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Correlation of Gastric Aspirate Polymorphs And Acute Phase Reactants (M-Esr, Crp And Band Cell Count) With Blood Culture In Early onset Neonatal Sepsis – A Tertiary Care Study

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Abstract
Introduction*: Mortality due to early onset neonatal sepsis is much higher than late onset sepsis. Clinical manifestations of the early onset sepsis are non specific. Delay in treatment can lead to complications and death of the neonates.*
Objective: *To detect the sensitivity, specificity and the positive predictive values of the gastric aspirate polymorphs and the acute phase reactants in relation with the blood cultures of the neonates with early onset sepsis.*
Materials And Methods: *Study was conducted at a tertiary care center. 50 neonates were included in the study. Investigations like blood culture, CRP, micro ESR, band cell count and gastric aspirate polymorphs count was done. All the observations were recorded. The sensitivity, specificity, positive predictive value and the negative predictive values were calculated based on the observations.*
Results: *In the present it was seen that 41.02% of the cases of neonatal sepsis with GA polymorphs have a sensitivity of 72.72 %, and a positive predictive value of 41.02 % with blood culture. In regard to neonatal sepsis, m-ESR was found to be correlated with a sensitivity and specificity of 54.54% and 67.85 % respectively. In cases of neonatal sepsis, sensitivity and specificity of band forms and blood culture is 78.57% and 75% respectively.*
Conclusion: *The present study concludes that CRP and Band forms are useful in the early detection of early neonatal sepsis as both have high sensitivity, specificity and positive predictive values.*
Keywords: *Band forms, blood cultures, CRP, early onset neonatal sepsis, gastric aspirate polymorphs, micro ESR, positive predictive values, sensitivity, and specificity.*

I. Introduction

Sepsis is a major cause of morbidity and mortality in the neonatal period[1]. Neonatal sepsis is classified depending on the hours of presentation into [2]1) Early onset: within first 72 hours of life. 2) Late onset: occurring after 72 hours of life. Early onset neonatal sepsis is often due to organisms present in the maternal vaginal flora.[2] Mortality in this condition is much higher than in late onset sepsis. Early diagnosis and prompt antimicrobial therapy is necessary for managing this condition. Infection in early neonatal period is one of the important factors responsible for high perinatal mortality and neonatal morbidity in developing countries. Early manifestations of neonatal septicemia are vague and nonspecific[2]. Delay in the institution of antimicrobial therapy is fraught with dangers of several complications and increase in mortality. Isolation of the infecting organism from blood provides the definitive diagnosis and is considered as the 'gold standard'. However, this culture procedure takes at least 48 hours to confirm the diagnosis. Therapy cannot wait this long in a critically sick neonate. On the other hand the indiscriminate overuse of antibiotics on the basis of clinical suspicion alone is hazardous for any neonatal unit, because it will lead to emergence of resistance. Hence, to rationalize antimicrobial therapy in neonatal sepsis, certain indirect early markers of neonatal infections have been identified.

There are various predisposing factors that lead to an increased neonatal susceptibility to infection. These include[1]:a) VLBW(<1500gms) or Preterm baby, b) Febrile illness in the mother during or within two weeks of delivery, c) Foul smelling liquor, d) PROM >12hrs, e) Frequent vaginal examinations (> three), f) Prolonged and difficult labor with instrumentation, g) Birth asphyxia and difficult resuscitation, h) Pathological evidences of funisitis or presence of polymorphs in the gastric aspirate. These risk factors operating during perinatal period are precise determinants of the ultimate neonatal outcome.
Markers for infection which are used for diagnosing are as follows[1]:

I) **Direct Markers Of Neonatal Infection[1]:** Cultures of blood, cerebrospinal fluid (CSF) and urine are taken before initiating antibiotic therapy.
II) **Indirect Markers Of Neonatal Infection[1]:** A number of early indirect markers of infection can be used as a mean of suspecting diagnosis of neonatal septicemia:
i) Leukocyte counts: ratios and morphology
ii) Micro erythrocyte sedimentation rate (m-ESR)
iii) Acute phase proteins: A number of acute phase proteins serve to indicate the presence of infection in the neonate.
a) Those increasing with inflammation are: i) CRP, ii) Alpha 1 acid glycoprotein, iii) Haptoglobin, iv) Alpha 1 antitrypsin, v) Fibrinogen
b) Those decreasing with inflammation are: i) Pre-albumin, ii) Transferrin

Role of gastric aspirate in the diagnosis of early neonatal sepsis[2]:

Several screening procedures have been in use like cultures of the cord blood, peripheral blood, ear canal debris, and histology of the umbilical placenta, whole mount of amnion and frozen sections of umbilical cord for evidence of vasculitis. Recently, microscopic appearances of fluid from the ear canal and gastric aspirate have been used as evidence of bacterial sepsis acquired in utero. Blanc[3] detected evidence of inflammation from a smear of the fetal surface of the placenta and presence of leucocytes in the gastric aspirate of the fetus. Bernirschke[4] introduced the technique of microscopic examination on rapid frozen sections of the umbilical cord and correlated umbilical wall inflammation with infection. Oliver[5] has suggested a relationship between the presence of polymorph nuclear cells in the gastric aspirate and the possibility of subsequent infection of the newborn. This method of using criteria of cells in the gastric fluid of an infant appears to be the simplest and one of the most readily carried out investigation without the requirement of specialized personnel and equipment. It can be done in a side laboratory. Thus, demonstration of bacteria and inflammatory cells in the gastric aspirate on the first day of life (within an hour of life) may reflect maternal amnionitis. Present study is conducted to correlate the gastric aspirate polymorphs and acute phase reactants (m-ESR, CRP and BAND Cell Count) with blood culture in early neonatal sepsis.

II. Aims And Objectives

a) To detect sensitivity; specificity & positive predictive value of Gastric Aspirate (GA) Polymorphs and Acute Phase Reactants (m-ESR, CRP and Band Cell Count) to diagnose early onset neonatal sepsis (i.e., with in 72 hrs of life).
b) To correlate between duration of rupture of membranes & other maternal risk factors (fever within 2weeks prior to delivery; foul smelling liquor) for positive sepsis screen with gastric aspirate polymorphs and Acute Phase Reactants.

III. Materials And Methods

The study was conducted in Department of Paediatrics, Niloufer hospital, which is a teaching institute and an allied hospital under Osmania Medical College, Hyderabad. The hospital is a tertiary care referral centre for both obstetric and pediatric patients. The hospital has a Level III NICU for neonatal emergencies. Fifty neonates with signs of early onset sepsis or with maternal risk factors for sepsis were included in the study.

The inclusion criteria for this study:

a. Neonates with symptoms & signs of sepsis.
b. Preterm less than 36 weeks or low birth weight less than 2500gms.
c. Maternal fever in preceding 2weeks.
d. Foul smelling liquor.
e. Premature rupture of membranes. (More than 12hours).
f. More than 3 vaginal examinations in labour.
g. Prolonged or difficult delivery with instrumentation.

The exclusion criteria for this study:

1. Full term healthy neonates with no maternal risk factors.
2. Inborn errors of metabolism, birth asphyxia & Meconium Aspiration Syndrome.
3. Transient metabolic states i.e. hypoglycaemia.
4. Physiological hypothermia.

After selecting the neonate for study, their details were recorded as per fixed proforma containing identification data, detailed history,findings of clinical examination & investigation results.

The following investigations were done for all the neonates selected for the study:-

a. Gastric aspirate for polymorphs.
b. Haemoglobin, TC, DC with Band Cell Count.
c. Peripheral smear for toxic granules.
d. Micro ESR.
e. CRP.
f. Blood culture.
g. CSF analysis (when indicated).
h. Urine, pus (from superficial focus) Culture [when indicated].
i. Babies were subjected to radiological investigations (when indicated).

Procedure of gastric aspirate cytology in neonates:

Immediately after baby was born with risk factors, NG tube was inserted and gastric fluid was collected and sent to the pathology department. There smear was done by standard technique by Leishman's stain and 200 cells were counted. The percentage of polymorph nuclear cells was calculated. The percentage of more than 5 cells per HPF was considered as positive for infection.

Interpretation of results: The results of the above sepsis screen panel were interpreted in the following manner.

a. GA showing > 5 polymorphs/high power field (HPF) is considered positive.
b. CRP was done by a semi quantitative method and a value of > 1 mg/dL has been considered positive.
c. Band cell count of more than 20% of total leukocyte is considered as positive
d. Micro-Erythrocyte Sedimentation Rate (micro-ESR) value greater than 15 mm after 1 hour at any age has been considered positive.
e. Blood culture done in every case of suspected sepsis and the results compared to that of the screening tests.

Blood Culture and antibiotic sensitivity was done using appropriate media and disk diffusion method respectively.

The following investigations were done for all the mothers selected for the study:-

a. High vaginal swab during labour.
b. Total & differential counts.

Iv. Observations & results

Out of the 56 cases of suspected neonatal sepsis that were selected for the study, six cases were excluded from the study as they manifested features of hypoglycemia which was confirmed by glucose estimation (<40.0mg/dL). Hence, only 50 cases were included in the study (N=50).

Table I Sex Wise Distribution Of The Neonates With Sepsis (N=50)

Sex	N=50(%)
Male	28 (56%)
Female	22 (44%)

In present study, males (56%) are more than females (44%) with a ratio of 1.27: 1

Table Ii Positivity Of Ga Polymorphs, Acute Phase Reactants (M-Esr, Crp, Band Cell Count) And Blood Culture In Neonatal Sepsis (N= 50)

Serial No	Criteria	Positive (%)	Negative (%)
1	Ga For Polymorphs	39 (78%)	11 (22%)
2	Micro Esr	21 (42%)	29 (58%)
3	Crp	22 (44%)	28 (56%)
4	Band Cell Count	24 (48%)	26 (52%)
5	Blood Culture	22 (44%)	28 (66%)

Gastric aspirate for Polymorphs were observed in a maximum (78%) number of cases, and in a minimum (42%) in the 'increased micro ESR group. The gold standard of diagnosis, i.e. blood culture, was positive in 44% of the cases.

Table III correlation Between Sexes Of Neonates With Positive Blood Cultures (N=50)

Sex	No Of Cases=N (%)	Blood Culture +Ve=N (%)
Male	28 (56%)	12 (54.54%)
Female	22 (44%)	10 (45.45%)

In the present study, blood cultures were positive more in male neonates (54.54%) than in females (45.45%).

Table IV Comparision Of Ga Polymorphs And Blood Culture In Neonatal Sepsis (N=50)

Ga Polymorphs	Blood Culture	
	Positive	Negative
Positive (39)	16 (True Positive)	23 (False Positive)
Negative (11)	6 (False Negative)	5 (True Negative)
Total N=50	22	28

Sensitivity =16/22 x 100=72.72%,
Specificity=5/28 x 100=17.85%,
Positive predictive value=16/39 x 100=41.02%,
Negative predictive value=5/11 x 100=45.45%

From the above it is observed that in cases of neonatal sepsis, 41.02% of positive GA polymorphs were also blood culture positive. It could also be seen that 41.02% of the cases of neonatal sepsis with GA polymorphs have a sensitivity of 72.72 %, and a positive predictive value of 41.02 % with blood culture.

Table v
Comparision of m-esr and blood culture in neonatal sepsis (n=50)

M-Esr	Blood Culture	
	POSITIVE	NEGATIVE
Positive 21	12 (True Positive)	9 (False Positive)
Negative 29	10 (False Negative)	19 (True Negative)
Total N=50	22	28

Sensitivity =12/22 x 100=54.54%,
Specificity=19/28 x100=67.85%,
Positive predictive value=12/21 x 100=57.14%,
Negative predictive value=19/29 x 100=65.51%
With regards to neonatal sepsis, m-ESR & Blood culture was found to be correlated with a sensitivity and specificity of 54.54% and 67.85 % respectively.

Table Vi Comparison Of Crp And Blood Culture (N=50)

Crp	Blood Culture	
	Positive	Negative
Positive (22)	17 (True Positive)	5 (False Positive)
Negative (28)	5 (False Negative)	23 (True Negative)
Total N=50	22	28

Sensitivity =17/22 x 100=77.27%,
Specificity=23/28 x 100=82.14%,
Positive predictive value (PPV) =17/22 x 100=77.27%,
Negative predictive value (NPV) =23/28 x 100=82.14%
In cases of neonatal sepsis, CRP and blood culture was found to be correlated with a sensitivity and specificity of 77.27%and 82.14% respectively, with PPV of 77.27% and an NPV 0f 82.14%

Table Vii Comparison Of Band Forms And Blood Cultures (N=50)

Band Forms	Blood Culture	
	Positive	Negative
Positive (24)	18 (True Positive)	6 (False Positive)
Negative (26)	4 (False Negative)	22 (True Negative)
Total N=50	22	28

Sensitivity =18/22 x 100=81.81%,
Specificity=22/28 x 100=78.57%,
Positive predictive value (PPV) =18/24 x 100=75.0%,
Negative predictive value (NPV)=22/26 x 100=84.61%
In cases of neonatal sepsis, sensitivity and specificity of band forms and blood culture is 81.81% and 78.57% respectively, with PPV of 75% and an NPV of 84.61%.

Table Viii Correlation Of Ga Polymorphs & Acute Phase Reactants With Maternal Risk Factors (N=50)

Serial No	Criteria	Prom (N=7) (%)	Perinatal Fever (N=1) (%)	Foul Smelling Liquor (N=1) (%)
1	Ga Poly Morphs	5 (71.42%)	0	1 (100%)
2	M-Esr	2(28.7%)	0	0
3	Band Cell	1(14.28%)	0	0
4	Crp	1(14.28%)	0	1 (100%)
5	Blood Culture	2(28.7%)	0	0

Neonates born to mothers of PROM had GA polymorphs in 71.42%, whereas blood culture positive was seen in only 28.7%.

V. Discussion

Neonatal septicemia is a leading cause of mortality and morbidity in neonates. Early diagnosis will help the clinicians to decide on the usage of proper antibiotics which will help in reducing the morbidity and mortality. A positive blood culture is the only definitive method of confirming a case of septicemia. Culture and sensitivity tests require a minimum period of 48 hours which is a precious time in making decisions in the treatment of sepsis in newborns. Rapid Diagnosis by doing band cell count and CRP estimations give a reasonable degree of accuracy in diagnosis of neonatal septicemia. High index of clinical suspicion and early investigation helps clinicians in diagnosis and appropriate treatment. Abuse of antibiotics in case of conditions which simulate septicemia can thus be avoided.

Table Ix Comparative Study Of Blood Culture Positivity In Neonatal Sepsis

Serial No	Author	Percentage Of Positive Blood Culture
1	Guha Et Al[6]	40%
2	Namdeo Et Al[7]	50.08%
3	Rao P.S Et Al[8]	40%
4	Present Study	44%

In the present study, blood culture positivity is similar to studies by others.[6,7,8] In the present study blood culture positivity is found to be 44.0% The success in achieving a positive culture among other studies: Guha etal[6] reported 40.0%, Namdeo etal[7] reported 50.0% and Rao PS etal[8] reported 40.0%. However negative cultures do not rule out sepsis**.** Guha etal[6], 1978 reported 7 cases with negative blood culture but with fatal outcome and postmortem evidence of infection.

Table X Comparitive Study Of Ga Polymorphs In Early Neonatal Sepsis

Serial No	Author	Positivity (%)
1	Je Hg Jeoung Etal[9]	75%
2	Chandana Etal[10]	44%
3	Present Study	78%

In the present study positivity of GA polymorphs (78.0%) is comparable with Je HG Jeoung.YM etal[9]. Others[10] reported fewer figures due to the fact that the study included a less number of cases with maternal risk factors.

Table Xi Comparitive Study Of Micro Esr In Early Neonatal Sepsis

Serial No	Author	Sensitivity (%)	Specificity (%)
1	Anitha Sharma Etal[11]	60%	62.5%
2	P.K.Mishra Etal[12]	79%	82%
3	Walliullah Etal[13]	63.3%	60%
4	Present Study	54.54%	67.85%

The present study is similar to studies done by others [11, 13]. P.K. Mishra[12] observed the sensitivity and specificity to be higher than the present study as they considered more than 8mm in the first one hour as an increased m-ESR value.

Table XII Comparative Study Of Sensitivity&Specificity Of Band Forms In Early Neonatal Sepsis

Serial No	Author	Sensitivity (%)	Specificity (%)
1	Gerdes Js Etal[14]	65%	73%
2	S.N.Parida Etal[15]	84%	66%
3	Present Study	81.81%	78.57%

The present study is similar with other studies[14, 15]. In the past, the changes in the white blood cell parameters among neonates were regarded least useful for the diagnosis of sepsis as these values were thought to be too erratic. Gerdes JS etal[14] studied these changes more precisely in healthy and diseased neonates and established its usefulness as a supportive test for the diagnosis of neonatal sepsis. In the present study emphasis was placed on band forms because they constitute the first line of defense. More over neutrophils comprise the major cell population during immediate neonatal period. Present study correlate closely with the findings of other workers[14, 15.]Though the neonates are at a disadvantage due to poorly developed immune response, nonetheless they do respond to an infective insult as an older child. During an acute infection neutrophils are rapidly released from the neutrophils storage compartment to circulation, which manifest as band forms and provide potent cells for migration to infected tissues. In S.N.Parida etal[15] study, 7babies from both the groups had leucopenia and 71.0% of them died. This was due to either due to marrow failure or increase sequestration. This finding is remarkable when viewed in context that total neutrophils in both the groups did not differ significantly. Present study observations are in agreement with those of S.N.Parida etal[15,] who have cautioned that one should not be deceived by neutrophils count alone without noting alteration in the ratio of mature and immature neutrophils. Increased band count as a sensitive indicator of sepsis, as observed in present study has also been documented by other workers. It is apparent that while investigating septic neonates, increase in percentage of band forms in peripheral blood smear as an acceptable predictive value of 75 % as was observed in the present study. In neonates with fulminant infections, leucopenia may occur and band count is often unaltered.

Table Xiii Comparitive Study Of Sensitivity&Specificity Of Crp In Neonatal Sepsis

Serial No	Author	Sensitivity (%)	Specificity (%)
1	I.M.Singh Etal[16]	80%	91%
2	P.Kite Etal[17]	61.8%	81.2%
3	Berger Etal[18]	75%	86%
4	Present Study	77.27%	82.14%

In the present study, sensitivity, specificity of the CRP is similar to other studies[16, 17, and 18]. In the present study the blood culture was positive in only 44% cases**.** The low positivity of blood culture underlines the need of other tests in diagnosing neonatal septicemia. Out of the various individual tests for rapid diagnosis of neonatal septicemia, in proved sepsis group CRP was the one with maximum sensitivity (77.2%) and specificity of a (82.14%). Other workers have also observed similar high sensitivity and specificity with CRP, P. Kite etal[17] (61.80%, 81.20%) and Berger etal[18] (75%, 86%) respectively. Of the rapid diagnostic tests, CRP was found to be most useful when taken singly. Its elevation and returning to normal levels once the infection is controlled occurs in a matter of a few hours. Kite etal[17] have reported elevated CRP levels in 80%of cases of neonatal sepsis.

Table Xiv Comparitive Study Of Maternal Risk Factors With Blood Culture In Neonatal Sepsis

S No	Author	Prom	Culture Proven	Perinatal Fever	Culture Proven	Foul Smelling Liquor	Culture Proven
1	Betty Chacko Etal[19]	21	6 (5.7%)	1	0	3	0
2	Sangamitra Etal[20]	10	1 (1%)	1	1 (4%)	4	1 (4%)
3	Present Study	7	2 (28.5%)	1	0	1	0

In the present study, culture proven cases are more (28.5%) in PROM as compared to other studies[19, 20]. It could be due to intra partum antibiotics administration in other studies.

VI. Conclusions

Fifty cases of neonatal sepsis were studied to correlate the gastric aspirate polymorphs and acute phase reactants (mESR, CRP and BAND CELL COUNT) with blood culture in early neonatal sepsis. In present study, males (56%) are more than females (44%) with a ratio of 1.27: 1. Gastric aspirate for Polymorphs were observed in a maximum (78%) number of cases, and in a minimum (42%) in the ‘increased micro ESR group. The gold standard of diagnosis, i.e. blood culture, was positive in 44% of the cases. In the present study, blood cultures were positive more in male neonates (54.54%) than in females (45.45%). It is observed that in cases of neonatal sepsis, 41.02% of positive GA polymorphs were also blood culture positive. It could also be seen that 41.02% of the cases of neonatal sepsis with GA polymorphs have a sensitivity of 72.72 %, and a positive predictive value of 41.02 % with blood culture. In regard to neonatal sepsis, m-ESR was found to be correlated with a sensitivity and specificity of 54.54% and 67.85 % respectively. In cases of neonatal sepsis, sensitivity and

specificity of band forms and blood culture is 78.57% and 75% respectively and PPV was 81.82% and NPV was 84.61%. Neonates born to mothers of PROM had GA polymorphs in 71.42%, whereas blood culture positive was seen in 28.7%.

CRP can be used for screening of early neonatal sepsis as its sensitivity, specificity and positive predictive value is high, i.e. 72.2%, 82.14% and 77.2% respectively. Band Forms is one of the useful indicators for diagnosing neonatal Sepsis as its sensitivity, specificity and positive predictive values are high, i.e. 81.81%, 78.57%,75.0% respectively. Premature rupture of membranes (PROM) is a common maternal risk factor for early onset neonatal sepsis, as blood culture is positive in 28.7%. Sensitivity, specificity and positive predictive value of GA Polymorphs are 72.72%, 17.85%, 41.0% and micro ESR 54.54%, 67.85%, 57.14% respectively. In conclusion, CRP and Band forms are more useful than GA polymorphs and micro ESR in screening of early neonatal sepsis.

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