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Research Article

A ONE-YEAR STUDY ON DIAGNOSTICS FOR EARLY DETECTION OF NEONATAL SEPSIS

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A B S T R A C T

It is necessary for a time demanding diagnostic modality to be rapid, sensitive and cost-effective with higher specificity to reduced neonatal mortality and morbidity. The study was carried out to find out the diagnostic utility of haematological scoring system (HSS) for early detection of neonatal sepsis. This prospective study was conducted in Armed Forces Institute of Pathology (AFIP), Dhaka from May 2018 to April 2019. 100neonates with predisposing perinatal risk factors for sepsis were enrolled in the study. The haematological findings were analyzed according to the haematologic scoring system (HSS) of Rod well *et al*. On evaluation of various laboratory test, IT ratio (>0.2), IM ratio (> 0.3), total immature PMNs count, platelet count were found to have optimal sensitivities and negative predictive values. This study implies that HSS score >2 are more reliable as a screening tool for sepsis than any of the individual haematological parameter.

INTRODUCTION

Sepsis is defined as a systemic inflammatory response syndrome (SIRS) associated with infection diagnosed either on microbiological cultures or strong clinical evidence of infection [1]. Neonatal sepsis is a clinical syndrome resulting from pathophysiologic effects of local and systemic infection in the 1st month of life. Septicaemia usually consists of bacteraemia with a constellation of signs and symptoms caused by microorganisms or their toxic products in the circulation[2]. Neonatal infections currently cause 1.6 million deaths annually in developing countries. Sepsis and meningitis responsible for most of these deaths [3]. Neonatal sepsis is an important cause of neonatal morbidity and mortality; it is responsible for about 30-50% of total neonatal deaths in developing countries[4]. According to UNICEF the Neonatal Mortality Rate of Bangladesh in 2017 is 18.4 per 1000 live births [5].The newborn infants are more prone to bacterial invasion than the older children and adults due to weaker immune system[6] . The infection can be contracted either from mother via trans-placental route, ascending infections, during passage through an infected birth canal or exposure to infected blood at delivery [7]. Group B Streptococcal (GBS) disease is the most important cause of neonatal sepsis in Europe and North America, but there is preponderance of gram negative organism in tropical and developing countries[8]. It has been seen that gram negative organism are leading pathogen in Bangladesh [9].

Diagnosis of neonatal septicemia may be difficult as early signs are subtle and nonspecific, but its early detection is critical also, as the illness can be rapidly progressive and sometimes fatal. Blood culture is still considered as a gold standard for diagnosis of septicemia, however it is time consuming, requires well equipped set up and sometimes yield is low Therefore to avoid irrational use of antibiotics just based on clinical suspicion, various other reliable hematological laboratory tests giving quick results have also been evaluated. Among them complete blood count along with the various PMN parameters and C- reactive protein are most frequently used at different diagnostic centre as well as Armed Forces Institute of Pathology(AFIP). Considering above all drawbacks of blood culture, the present study was done to evaluate and highlight the importance of simple, quick, cost effective, commonly used diagnostic tests which may aid clinicians to reach a probable diagnosis, avoiding unnecessary use of antibiotics and decreasing death toll.

Objectives of the Study

General objectives

To study different diagnostic test commonly done for early detection of neonatal sepsis in AFIP in last one year (May 2018 to April 2019).

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Specific objectives

1. To analyze the diagnostic utility of hematological scoring system (HSS) and its correlation with C-reactive protein and blood culture in neonatal sepsis.
2. To assess the role of HSS in early detection of neonatal sepsis.

MATERIALS and METHODS

This was a prospective cross sectional study conducted in Armed Forces Institute of Pathology (AFIP), Dhaka cantonment, Dhaka during a period of 12 months from 1st May 2018 to 30th April 2019. Study population was 100 patientswho were clinically diagnosed as a case of Neonatal Sepsis & got admitted at Department of Neonatology, Combined Military Hospital (CMH), Dhaka and different blood specimen sentto AFIP for early detection.

Selection criteria

Inclusion criteria

Neonates were enrolled in the study if there were predisposing perinatal factors or if there was clinical suspicion of sepsis.

Exclusion criteria

a. Neonates with major congenital anomalies
b. Neonates with inborn errors of metabolism, haemolytic jaundice.

Procedure of collecting data

CBC, CRP, Blood C/S reports of patients sample in AFIP from May 2018 to April 2019 were reviewed of total 100 neonates who were clinically suspected with sepsis were selected for the study.

Ethical measures

a. Participation was volunteered.
b. Verbal consent was obtained after a brief of the study to parents of all patients.
c. It was made clear to them that they were free to take part or refuse any part of the study.
d. All the investigation reports were kept confidential.

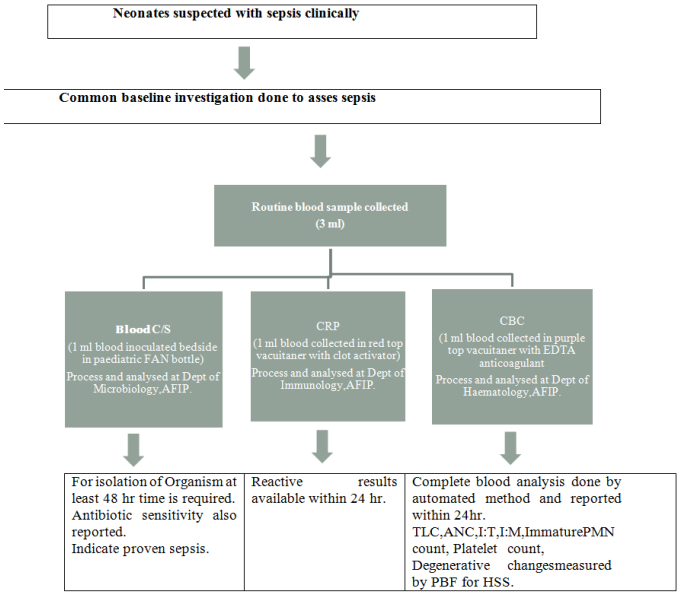
Data analysis

After completion data were checked, verified, edited, and coded. Data was compiled and statistically analyzed by using IBM SPSS 20 software. For any analytical test the level of significance is 0.05 and p value <0.05 will be considered significant.

Collection and processing of specimens

Newborn babies with sign and symptoms of septicemia and aged 0 to 28 days were included in this study. Sample collection was done under all aseptic precautions. The phlebotomist wears a sterile gloves prior to the procedure & prepared a patch of skin approx. 5-cm in diameter over the proposed venipuncture site. This area was cleansed thoroughly with alcohol including 1.5% chlorhexidine, followed by povidine iodine & followed again by alcohol including 1.5% chlorhexidine. Povidine iodine was applied in concentric circles moving outwards from centre. The skin was allowed to dry for at least 1 minute before the sample was collected. With all aseptic precaution at least 3 ml of blood was withdrawn from suspected sepsis patients in within 24 hours of admission. The top of the rubber stopper of the blood culture receptacle were disinfected with 70% alcohol and 1 mL of blood was introduced into blood culture FAN bottle at bed side and sent to department of microbiology, AFIP for culture and sensitivity. 1 ml sample was taken in red top vacutainer for C reactive protein and semple send to department of Immunology, AFIP. 1 mL sample was anticoagulated with EDTA in purple top vacutainer and using SYSMEX XT 2000i automated haematology analyzer, (JAPAN), values of total leucocyte count (TLC) and platelets were noted . Peripheral blood smears were stained by Leishman method. Differential leucocyte counts (DLC), total neutrophil count (TNC), immature neutrophil count (I) (including band form) mature neutrophil count (M) were performed. IT (immature to total neutrophil) ratio and IM (immature to mature neutrophil) ratio were calculated. IT ratio is calculated dividing the total immature count by total neutrophil count (including both mature and immature neutrophil count). Degenerative changes (toxic granulation, vacuolation and Dohle bodies) which were seen with Leishman stained slides and graded as 0-4+ according to Zipusky*et al.*[10]. Sensitivity, Specificity, PPV and NPV were calculated for hematologic score. Rodwell *et al.* formulated a scoring system in their study based on normal values, defined by Manroe*et al.*[11].

Order of Study



Clinically used HSS for early detection of Neonatal Sepsis:

To assess the neonates clinically presented with sign symptom of sepsis the following scoring system (HSS) used worldwide since 1988 Rodwell *et al.*[11].

Haematological scoring system (HSS)

Criteria	Abnormality	Score
TLC(cells/cmm)	<5,000 or >20,000 at Birth <5,000 or >30,000 at 12-24h <5,000 or >21,000 at day 2 onward	1
ANC(cells/cmm)	7,800-14,500(<72hours) 1,750-4,500(>72hours)	1
Immature PMN count(cells/cmm)	500-1,450(<72hours) 500(upto 28 days)	1
I:T	≥0.2	1
I:M	≥0.3	1

Platelet count (cells/cumm)	<150,000	1
Degenerative changes in neutrophils	Toxic granules, cytoplasmic vacuoles and dohle bodies	1

Interpretation of HSS

Score	Interpretation:
< 2	Sepsis is very unlikely
>2	Sepsis is suspected

Minimum score: 0 Maximum score: 8(If no mature PMNs are seen in blood film, score 2 rather than 1)

RESULTS

Studied Population

Study population was patientswho were clinically diagnosed as a case of Neonatal Sepsis & was admitted at Department of Neonatology, Combined Military Hospital , Dhaka and different blood specimen sent to AFIP for early detection from 1st May 2018 to 30th April 2019.

Table I Distribution of sex of the patients(n=100)

Sex	Frequency	Percent
Male	69	69%
Female	31	31%
Total	100	100%

Table- I revealed that out of the 100 neonates, 69 (69%) were males and 31(31%) were females resulting in an overall male to female ratio of 2.22:1.

Distribution of EONS & LONS

Neonatal sepsis may be classified according to the time of onset of the disease: early onset (EOS) and late onset (LOS). The distinction has clinical relevance, as EOS disease is mainly due to bacteria acquired before and during delivery, and LOS disease to bacteria acquired after delivery (nosocomial or community sources). In the literature, however, there is little consensus as to what age limits apply. A few papers distinguish between early onset (within 72 hours), EONS, and LONS (more than 4 days) sepsis. Very late onset sepsis is demarcated by onset at >30 days of age.

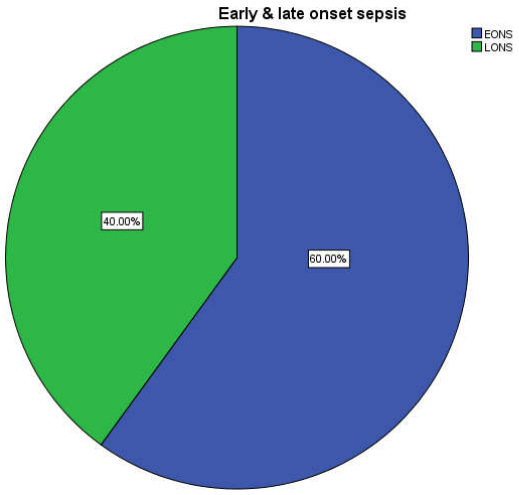


Fig 1 Pie diagram for distribution of EONS& LONS

Fig- 1 showed that 60(60%) neonates presented with sepsis within 3 days of life, classified as Early Onset Neonatal Sepsis (EONS) and 40 (40%)neonates presented later within 4days to 28days recognized as Late Onset Neonatal Sepsis(LONS) group.

Distribution of CRP result

CRP is one of the most extensively studied, most available, and most frequently used laboratory tests for the diagnosis of neonatal sepsis . CRP is an acute phase reactant synthesized by the liver. It has a half- life of 24–48 h. It takes 10–12 h for CRP to change significantly after onset of infection. Serial determination of CRP increases its sensitivity. Serial CRP measurements may also be helpful in monitoring the response to treatment in infected neonates and thus may help clinicians guide the duration of antibiotic therapy. The specificity and positive predictive value of CRP ranges from 93–100%. Thus, CRP can be considered as a "specific" but "late" marker of neonatal infection. If the CRP levels remain persistently normal, it correlates strongly with the absence of infection thereby guiding safe discontinuation of antibiotic therapy.

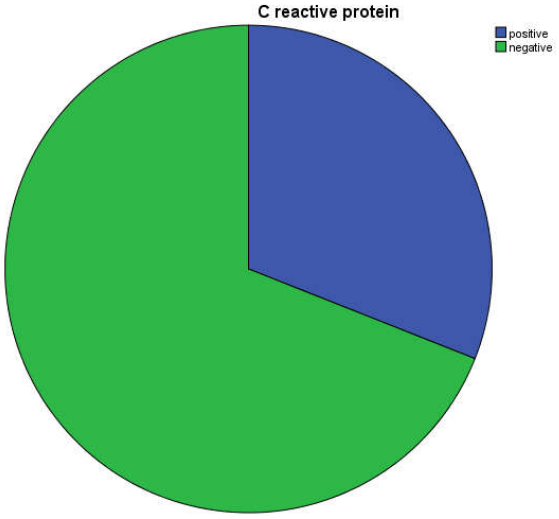


Fig 2 Pie chart for distribution of CRP result

Fig 2 showing out of 100 neonates, CRP was positive (>6 mg/L) in 31(31%) cases.

Blood culture study

Since sepsis is a systemic inflammatory response to infection, isolation of bacteria from blood is considered the gold standard for the diagnosis of sepsis. However, it takes 24–48 h for culture results. Inoculation of only 0.5–1.0 ml of blood decreases its sensitivity, as approximately 60–70% of infants have a low level of bacteremia. Theoretically, for optimal results, 6 ml of blood would be required which is not feasible. Sepsis cannot always be excluded even when blood cultures are found to be negative. Conversely, isolation of bacteria in a blood culture may reflect asymptomatic bacteremia or contamination. Morever, it is not error free because it can be falsely sterile because of insufficient sample volumes, intermittent or low-density bacteremia, or suppression of bacterial growth by earlier antibiotic administration.

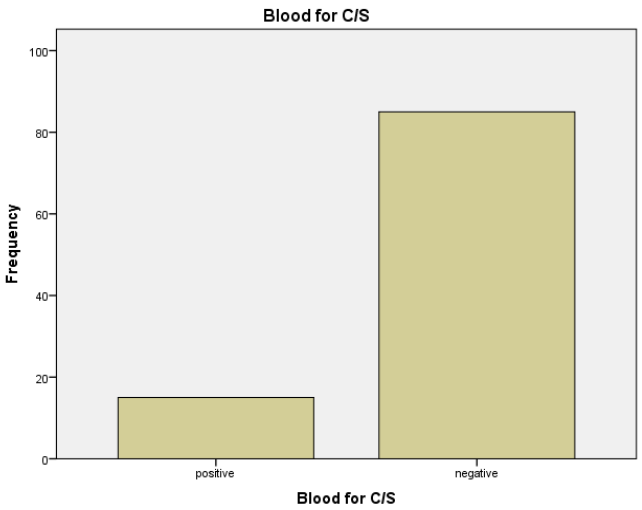


Fig 3 Bar Diagram showing distribution of blood culture result

Fig- 3 revealed that out of 100 neonates, culture was found positive in21(21%) cases and negative in 79 (79%) cases.

Table II Spectrum of organism in NICU(n=21)

Organism	Frequency	Percent
Staphylococcus aureus including MRSA	4+5	42.86%
Coagulase Negative Staphylococcus	2	9.52%
Pseudomonas	4	19%
Stenotrophomonasmaltophilia	1	4.76%
Klebsiella	3	14.29%
Acinetobacter	2	9.52%
Total growth in blood culture	21	100%

Table- II showing out of21 culture positive cases,9 (42.86%) cases were found culture positive with Staphylococcus aureus along with 5 MRSA cases. Pseudomonus species and gram negative organisms were also isolated.

Haematological parameters

In order to improve the outcome associated with neonatal sepsis, it is necessary for a diagnostic test to be rapid and sensitive to decrease delay in treatment. At the same time in order to avoid unnecessary exposure to antibiotics and invasive procedures, a test with higher specificity is needed. A large number of studies have been performed to evaluate the use of complete blood count (CBC), differential count, and immature to total leukocyte ratio (I:T) for the diagnosis of neonatal sepsis. Although the CBC has a poor predictive value, serial normal values can be used to enhance the prediction that bacterial sepsis is not present. Low WBC and absolute neutrophil counts, as well as high immature-to-total neutrophil ratio (I:T) are associated with an increased risk of infection. However, the sensitivity for detection of sepsis is low. Two serial normal CBCs, performed 8 to 12 h apart, and a negative blood culture at 24 h improve the predictive power to rule out EOS in the first 24 h after birth. Components of the white cell count, including absolute neutrophil count (ANC) and immature to total neutrophil ratio (I:T) have been shown to be more useful for excluding infants without infection rather than identifying newborns who are infected. The maximal (I:T) ratio in uninfected newborns is 0.16 in the first 24 h, which by 120 h decreases to 0.12.50 I:T ratio of >0.2 is suggestive of sepsis. However the WBC, ANC, and I/T ratio have significant limitations in the diagnosis of neonatal sepsis.

Table III Comparison of hematological scoring system with culture results (n=100)

Hss	Culture positive	Culture negative	Total
<2	**6**	**49**	**55**
>2	**15**	**30**	**45**
TOTAL	**21**	**79**	**100**

Table- III revealed that among 21 culture-positive cases, 15(71.43%) showed hematological score >2 and 6(28.57%) showed score <2. Out of 79 culture-negative cases, 49 (62%) cases had score <2 and 30 (38%) cases had score >2.

From Table-III, performance of HSS with proven sepsis has been carried out as follows:

Sensitivity – 71.43%
Specificity – 62%
PPV – 33.33%
NPV – 89%

Table IV Haematological scoring system comparison with C‑reactive protein (n=100)

HSS	CRP (+)	CRP(-)	Total
<2	8	45	53
>2	23	24	47
TOTAL	31	69	100

Table- IV showing out of 100 cases, 31 (31%) patients were positive for C-reactive protein (CRP), among them 23(74%)cases had haematological score >2 and 8(26%) cases with score <2. Out of 15 culture-positive patients, 8(53%) cases were also CRP reactive and 7(47%) cases showed CRP non-reactive.

Table V Performance of individual haematological findings in 15 neonates with proven sepsis

Haematologic Test	Sensitivity%	Specificity%	Positive predictive value%	Negative predictive value%
TLC	33	83	25	88
Total PMNs	53	47	15	85
I:T ratio (>0.2)	93	86	53	99
I:M ratio (> 0.3)	93	88	58	99
Immature PMNs	86	74	37	97
Platelet count (<150/mm3)	33	85	28	88

Table- V showed total leucocyte count(TLC) showed high specificity (83%) but least sensitivity (33%). ANC showed high NPV (85%) but least PPV (15%). I:T ratio showed high specificity (86%) and high sensitivity (93%). I:M ratio showed high specificity (88%) and high sensitivity (93%). Immature PMNs showed High sensitivity (86%) and high NPV(97%). Platelet count showed high NPV (88%) and low positive predictive value (PPV) (28%).

DISCUSSION

The early diagnosis of neonatal septicemia is primarily based on clinical evaluation but laboratory diagnosis requires a microbiologic-clinical correlation. In this study 15% neonates were considered as proven sepsis by blood culture. However suspected sepsis groups (85%) comprises a difficult diagnostic group and could not be ignored, because fatal infection had been reported in other study in the presence of negative blood culture[11]. Total leukocyte count (TLC) is of little clinical use in the diagnosis of neonatal infection because of wide variation

in values. In this study TLC was not increased in all cases due to early collection or previous low level.

Sensitivity of TLC was 33%, specificity of 83%, with PPV 25% and NPV 88% which were consistent with others[11,12]. So observation from this study showed that total leucocytes counts acts as a good parameters for confirmation of sepsis. Neutropenia has been more common in association with sepsis, compared with neutrophilia, probably because of increased adherence to altered endothelial cells and utilization at the site of infection[13]. In this study, total PMNs leucocytes count 1,750-4,500 cells/mm^3 (<72 hrs) and 7,800-14,500 cells/mm^3 (>72 hrs) had a sensitivity of 53%, specificity 47%, PPV 15% and NPV 85%. Similar results were observed by various studies[14-15]. In this study the total PMNs count was associated with low positive predictive value and low specificity. Therefore, it should not be used in isolation as a predictor of sepsis. A shift to the left in differential white cell count with a raised immature neutrophil count (band form) has been documented in patients with bacterial infection. In present study total PMNs count with cut off value 500- 1,450 cells/mm^3 (<72 hrs of age) and >500 cells/mm3 (>72 hrs of age) had sensitivity of 86%, specificity 74%, PPV 37% and NPV 97%. This result was similar to the observation of studies of Ghosh *et al.*[15], Rodwell, Lesilie, and Tudehope[11] except specificity and positive predictive value. In this study specificity was low due to higher number of false positive results. Despite a significant rise in immature neutrophil count in neonates with suspected infection, various cut off values were examined which gave low specificity and large number of false positive result. Therefore this parameter alone should not be evaluated for diagnostic purpose. In the present study, I/T ratio >0.2 had a sensitivity, specificity, PPV and NPV of 93%, 86%, 53% and 99% respectively. In this study specificity and positive predictive value was low because of large number of false positive results. While an I/T ratio >0.2 suggested by Rodwell, Lesilie, and Tudehope[11] had a sensitivity of 96%and NPV of 99%. So this result for an elevated I/T ratio were consistent with other reports[12,13]. The sensitivity of I/M ratio (>0.3) was 93%, specificity 88%, PPV 58% and NPV 99%. Rodwell, Lesilie, and Tudehope[11] used I/M ratio (>0.3) as a predictor of infection and sensitivity 93%, specificity 81%, PPV 32%and NPV was 99%. Gosh *et al.*[15] found similar results. Considering high mortality and morbidity associated with sepsis, tests with high sensitivity and NPV are mostdesirable because all infants with sepsis have to beidentified[14].

Neonates with sepsis develop thrombocytopenia, possibly because of disseminated intravascular coagulation (DIC) and the damaging effects of endotoxin on platelets. In this study we found thrombocytopenia in 18% cases with sensitivity of 33%, specificity 85%, PPV 28% and NPV88%. This parameter could be used as an early but nonspecific marker for sepsis. These results were consistent with other study[16,17]. To minimize the unnecessary use of antibiotics in false positive cases, tests need tohave a reasonably high specificity and good predictive value. As no single individual haematological parameter is superiorin comparison to another in predicting neonatal sepsis, acombination of these parameters in the form of HSS hasbeen recommended. Haematologic scoring system (HSS) should improve the efficiency of the CBC as a screeningtest for sepsis until a reliable diagnostic test is available. The HSS has practical advantages; it is applicable to all infants, including those who have received antibiotic therapy prior to evaluation and simplifies the interpretation of haematologic profile. In this study score >2 was highly significant ($P<0.05$), but sensitivity of 71.43%, specificity of62%, PPV 33.33%, NPV 89%. These results were consistent with other studies[11,18]. Considering the high sensitivity and negative predictive value this study implies that score > 2 was more reliable as a screening tool for sepsis than any of the individual hematological parameter. Neonatal sepsis is a life-threatening yet treatable condition. Non- infectious disorders may produce haematological changes similar to those seen with infection, thereby compromising the specificity and positive predictive value of the screening tests.

CONCLUSION

Haematological scoring system (HSS) are simple, quick, and cost-effective tool even at the primary health care center level as routine screening of all clinically suspected cases of neonatal septicaemia. In our study HSS (score >2) may provide an effective guideline regarding judicious use of antibiotic therapy which will be life-saving, provide early cure, reduced mortality, shorten the hospital stay, and minimize the risk of emergence of resistant organism due to misuse of antibiotics. A comprehensive laboratory information system in connection with hospital is the utmost important for early detection of neonatal sepsis and follow-up.

Recommendation

Based on the study findings the following recommendation can be made

- As the normal range of TLC, ANC varies with age of the neonates in hour, in test requisition age of the patient in hour need to be mentioned specially 1st day of life.
- Serum Procalcitonin can be used in sepsis screening as this acute phase protein detection test is currently available.
- Further studies are also required to determine a novel marker for early detection of neonatal sepsis.

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