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Identifying early surrogate markers for blood culture positive sepsis in an urban NICU-A retrospective observational study

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ABSTRACT

Background: Neonatal sepsis is a major problem worldwide. Positive blood culture, the diagnostic gold standard is expensive, time consuming and yields result in limited cases. Hence reliable surrogate markers are needed.

Aims and Objective: To ascertain haematological parameters which are reliable adjuvants to blood culture for diagnosing Neonatal Sepsis.

Materials and Methods: A retrospective observational study was carried over two years in a level 3 NICU among neonates admitted with suspected sepsis. Data on demographics, clinical background, blood laboratory results were extracted from medical records and statistically analysed by multivariate regression analysis to identify surrogate markers for sepsis.

Results: Over two years, 182 neonates admitted with Suspected Sepsis were enrolled in the study. In all clinical examination followed by laboratory investigations viz CBP (TLC, ANC, ITR, degenerative changes, platelet count), CRP and blood culture was carried out prior to treatment. A total of 64 (35.2%) were blood culture positive. On multivariable regression analysis, ITR >0.2 [OR 16.3; 95% CI (1.5-176.8), platelet count < 150,000/ml (OR 15; CI, 6.4-35.2) and cytotoxic degenerative changes in neutrophils (OR 4.34; CI, 1.82-10.4), were significantly associated with culture proven neonatal sepsis. ANC<1500/mm^3 showed a trend towards higher culture positivity though statistically insignificant.

Conclusions: The study revealed that Immature to total neutrophil ratio >0.2, platelet count< 150,000/ml and cytotoxic degenerative changes in neutrophils were significantly associated with blood culture positive neonatal sepsis. ANC<1500/mm^3 showed a trend towards higher culture positivity though statistically insignificant. These are reliable surrogate markers of Neonatal Sepsis which would enable us to identify and treat the neonate at risk with early antibiotic therapy.

Key Messages: 1. Blood culture, the gold standard for diagnosing neonatal sepsis is expensive, time consuming and yields positive results in limited cases. 2. Effective surrogate markers are Immature to total neutrophil ratio (ITR), thrombocytopenia and cytotoxic degenerative changes in neutrophils. 3. These surrogate markers would identify the neonate at risk requiring early antibiotic therapy.

1. Introduction

Sepsis is a leading cause of morbidity and mortality in neonates and is recognised as a global health challenge.[1–3] Its incidence in India ranges from 20-30/1,000 live birth of which blood culture-proven sepsis occurs in 6.2-60 %.[4] Sepsis contributes to a quarter of the neonatal deaths in India.[5] Therefore, it constitutes a significant health burden.[6]

Blood culture, the gold standard for diagnosis of neonatal sepsis is time consuming, expensive and yields positive

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results in limited cases due to inadequate sampling, low yield of organism, prior antibiotic exposure etc.[5,7] Thus the diagnosis of sepsis may be missed out in these neonates who are often empirically treated. Establishing alternate diagnostic markers which are easily available, give quick results and are inexpensive will enable early appropriate treatment and reduce injudicious antibiotic usage thus curbing the emergence of multidrug-resistant micro-organisms.

1.1. Need of the study

This study was undertaken to ascertain early, reliable and inexpensive surrogate markers to blood culture for early detection of neonatal sepsis which would enable early and appropriate treatment and avoid unnecessary antimicrobial therapy.

2. Aim and Objectives

To ascertain haematological parameters which are reliable adjuvants to blood culture for diagnosing Neonatal Sepsis.

3. Materials and Methods

A retrospective cohort study was undertaken in neonates hospitalized in an urban, tertiary care Neonatal Intensive Care Unit (NICU) over a period of 24 months viz May 2017 to April 2019. Data was obtained from medical records of neonates hospitalized with a diagnosis of neonatal sepsis. Clearance from Institutional Ethics Committee and Hospital Research Committee was obtained. Given retrospective nature of study, waiver of informed consent was approved for the study.

During the study period, neonates hospitalised with perinatal risk factors and those with clinical features suggestive of sepsis were enrolled in the study. Those infants hospitalised with a diagnosis of sepsis but in whom complete laboratory investigations could not be carried out were excluded.

For all enrolled neonates, a detailed maternal history including antenatal, natal & postnatal data was recorded. Details of mode of delivery, resuscitation and relevant postnatal history prior to hospitalization was obtained. The risk factors of infection i.e. maternal, natal or postnatal factors were noted. The other parameters collected included gestational age, birth weight, and gender. Detailed clinical examination including vital parameter recordings, general and systemic examination was carried out and recorded on admission and during course of hospitalization.

Laboratory investigations done included Blood Culture, Complete Blood Picture (CBP) and C Reactive Protein (CRP). Blood was collected for culture under sterile precautions at admission and during trough phase in case of prior exposure of antibiotics. It was inoculated into the BD Bactec 9050 machine. In case of growth of organism, sub-culturing was done, organism identified and antibiotic sensitivity obtained.

For haematological studies, 1.0 ml of blood was collected under sterile precautions in an EDTA vacutainer and analysed in a cell counter viz Mindray BC 5150 5 Parts Analyser. Haemoglobin, hematocrit, total & differential leucocyte counts (TLC & DLC), platelet count, immature neutrophil count, IT (immature to total neutrophil) ratio were obtained. Absolute neutrophil count was calculated. Morphology for degenerative changes viz toxic granulation, vacuolation and Dohle bodies were reported by a pathologist on examination of peripheral smear. Quantitative CRP was measured.

The course in hospital and outcome viz hospitalization duration, discharge/death was recorded along with laboratory investigation results in a pre-designed, structured proforma. These were the subjected to statistical analysis.

3.1. Statistical analysis

Data were analyzed using Stata14 (StatCorp, College Station, TX). Categorical variables were compared using the Yates-corrected chi-squared test and continuous variables using the Mann-Whitney U test. A p-value <0.05 was considered statistically significant. Variables hypothesized to be associated with culture positive neonatal sepsis were first tested in univariate analysis using logistic regression. A multivariable logistic regression model was then performed to evaluate the independent effect of significant variables using backward selection.

4. Results

During the study period viz between April 2017-May 2019, incidence of Neonatal Sepsis was 14.9% (212/1420). Out of the 212 patients diagnosed to have Neonatal Sepsis, 182 patients met the inclusion criteria and were enrolled in the study. Clearances including from the Institutional Ethics Committee and Hospital Research Committee were obtained. Given retrospective nature of study, waiver of informed consent was approved for the study. Data was recorded on a master sheet and analyzed.

4.1. Clinical data

4.1.1. Maternal data

The maternal data of the study population is shown in Table 1. Of these, 31 were born by vaginal delivery and 151 by Caesarian section. It was seen that 45.2% of the babies born vaginally developed culture positive sepsis as compared to 33.1% of those born operatively. There were only 8 cases of maternal pyrexia and all of their babies were blood culture negative. Prolonged rupture of membranes >18 hours was seen in 20 cases of whom 9 babies had culture proven sepsis.

Babies born by NVD (45.1%) were more likely to develop culture positive neonatal sepsis in our cohort than those delivered through LSCS (33.1%) but the finding was not statistically significant. Also PROM (>18 Hours) were more likely to be associated with culture positive neonatal sepsis in our cohort but the finding did not reach levels of statistical significance.

4.1.2. Intrauterine crowth pattern

Of the study population 155 babies were appropriate for gestation age, 22 were small for gestational age and 5 large for gestational age as shown in Table 2 below. SGA babies (40.9%) were more likely to develop culture positive neonatal sepsis in our cohort than AGA (35.4%) or LGA babies (0%).

4.1.3. Neonatal demographics

The clinical data of the neonates in the study are shown in Table 3 . There was an increasing risk of culture positive neonatal sepsis with decreasing gestation from term (33.3%) to late preterm (34.9%) to moderate preterm (35%) to very preterm (40%) infants in our cohort but the finding was not statistically significant. Similarly, there was an increasing risk of culture positive neonatal sepsis from >2500 grams at birth (31.7%) to 1500-2499 grams at birth (35.9%) to 1000-1499 grams at birth (37.9%) to <1000 grams at birth (50%) infants in our cohort but the finding was not statistically significant. Thus there was an increasing trend to blood culture positive sepsis with reducing gestational age as well as birth weight.

The percentage risk of neonatal sepsis (suspected/probable/culture positive) in males admitted in NICU was 12.2% and 13.8% in females. However, the risk of culture positive neonatal sepsis among those admitted for sepsis was found higher in females (42.1%) than males (30.2%) which was statistically significant. On univariate analysis, there was a trend towards increased association of culture positive neonatal sepsis with female gender (Odds ratio [OR] 1.68; 95% confidence interval [CI], 0.92-3.11, p value 0.1) as compared to males.

4.1.4. Clinical features

In the study cohort, it was seen that the most common symptoms were lethargy, bleeding manifestations and seizures. There occurrence is shown in Table 4 below. It was seen that while all three symptoms occurred more in babies with proven sepsis, lethargy was the commonest and reached levels of statistical significance.

4.2. Laboratory investigations

4.2.1. Hematological parameters

In this study, the significant hematological parameters predicting culture positive sepsis were absolute neutropenia, thrombocytopenia, IT ratio and degenerative changes in neutrophils as shown in Table 5.

All of these parameters were effective surrogate markers which reached levels of high statistical significance.

4.2.2. CRP positive

In our study population, 54.9% of the babies had significantly raised CRP levels. Of the culture positive babies, 65.6% had raised CRP as compared to 49.15% in the culture negative babies as shown in the Table 6.

This finding of raised CRP in babies with blood culture positive sepsis reached levels of statistical significance.

4.2.3. Blood culture positivity

Of the study population 64 (35.16%) of the cases had blood culture positive sepsis. The most common organism that grew in blood culture was Klebsiella species (67.2%) (n=43) followed by Pseudomonas aerogenosa (n=8), Staphylococcus aureus (n=8), Candida (n=3), E coli (n=1) and Streptococcus agalactae (n=1) as shown in Table 7.

4.3. Univariate analysis

All of the factors studied were subjected to univariate analysis to determine the significant surrogate markers of sepsis in the neonate as shown in Table 8.

On the univariate analysis**,** lethargy (OR 2.33; CI 1.2-4.53), CRP positive (OR 1.98; CI 1.05-3.71), absolute neutrophil count <1500/mm^3 (OR 4.99; CI 1.17-30.66), immature to total neutrophil ratio (ITR) >0.2 (OR 14.37; CI, 1.73-119.58), platelet count < 150,000/mm^3 (OR 16.34; CI, 7.58-35.25) and cytotoxic degenerative changes in neutrophils (OR 3.34; CI, 1.74-6.39), were associated with culture positive neonatal sepsis and were statistically significant. There was a trend towards association of female gender (OR 1.68; CI 0.91-3.11) with culture positive neonatal sepsis.

5. Multivariate Analysis

All of the factors found significant in univariate analysis were subjected to multivariate regression analysis to determine the significant surrogate markers of sepsis in the neonate as shown in Table 9.

On multivariable logistic regression analysis, female gender (Odds ratio [OR] 2.59; 95% confidence interval [CI], 1.1-6.0), immature to total neutrophil ratio (ITR) >0.2 (OR 16.3; CI, 1.5-176.8), platelet count less than 150,000/mm^3 (OR 15; CI, 6.4-35.2) and cytotoxic degenerative changes in neutrophils (OR 4.34; CI, 1.82-10.4), were associated with culture positive neonatal sepsis. There was a trend towards higher culture positive neonatal sepsis in babies with absolute neutrophil count <1500/mm^3 but it was not statistically significant.

Table 1: Maternal Demographics-Study Population

Mode of Delivery	Study Population				Total	Statistics OR	CI	p value
	Culture Nos	Positive %	Culture Nos	Negative%				
VD	14	45.2	17	54.8	31	1.66	0.75-3.64	0.2
LSCS	50	33.1	101	66.9	151			
Total	64		118					
Maternal Pyrexia								
Present	0	0	8	100	8	ID	ID	ID
Absent	64	100	110	93.2	174			
PROM>18 hours								
Present	9	45	11	55	20	1.59	0.62-4.07	0.33
Absent	55	33.9	107	66.1	162			

Legend
Maternal demographics of the study population showing mode of delivery, maternal pyrexia and PROM>18 hours and its association with neonatal sepsis
Abbreviations: VD: Vaginal delivery; LSCS: Lower segment caesarian section; PROM: Premature rupture of membranes; ID Indeterminate

Table 2: Intrauterine growth pattern in study population

Intrauterine Growth Pattern	Study population		Total	%	OR	CI	P Value
	Culture positive	Culture negative					
AGA	55	100	155	35.4%	Ref #	Ref #	Ref #
SGA	9	13	22	40.9%	1.26	0.51-3.13	0.62
LGA	0	5	5	0%	ID*	ID*	ID*
TOTAL	64	118	182	35.1			

Legend
Intrauterine growth pattern in babies and its association with neonatal sepsis. It is seen that incidence of culture positive neonatal sepsis is highest in SGA babies. (IS)
Abbreviations: AGA Appropriate for gestational age; SGA Small for gestational age; LGA Large for gestational age; ID* means indeterminate

Table 3: Neonatal demographics-study population

Gestational Age	Totalstudy cases		Study population				Statistical Analysis		
			Suspected Sepsis	Probable Sepsis	Culture Positive Sepsis	%Culture Positive	OR	CI	P Value
>37 weeks	649	84	24	32	28	33.3	Ref#	Ref#	Ref#
34-37 weeks	481	43	16	12	15	34.9	1.07	0.49-2.32	0.86
32-34 weeks	159	20	8	5	7	35	1.08	0.39-3.0	0.89
<32 weeks	131	35	12	9	14	40	1.33	0.59-3.01	0.49
Birth Weight (grams)									
2500&>	696	79	23	31	25	31.7	Ref#	Ref#	Ref#
1500-2499	548	64	25	16	23	35.9	1.21	0.61-2.43	0.59
1000-1499	126	29	9	9	11	37.9	1.32	0.54-3.2	0.54
<1000	50	10	3	2	5	50	2.16	0.57-8.14	0.26
Gender									
Female	550	76	25	19	32	42.1	1.68	0.91-3.11	0.1
Male	870	106	35	39	32	30.2			
Total	1420	182	60	58	64	35.1			

Legend
There was an increasing risk of culture positive neonatal sepsis with reducing gestational age and birth weight and female gender.

Table 4: Clinical Featuresvs Culture Positive Sepsis

Symptom	Total	Cases %	Study Population		Statistics		
			Culture Positive	Culture Negative	OR	CI	P Value
Lethargy	111	60.98	47(42.3%)	64(57.7%)	2.3	1.2-4.53	0.01
Bleeding Manifestations	7	3.84	4(57.1%)	3(42.3%)	2.5	0.55-11.7	0.22
Seizures	11	6.04	4(36.4%)	7(63.6%)	1.05	0.29-3.7	0.93

Legend
howing clinical features most often seen in the study population. Of these lethargy reached level of statistical significance

Table 5: Hematological Parameters

	Total	Cases %	Study population		Statistical analysis		
			Culture positive	Culture negative	OR	CI	p value
ANC COUNT <1500	8	4.39	6(75%)	2(25%)	6	1.17-30.66	0.03
Platelet count <150,000/mm^3	58	28.6	44(75.9%)	14(24.1%)	16.3	7.58-35.3	<0.001
I:T Ratio>0.2	8	4.39	7(87.5)	1(12.5)	14.4	1.73-119.6	0.01
Degenerative Changes In Neutrophil	94	51.64	45(47.87)	49(52.13)	3.34	1.74-6.38	<0.001

Legend
hows statistically significant hematological parameters observed in blood culture positive sepsis which would be effective surrogate markers
Abbreviations: ANC Absolute neutrophils count; IT Ratio Immature to total neutrophils ratio

Table 6: CRP positivity in study population

	Study Population		Total	Statistical Analysis			
	Culture positive	Culture negative		% Culture Positive	OR	CI	p value
CRP Positive							
Yes	42	58	100	42	1.98	1.05-3.71	0.03
No	22	60	82	26.8			
Total	64	118	182	35.1			

Legend
Table Shows CRP as a statistically significant parameter observed in blood culture positive sepsis

Table 7: Organisms growing in blood culture

Organism	Frequency (n)	%
Klebsiella species	43	67.2
Pseudomonas aerogenosa	8	12.5
Staphylococcus aureus	8	12.5
Candida albicans	3	4.7
E coli	1	1.6
Streptococcus agalactae	1	1.6

6. Discussion

In this retrospective cohort study during the study period between April 2017-May 2019, 212 out of total of 1420 patients were admitted in the NICU with a diagnosis of suspected neonatal sepsis and were considered for the study. Among them, 30 neonates were excluded from the study due to unwillingness for investigations or discharge prematurely against medical advice. A cohort of 182 patients met the inclusion criteria and were enrolled in the study. Clearances including from the Hospital Research Committee and Institutional Ethics Committee were obtained. Data was recorded on a master sheet and analysed.

In our study cohort, out of the 182 blood cultures sent, 64(35.2%) were positive blood cultures. This is comparable to positivity rates in other studies in developing countries such as Pruthadesai et al in which out of a cohort of 120 patients, 60(50%) were positive blood cultures, D. Jeyaganguli et al in which out of a cohort of 60 patients, 26(43%) were positive blood cultures and Kajal Basavaraj Punyashetty et al in which out of a cohort of 100 patients, 42(42%) were positive blood cultures.[3–10]

Table 8: Univariate analysis

Factors associated with culture positive neonatal sepsis	OR	CI	P value
[a]Female gender	1.68	0.91-3.11	0.1
Term (>37 weeks) at birth	Ref [#]	Ref [#]	Ref [#]
Late preterms (>34-36 weeks) at birth	1.07	0.49-2.32	0.86
Moderate preterm (>32-34) weeks at birth	1.08	0.39-3.0	0.89
Very preterms (<32 weeks) at birth	1.33	0.59-3.01	0.49
>2500 grams at birth	Ref [#]	Ref [#]	Ref [#]
1500-2499 grams at birth	1.21	0.61-2.43	0.59
>1000-1499 grams at birth	1.32	0.54-3.2	0.54
<1000 grams at birth	2.16	0.57-8.14	0.26
[a]NVD vs LSCS	1.66	0.75-3.64	0.20
AGA	Ref [#]	Ref [#]	Ref [#]
SGA	1.26	0.51-3.13	0.62
LGA	ID*	ID*	ID*
[a]Maternal fever	ID*	ID*	ID*
[a]PROM >18 Hours	1.59	0.62-4.07	0.33
[a]Lethargy	2.33	1.2- 4.53	0.01
[a]Bleeding Manifestations	2.5	0.55-11.7	0.22
[a]Seizures	1.05	0.29-3.7	0.93
[a]CRP positive	1.98	1.05-3.71	0.03
[a]Absolute neutrophil count <1500/mm^3	6	1.17-30.66	0.03
[a]Immature to total neutrophil ratio (ITR) >0.2	14.4	1.73-119.6	0.01
[a]Platelet count less than 150,000/mm^3	16.3	7.58-35.3	<0.001
[a]Cytotoxic degenerative changes in neutrophils	3.34	1.74-6.38	<0.001

Abbreviations: OR, odds ratio; CI, confidence interval; [a] Variables in the table analyzed as categorical (Yes vs No) variables; [#]Ref = reference group;*ID=indeterminate sincenone of the patients with history of maternal fever and LGA developed culture positive neonatal sepsis

Table 9: Multivariate Analysis

Factors associated with culture positive neonatal sepsis				
	Univariate Analysis OR (95% Cl)	p value	Multivariable Analysis OR (95% CI)	p value
Female gender [a]	1.68(0.91, 3.11)	0.1	2.59(1.1, 6.0)	0.03
Absolute neutrophil count <1500/mm^3[a]	6(1.17, 30.66)	0.03	6.83(0.67, 70.1)	0.10
Immature to total neutrophil ratio (ITR) >0.2 [a]	14.4(1.73, 119.6)	0.01	16.3(1.5,176.8)	0.02
Platelet count less than 150,000/mm^3[a]	16.3(7.58, 35.3)	<0.001	15(6.4,35.2)	<0.001
Cytotoxic degenerative changes in neutrophils [a]	3.34(1.74, 6.38)	<0.001	4.34(1.82, 10.4)	0.001

Abbreviations: OR, odds ratio; CI, confidence interval. [a] Variables in the table analyzed as categorical (Yes vs No) variables;

The most common organism that grew in blood culture was Klebsiella (67.2%) (n=43) followed by Pseudomonas (n=8), Staphylococcus aureus (n=8), Candida (n=3), E coli (n=1) and Streptococcus agalactae (n=1). The aetiology of culture positive neonatal sepsis is similar to other studies in developing countries like Pruthadesai et al, D. Jeyaganguli et al, Kajal Basavaraj Punyashetty et al.[8–10]

6.1. Demographics

In our cohort of patients, it was seen that there was an increasing incidence of culture positive sepsis with reducing gestational age and birth weight. Further there was an increasing trend of incidence of culture positive sepsis in SGA babies. However, these trends did not reach levels of statistical significance. In our cohort of patients, more males were present than females. The percentage risk of neonatal sepsis (suspected/probable/culture positive) in males admitted in NICU was 12.2% in males and 13.8% in females. However, the risk of culture positive neonatal sepsis among those admitted for concern for sepsis was found higher in females (42.1%) than males (30.2%) which was statistically significant. This is in contrast to other studies in India such as Pruthadesai et al, D. Jeyaganguli et

al, Kajal Basavaraj Punyashetty et al in which male admitted in NICU were at higher risk of sepsis than females. This may be because in our population, females are admitted when they were sicker than males perhaps because of the local ethos.[8–10]

6.2. Clinical factors

Maternal Factors: In our study it was observed that vaginal delivery and premature rupture of membranes (PROM) >18 hours prior to delivery had an increased association with blood culture positivity but these findings did not reach levels of statistical significance. Our observation is in concordance with other studies.[11] In our study population, none of the mothers gave a history of peripartum febrile illness. This may have been due to limited ability to report fevers during admission of baby. Also, the number of mothers with history of fever prior to delivery may have been few and given our limited sample size may not have been captured by chance alone.

6.3. Neonatal factors

Of clinical features, 42.3% of patients with lethargy developed culture positive sepsis while 23.9% of those with no lethargy developed culture positive sepsis; this difference reached levels of statistical significance (p=0.01) on univariate analysis. Our observation is in concordance with other studies.[12] Of the clinical features, 57.1% of patients with bleeding manifestations developed culture positive sepsis while 34.2% of those with no bleeding manifestation developed culture positive sepsis; this finding did not reach levels of statistical significance on univariate analysis as with occurrence of seizures.

6.4. Laboratory parameters

In our study it was seen that positive CRP, Absolute neutrophil count <1500/mm^3, Platelet counts < 150,000/mm^3, Immature to total neutrophil ratio (ITR) >0.2 and presence of degenerative changes in WBC had a statistically significant association with blood culture positivity on univariate analysis. Our observation is in concordance with other studies.[13–16] However, in the multivariable analysis adjusted for other variables, only immature to total neutrophil ratio (ITR) >0.2, platelet count less than 150,000/ mm^3, and cytotoxic degenerative changes in neutrophils were associated with culture positive neonatal sepsis. There was a trend towards higher culture positive neonatal sepsis in babies with absolute neutrophil count <1500/mm^3 but it was not statistically significant.

7. Conclusion

Neonatal sepsis is a common occurrence in NICU. Early detection and institution of definitive treatment enables more effective recovery. Blood culture is gold standard tool for diagnosis though time consuming. Hence identification of early surrogate markers would enable early institution of definite treatment. This study identified female gender, I:T ratio >0.2, cytotoxic changes in neutrophils and platelet count less than 150,000/mm^3 to be effective surrogate markers for blood culture positive neonatal sepsis. These markers would enable an early inexpensive and easily available alternative to blood culture positivity in diagnosis and appropriate management of neonatal sepsis.

8. Limitations

Although our cohort was of reasonable size, our study was in a single center with its own distinct demographics, admission rates and practice habits. Our study may have been underpowered to detect the importance of some clinical factors that could have independently predicted culture positive neonatal sepsis. The retrospective scope of the study also limited the number of variables we could test in our study.

9. Conflicts of Interest

All contributing authors declare no conflicts of interest.

10. Source of Funding

None.

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