflammatory response of the body to an infection which occurs in first 28 days of life.[1] As per National Neonatal Perinatal Data base (NNPD) 2002-2003, the incidence of neonatal sepsis in India was 30 per 1000 live births.[2] It is an important cause of morbidity and mortality among neonates in India, with an estimated incidence of approximately 4% in intra mural live births.[3]

The most common causative organisms are Group B Streptococcus (GBS), E.Coli, listeria monocyto-genes, gram negative rods (enterobacteriaceae, klebsiellaspp, serratiaspp, coagulase –negative

staphylococci and staphylococcus aureus), fungal infection, herpes simplex virus, enteroviruses and parvo viruses). GBS is the most common etiologic agent, while escherichia coli is the most common cause of mortality. Current efforts toward maternal intrapartum antimicrobial prophylaxis have significantly reduced the rates of GBS disease but have been associated with increased rates of Gram–negative infection especially among very low birth weight infants.[4]

The most common risk factors are pre maturerupture of membrane (>18 hr prior to delivery), maternal fever, maternal urinary tract infection, vaginal colonization with GBS, low levels of maternal antibody to GBS, and the presence of chorioamnionitis,[5] foul smelling liquor, multiple digital vaginal examinations, poor maternal nutrition, prematurity/Low birth weight, congenital anomalies, complicated or instrument – assisted delivery, low sapgar score (score of <6 at 5 min) and low socio economic status.[4]

Sepsis in neonates may be difficult to differentiate from other conditions because the clinical signs are nonspecific. Delay of even a few hours in initiating treatment can considerably increase the morbidity and mortality.[5]

Traditional methods, such as blood culture (gold standard) do not provide a rapid diagnosis. In acute phase the concentration of many serum proteins rises in response to inflammation, infection or tissue damage and mainly C-reactive protein (CRP), haptoglobulins and fibrinogen. They can be used as non specific indicators of bacterial sepsis.[5]

The ratio of immature to total neutrophil count may indicates presence of significant infection in a neonate.[9] An I/T ratio of over 0.2 is highly sensitive marker of neonatal sepsis.[6] A normal neonate may show a ratio around 0.11 during the first 48 hours after delivery. A ratio >0.8 indicates that there is depletion of the myeloid reserves within marrow. This finding may precede death in a septic neonate.[7]

The presence of 20% band forms on first day of life15% on the second day and above 8% from the third day is in pathological range. The percentage of band forms and the ratio of band forms to segmented neutrophils are almost always abnormally elevated. Among the different criteria the percentage of band forms is evidently the most practical and most significant.[8]

Detection of degenerative changes of neutrophils (DCN) including vacuolization and toxic granulation in peripheral blood smear were found to be of value in identifying neonates with infection. Vacuolization and/or toxic granulation in neutrophils varied from 0% to 50% per 100 neutrophils scanned. The positive predictive accuracy and specificity increases with the degree of DCN from 24.7% to 100% respectively, but the sensitivity decreased accordingly when DCN was less than 10%, the chance of sepsis was less than 5%.[8]

CRP, an acute phase reactant that has the advantages of low serum levels in normal infants shows a rapid rise after 12 to 24 hours of sepsis and a massive rise thereafter as long as inflammatory stimuli persist.[2] CRP can be used to predict neonatal sepsis early with reasonable accuracy. It has the highest sensitivity (86.6%). CRP positivity is the single and most useful parameter for early diagnosis of neonatal sepsis.[2]

The value of hematological and immunological parameters, singly and in combination, is having significant role in early diagnosis of neonatal sepsis. The four useful tests were I/T ratio, morphological changes in neutrophils, m-ESR, and CRP; and role of these tests in early diagnosis of neonatal sepsis were statistically significant. The most sensitive was CRP (84%). A combination of three or all of these tests was highly specific (95%-100%).[9]

Definitive diagnosis of neonatal sepsis is made by demonstration of organisms in culture (gold standard), but it takes long time (2-8 days) for positive blood culture.[2]

The Septic Screen for neonatal sepsis according to IAP 2006 guidelines are

| SEPTIC SCREENING PARAMETERS | |
|---|---|
| TOTAL LEUCOCYTE COUNT | <5000/cumm |
| ABSOLUTE NEUTROPHIL COUNT | <1800/cu mm |
| IMMATURE/TOTALNEUTROPHIL RATIO | >0.2 |
| C-REACTIVE PROTEIN | >1 mg/dl |
| Micro-ESR | <15 mm |

Out of these five tests, if two tests are positive it indicates neonatal sepsis[10].

In the present study total leucocyte count; absolute neutrophil count; immature to total leucocyte ratio and C-reactive protein shall be carried out in all the cases to evaluate neonatal sepsis.

Reports of blood culture shall be correlated with above parameters.

## Material and Methods

This was a descriptive prospective study carried out in SGT Medical College, Gurugram, Haryana. For ethical issues confidentiality of patient's information was considered and ethical clearance was duly taken from institutional ethics committee and progress of study was duly intimated to the ethics committee time to time. All the neonates admitted to the baby nursery between January 2016 to January 2017, with signs and symptoms of sepsis or presence of predisposing factors for development of sepsis,were included in this study.

### Inclusion criteria

Neonates were enrolled on the basis of signs and symptoms of clinical sepsis after thorough clinical examination and proper history taking. The clinical criteria considered were – Neonates with temp >37.5°C or < 36.5°C; tachycardia / bradycardia; infants with respiratory instability; infants with GI intolerance; lethargic infants; refusal to feed; abdominal distension; vomiting; shock; bleeding and renal failure.

### Exclusion criteria

Neonates with major primary hematological disorders, patients who are already on antibiotic therapy prior to haematological evaluation were excluded.

Each patient was studied in a methodical manner using a proforma. Myriads of clinical profile of neonatal septicemia amongst all cases of neonatal sepsis (with emphasis on sepsis screen positive and/or bacteriologically positive i.e. blood culture positive cases) were studied. Correlation between early indicators of sepsis screen and their statistical correlation with blood culture in neonatal septicemia was performed. Following investigations were included in the study.

**i. Sepsis screen (according to NNF criteria)**

a. Total leukocyte count
b. No. of band cell
c. I/T ratio (band cell ratio)
d. Absolute neutrophil count
e. C reactive protein

**ii. Blood culture**

**Statistical analysis and ethical clearance was performed**

It was done as per standard statistical tools. Some help was taken from statistical package for social sciences (SPSS, Version 21) software.

## Results

Out of 100 suspected neonatal sepsis patients, 65 (65.0%) were males and 35 (35.0%) were females. Thus it was inferred that male babies were more affected by suspected neonatal sepsis than female babies.

**Table 1:** Age Distribution of the Neonates

| AGE | SEPSIS PROVEN | SEPSIS PROBABLE | TOTAL |
|---|---|---|---|
| EARLY NEONATE | 36(94.7%) | 57(91.9%) | 93(93.0%) |
| LATENEONATE | 2(5.3%) | 5(8.1%) | 7(7.0%) |
| TOTAL | 38(38.0%) | 62(62.0%) | 100(100%) |

Out of the 38 culture positive cases, early onset septicemia was found in 93.0% cases. Late onset septicemia was present in 7.0% cases.

**Table 2:** Common clinical features in cases presenting with features of sepsis

| Diagnosis | Clinical Symptoms | | | | | | |
|---|---|---|---|---|---|---|---|
| | Fever | Respiratory distress | Jaundice | CNS Symptoms | Vomiting | Others | Total |
| Sepsis Proven | 5(13.1%) | 18(47.3%) | 6(15.7%) | 0(0.0%) | 3(7.8%) | 6(15.7%) | 38(38.0%) |
| Sepsis Probable | 4(6.4%) | 36(58.0%) | 12(19.3%) | 0(0.0%) | 7(11.2%) | 3(4.8%) | 62(62.0%) |
| Total | 9(9.0%) | 54(54.0%) | 18(18.0%) | 0(0.0%) | 10(10.0%) | 9(9.0%) | 100(100%) |

Among the patients with suspected neonatal sepsis, the most common presenting clinical feature was respiratory distress followed by jaundice and feeding problems.

**Table 3:** Distribution of cases on the basis of Band Form

| Diagnosis | Band Forms | | |
|---|---|---|---|
| | Normal | Increased | Total |
| Sepsis Proven | 8(21.0%) | 30(78.9%) | 38(38.0%) |
| Sepsis Probable | 10(16.1%) | 52(83.9%) | 62(62.0%) |
| Total | 18(18.0%) | 82(82.0%) | 100(100%) |

Band forms of more than 10/100 cells is considered as increased number and less than 10/100 cells is considered as normal. While studying the distribution of cases on the basis of band forms, total number of band forms in sepsis proven (38/100) cases it was observed that 21.0% had normal band form, 78.9% had increased band forms. Similarly in the sepsis probable (total 62/100 cases) it was observed that 16.1% had normal band form, and 83.9% had increased band forms count.

**Table 4:** Distribution of cases on the basis of I:T Ratio

| Diagnosis | I:T Ratio | | |
|---|---|---|---|
| | Normal | Increased | Total |
| Sepsis Proven | 3(7.9%) | 35(92.1%) | 38(38.0%) |
| Sepsis Probable | 5(8.1%) | 57(91.9%) | 62(62.0%) |
| Total | 8(6.0%) | 92(92.0%) | 100(100%) |

While studying the distribution of cases on the basis of I:T ratio, total number of sepsis proven cases were (38/100) i.e 38% and sepsis probable were (62/100) i.e 62%. In the sepsis proven it was observed that 7.9% had normal I:T ratio, 92.1% had increased I:T ratio, Similarly in the sepsis probable (total 62/100 cases) it was observed that 8.1% had normal I:T ratio, 91.9% had increased I:T ratio (less than 10/100 cells).

**Table 5:** Distribution of cases on the basis of CRP

| | | CRP | | | Total |
|---|---|---|---|---|---|
| | | Normal | Increased | Decreased | |
| Diagnosis | Sepsis Proven | 7(18.4%) | 31(81.6%) | 0(0.0%) | 38(38.0%) |
| | Sepsis Probable | 8(12.9%) | 46(74.1%) | 8(12.9%) | 62(62.0%) |
| Total | | 15(15.0%) | 77(77.0%) | 8(8.0%) | 100(100.0%) |

Normal value of CRP in the neonates was taken as 10mg/dl. The value of CRP in the neonates more than 10mg/dl was taken as increased CRP. Amongst the sepsis proven cases, it was observed that 18.4% had normal CRP, 81.6% had increased CRP and no case had decreased CRP. Similarly in

the sepsis probable (total 62/100 cases) it was observed that 12.9% had normal CRP, 74.1% had increased count and 12.9% had decreased CRP.

**Table 6 :** Distribution of cases on the basis of Blood Culture

| Diagnosis | Blood Culture | | | Total |
|---|---|---|---|---|
| | No growth | Staphylococcus Aureus | Klebsiella Pneumonia | |
| **Sepsis Proven** | 0 (0.0%) | 30 (78.9%) | 8 (21.0%) | 38(38.0%) |
| **Sepsis Probable** | 62(100.0%) | 0(0.0%) | 0(0.0%) | 62(62.0%) |
| **Total** | 62(62.0%) | 30(30.0%) | 8(8.0%) | 100(100.0%) |

Bacteriologically culture positive cases were found in 38(38.0%) of the total 100 clinically suspected neonates. Bacteriologically culture negative but sepsis screen positive cases were found in 62 (62.0%) of the total 100 neonates. Bacteriologically negative, sepsis screen negative but clinical course compatible with sepsis were found in 45 (30%) neonates. There was marked association of neonatal sepsis with staphylococcus comprising 78.9% (n=38) in sepsis proven cases.

**Table 7:** Comparison of diagnostic performance of various laboratory parameters

| | TLC | ANC | Platelet Count | Band Form | I:T Ratio | CRP |
|---|---|---|---|---|---|---|
| **Sensitivity** | 63.2% | 21.1% | 28.9% | 78.9% | 38.0% | 81.6% |
| **Specificity** | 74.2% | 88.7% | 96.8% | 16.1% | 62.5% | 25.8% |
| **PPV** | 60.0% | 53.3% | 84.6% | 36.6% | 92.1% | 40.3% |
| **NPV** | 76.7% | 62.5% | 69.0% | 55.6% | 34.1% | 69.6% |
| **FP** | 25.8% | 11.2% | 3.2% | 83.8% | 37.5% | 74.2% |
| **FN** | 36.8% | 78.9% | 71.0% | 21.1% | 62.0% | 18.4% |

CRP had shown the highest sensitivity followed by band forms and the I:T ratio. Platelet count had shown the highest specificity followed by ANC and TLC. I:T ratio had shown the highest positive predictive value. TLC had shown the highest negative predictive value.

## Discussion

Definitive diagnosis rests upon a positive blood culture, to identify the pathogen and determine its antibiotic susceptibility pattern, but for better survival and outcome, simple and rapid diagnostics tests are required as adjuncts to the blood culture for early and effective initiation of treatment for the septicemia in neonates.

Neonatal sepsis continues to be major scare for its high risk of morbidity and mortality in developing countries. Neonatal sepsis in the developed countries is estimated to range from 10 to 25 %, while the exact figures for developing countries are not known. [11]

Diagnosis and management of sepsis is a great challenge which neonatologists are facing in the NICUs. Clinical diagnosis of presentation is difficult due to non specific signs and symptoms. [12]

Although blood culture is the "Gold Standard" for the diagnosis of sepsis, reports are available after 48-72 hours and they may be affected by intrapartum antibiotic administration to the mother.

A panel of these hematological parameters can provide valuable information to the clinician in suspected cases of neonatal sepsis. Hematological parameters are easy, quick and readily reproducible. [6]

**Incidence of sepsis:** In present study, out of the total 100 neonates evaluated, 38.0% showed positive blood culture and were reported as sepsis proven and 62.0% which showed negative blood culture were reported as sepsis probable due to

clinical parameters. Ghosh et al[14] studied 103 neonates, out of which 28.5% cases were reported as sepsis proven showing blood culture positive. K J Desai et al [15] studied 140 neonates and found blood culture positivity in 46.2% cases. Hence, our study also correlates well with these figures.

**Age and sex incidence**: Neonatal period ranges from birth to 28 days of life. In our study, out of 100 neonates, 65were males and 35 were females. In sepsis proven cases, 28(73.7%) were males. Similar findings as elicited in our study were cited by Mohammad f. Ibraheem[16],M Khassawne et al[17] stating male infants are more likely to develop sepsis than females.

**Gestational age:** In present study, 92.1 % of the cases of sepsis proven and 82.3% of sepsis probable cases had full term as gestational age. In our study 86.0% cases were full term and 12.0% cases were pre term. This findings also correlates well with the results of Makkar et al[18] study, where in (57.0%) cases were pre term and 43.0% were full term. Munazzasaleem et al[19] reported 63 (57.0%) neonates were preterm and 47 (43.0%) were full term.

**Clinical presentation:** The most commonly seen clinical feature of neonatal sepsis was respiratory distress which was also associated in some cases with grunting in the study of Ghosh et al [14], Tallur et al. [20] also noted in their studies that cardiorespiratory signs are the commonest form of presentation. Other clinical features found in our study were jaundice, fever, vomiting and CNS symptoms which is affirmed by the study of Mohammad f. Ibraheem. [16]

**Risk factors:** In our study, premature rupture of membranes (PROM) was seen in 43.0% of total cases of septicemia, meconium aspiration in 27.0% of total cases of septicemia and caessarian section was seen in 13.0% and the same correlates well with the studies of Mohammad f. Ibraheem[16] who cited PROM as a risk factor in 45.2% cases and caesarean section in 64.3%. Munazzasaleem etal [19] reported PROM constituting to 38.8 % cases and caessarian section to 35.8% cases.

**Organisms isolated:** In contrast to the developed world where GBS continues to be the most common bacterial pathogen, studies from developing countries have identified gram negative organism as the more frequent infecting agent. In some studies Staphylococcus Aureus was most frequently isolated. In our study, Staphylococcus Aureus and Klebsiella were the commonest organisms isolated.

| | Ghosh et al [14] | Mohammad f. Ibraheem[16] | Our study |
|---|---|---|---|
| Staphylococcus Aureus | 27% | 30.8% | 30.0% |
| Klebsiella Pneumoniae | 17% | 31.3% | 8.0% |
| E.coli | 30% | 68.4% | - |
| Pseudomonas Aeruginosa | - | 20 | - |

**C-reactive proteins:** C-reactive protein levels were raised in 31(81.5%) of sepsis proven cases and 46 (74.1%) of sepsis probable cases in the present study.

| | Sensitivity | Specificity |
|---|---|---|
| Our study | 81.6% | 25.8% |
| M Khassawne et al [17] | 88.9% | 85% |
| Chanden et al[21] | 83.0% | 42% |

A study by Chandana et al [21] revealed that CRP is the most useful single test with a high degree of sensitivity 83.0%, specificity 42.0% and positive predictive accuracy 57.0%.

**Performance of individual haematological findings**

1. Total band forms: Ghosh et al[14] and Narasi-mha[22] et al reported that Immature PMN count is sensitive indicator of neonatal sepsis. In our study 78.9% of neonates with culture positive sepsis and 83.9% of neonates of the probable sepsis had elevated band cell counts.

| | SENSITIVITY (%) | SPECIFICITY (%) |
|---|---|---|
| Present study | 78.9 | 16.1 |
| Ghosh et al [14] | 85 | 90 |
| Makkar et al [18] | 96.87 | 91.66 |

The present study showed band cell count is more sensitive indicator than specific.

2. **I/T ratio:** Ghosh et al[14] and Narasimha[22] **et al** reported that immature PMN count and I:T PMN ratio is sensitive indicator of neonatal sepsis.

| | SENSITIVITY (%) | SPECIFICITY (%) |
|---|---|---|
| Present study | 38.0 | 62.5 |
| Ghosh et al [14] | 93 | 89 |
| Narasimhaet al [22] | 93.75 | 94.44 |

Elevated I:T ratio was found to be the most reliable indicator of sepsis in Makkar et al[18] study, and also in various other studies like those done by Ghosh *et al*[14] and Narasimha *et al.*[22]

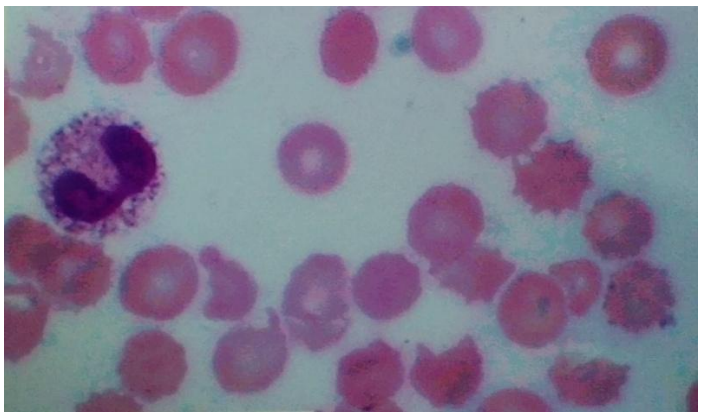

**Image 1:** Band cell with toxic granulation (10x100)

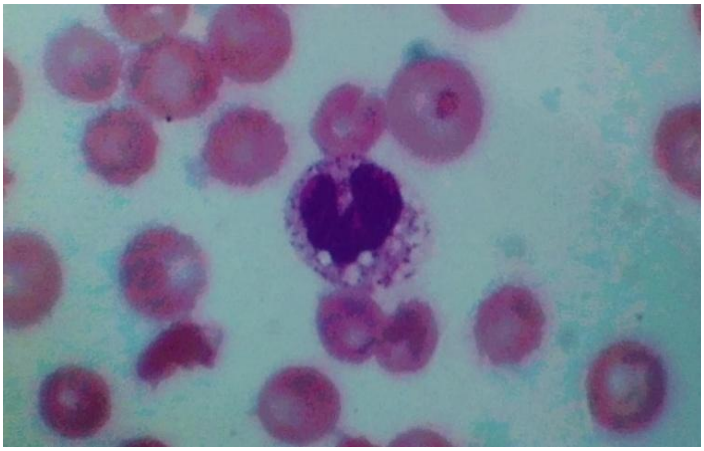

**Image 2:** Band cell with toxic vacuolization (10x100)

## Conclusions

The hematological profile of neonates suspicious of having sepsis can be useful in rapid detection and allow prompt treatment therapy in hospitals. It is not practicable to subject a patient to all the markers available. Hence, it is always better to consider the clinical situations while interpreting the battery of tests. Combinations of markers are always considered superior to a single test. Therefore, the quest for better markers is on the rise now a days.

Systemic bacterial infection in the newborn creates a significant burden due to its impact on neonatal mortality and long term morbidity. In spite of ongoing efforts in early diagnosis, treatment and prevention, neonatal sepsis still remains an enigmatic area for neonatologists due to changes in epidemiology and the lack of ideal diagnostic markers. The need for a biomarker with high diagnostic accuracy and reliability is paramount as a guiding tool for physician to assess the risk of infection and need for antibiotic therapy. Some studies are currently going on in search of a novel marker for neonatal sepsis.

The most common neonatal risk factors that increases the incidence of sepsis were the age of mother, home delivery, early rupture of membranes, fever and infection during pregnancy. Early onset sepsis was more common than the late onset one.

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