

A Study Of Early Onset Neonatal Sepsis With Special Reference To Sepsis Screening Parameters In A Tertiary Care Centre Of Rural India

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Citation

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Abstract

Objective: To study the maternal risk factors and clinico-bacteriological profile of early onset sepsis (EOS) and performance of sepsis screen parameter in a tertiary care neonatal unit. **Methods:** Relevant data of neonates born during the study period were obtained from their case records. A diagnosis of early onset sepsis was made if either clinical sepsis developed within 48 hours of life and based on the risk factors and/or clinical features were subjected to various hematological screening parameters and blood cultures. Data was analyzed using the SPSS software, Chi-square values, probability coefficients, sensitivity, specificity, positive predictive values and negative predictive values of the three diagnostic methods derived and the results correlated. **Results:** Among 3574 live births, a total of 189 episodes of sepsis occurred in 72 neonates (51.38% culture proven) with an incidence of 52.88 per 1000 live births. The incidence of EOS was 20.15 per 1000 live births and it constituted 38% of overall sepsis. Among the Perinatal risk factors assessed, a significant association of EOS with prolonged rupture of membranes, foul smelling liquor was observed ($p < 0.05$). Among infants at risk of EOS, 20.9% developed sepsis compared to only 0.32% of those without these risk factors ($p < 0.001$). *Klebsiella pneumoniae* being commonest (48.6%) isolate. A positive Buffy coat smear was the single best reliable sepsis screen test with a high specificity (82.7%) but, the positive predictive value and specificity was high when two or more sepsis screen tests were combined.

Conclusion: Screening for sepsis in an asymptomatic neonate is warranted only in the presence of a maternal risk factor even if the neonate is at high risk of developing sepsis due to associated problems of prematurity, low birth weight or asphyxia. The sepsis scoring system in predicting neonatal septicemia clinically needs further evaluation. Blood culture remains the gold standard for the diagnosis of neonatal septicemia. Combination of two or more sepsis screen parameters has better results in diagnosing neonatal septicemia compared to a single test while awaiting the blood culture results

INTRODUCTION

Almost 99% of the estimated 4 million annual neonatal deaths occur in developing country(1, 2). Although post-neonatal mortality rates have declined substantially, in large part due to successful child survival interventions, deaths in the neonatal period have been largely unaddressed as a global health concern and account for 40% of all deaths in children under 5(2, 3). Despite the current increased efforts, much more needs to be accomplished to reduce neonatal mortality rates from levels as high as 40 to 60 per 1000 live births, and to achieve the Millennium Development Goal for child survival(2, 3). Sepsis is the commonest cause of neonatal mortality; it is responsible for about 30-50% of the total neonatal deaths in developing countries(4, 5). It is estimated that up to 20% of neonates develop sepsis and approximately 1% die of sepsis related causes(5). The

incidence of neonatal sepsis according to the data from National Neonatal Perinatal Database (NNPD, 2002-03) is 30 per 1000 live births. The database comprising 18 tertiary care neonatal units across India found sepsis to be one of the commonest causes of neonatal mortality contributing to 19% of all neonatal deaths(6). Septicemia was the commonest clinical category with an incidence of 23 per 1000 live births while the incidence of meningitis was reported to be 3 per 1000 live births. Infection is the primary cause of mortality in 18.6% of intramural neonates in which *Klebsiella pneumoniae* is the most frequent bacterial isolate (32.5%), followed by *Staphylococcus aureus* (13.6%). Sepsis is 12 times more common in extramural admissions (39.7%). In extramural admissions, *Klebsiella* is the commonest bacteria responsible 27.5%, the next common being *S. aureus* (14.9%). Sepsis is responsible for death in 38.0% of these

extramural babies(6, 7). The gold standard for the diagnosis of neonatal septicemia is a positive Blood culture.(7, 8) Definitive culture results takes at least 48-72 hours resulting in treatment delays. Hence, certain rapid diagnostic tests such as C-reactive protein, Micro-erythrocyte sedimentation rate, Buffy coat smear examination, Total WBC count, Absolute neutrophil count, Immature/Total Neutrophil count ratio and Platelet count collectively termed as the 'Sepsis Screen' (9, 10), is used to diagnose septicemia early and initiate a presumptive treatment while awaiting culture report. The purpose of this study on early Neonatal sepsis is to evaluate the burden of disease, etiology, clinical and laboratory diagnosis, antimicrobial resistance, potential options for prevention and management of early neonatal sepsis.

MATERIAL AND METHODS

This study was conducted at Acharya Vinoba Bhave Rural Hospital, Sawangi (M), Wardha, for a period of two years, from 1st July 2008 to 30th Jun 2010. Neonates who were clinically suspected to have bacterial infections within the first 48 hours of life, based on the risk factors and/or clinical features, were subjected to various hematological screening parameters and blood cultures. Neonates developing symptoms after 48 hours of life and blood cultures which grew fungi were excluded. The investigations done were Blood culture, Buffy coat smear examination, C-Reactive protein (CRP) test, micro-Erythrocyte sedimentation rate (micro-ESR) estimation, Total leucocyte (WBC) count, Absolute neutrophil count (ANC), and Immature (band cells) count / Total neutrophil count ratio [I/T ratio]. The blood cultures were processed and the isolates identified by standard microbiological procedures.(11, 12) Cultures were reported as negative when they did not yield any growth at the end of 7 days. Buffy coat smear examination was done according to the technique described by Brooks and associates.(13) The CRP test was done by the rapid slide latex agglutination method using the diagnostic kit for the in-vitro detection of CRP in human serum supplied commercially by Span Diagnostics Ltd. The test was carried out as per the instructions described in the kit. Micro-ESR estimation was done by using commercially available (Greiner Bioone) standard heparinised micro-hematocrit capillary tubes. Blood was collected in the capillary tubes provided in the kit, from a heel prick of the neonate after disinfecting the area. One end of the tube was sealed with plasticin and the tubes were fixed vertically in an ESR stand. The rate of erythrocyte sedimentation was measured in

millimeters at the end of one hour. The total leukocyte count, differential count, ANC, I/T ratio and the Platelet count calculated as per standard hematological methods.(14)

The cut off values for the positive rapid screening tests in this study were as follows(10, 15):

All the findings were recorded and comparisons drawn between blood culture results and the sepsis screen tests. Data was analyzed using the SPSS software for Windows version 11 (Statistical Presentation System Software, SPSS Inc,1999, NewYork) and categorical tables, Chi-square values, probability coefficients, sensitivity, specificity, positive predictive values and negative predictive values of the three diagnostic methods derived and the results correlated. Conclusions were drawn from the tabulated results. A p-value of <0.05 was considered to be significant.

Ethical consideration- The ethical committee of Jawahar Lal Nehru medical college sawangi wardha had approved the study protocol.

RESULTS

Among the 3574 live birth during study period 189 episodes of Neonatal sepsis occurred, the incidence being 52.88/1000 livebirth. EOS occurred in 72 neonates with an incidence of 20.15/1000 live birth constituting 38% of overall neonatal sepsis. Male constitute 42 (58%) and females were 30(42%), ratio being 1.4:1.among the infant with EOS, 64(88.8%) were LBW, 26(36%) were VLBW and 63(87.5%) were Pre-term. The incidence of EOS in various categories of babies as shown in table.1 is significantly higher in preterm and LBW infants. Culture proven sepsis occurred in 37 cases constituting 51.38% of overall EOS. Among the culture positive cases, septicemia was more common among male neonates, seen in 22(59.5%) of the cases compared to female neonates 15(40.5%).

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Figure 1

Table 1-Neonatal Attributes and Maternal Risk Factors in EOS

LBW - Low Birth Weight
VLBW - Very Low Birth Weight
*** Maternal risk factors w/o risk factor P = 0.0
1 - LBW w/o Normal Weight P = 0.0
2 - VLBW w/o Normal Weight P = 0.0

SGA - Small for Gestational Age
LGA - Large for Gestational Age
P = 0.0
P = 0.0

Neonatal category	Total number	EOS/Risk factor***+ve	EOS/Risk factor-ve
Live birth	72/3754(1.92)	61/292(20.9)	11/3462(.32)
LBW	64/1074(5.96) ¹	57/189(30.15)	7/885(.8)
VLBW	26/202(12.87) ²	20/52(38.46)	6/150(4)
SGA	11/252(4.37)	9/26(34.6)	2/226(.88)
LGA	11/470(2.34)	8/26(31)	3/444(.67)
Pre-term	63/696(9) ³	55/177(31)	8/519(1.54)
<32wk	30/220(13.6) ⁴	24/54(44.4)	6/166(3.61)

3 - Preterm w/o Term P = 0.0
4 -< 32weeks w/o 32-36 weeks P = 0.0

Among a total of 292 neonates with underlying potential neonatal risk factor for sepsis 20.9% developed sepsis, while in those without risk factor EOS occurred in only 11 cases (0.32%) (p=.0000). Among the various high risk group of infants such as VLBW, Pre-term and SGA, the incidence of sepsis was negligible if maternal risk factor were absent(.67-4%) but in those cases where risk factor were present the incidence varied from 0.31-38.46%.

Figure 2

Table 2- Maternal and Neonatal Risk Factors in Early Onset Sepsis

(a) Perinatal risk factors

Risk factor	Total number	EOS		
		No. of cases	P value	Culture proven EOS
PROM	226	45(20%)	0.0	13(5.75%)
Peripartum fever	26	2(7.69%)	.22	0(0%)
Foul smelling liquor	22	8(36.4%)	.0009	5(22.7%)
Dei handling	43	7(16.3%)	.002	4(9.3%)
UTI	20	5(25%)	.01	5(25%)

(b) other associated factors

Apgar<6	377	42(11.14%)	0.0	22(5.83%)
One of twins	168	5(2.97%)	.48	0
Maternal diabetes	112	7(6.25%)	.09	0
MISAF	547	13(2.37%)	.01	11(2%)

PROM - prolonged rupture of membranes,
UTI - urinary tract infection,
MISAF - meconium staining of amniotic fluid

As shown in table -2a that 20% mother with PROM and 30% with foul smelling liquor has infant with EOS (p<.001) compared to those without these risk factors. There was no significant association of maternal diabetes, multiple

pregnancy and meconium staining of liquor with EOS(table-2b).Asphyxiated infants were more likely to have EOS(p<.0001).

Figure 3

Table 3. Associated Morbidity among Infants with Early Onset Sepsis (EOS)

Morbidity	EOS	
	Total cases(n=72)	Culture proven(n=37)
Pneumonia***	49(68%)	12(32%)
Shock	18(25%)	9(24%)
Metabolic acidosis	14(19.4%)	5(14%)
Necrotizing enterocolitis	11(15.3%)	8(21.4%)
Meningitis	6(8.3%)	6(16.21%)
Hypoglycemia	10(13.8%)	8(21.6%)
Pneumothorax	9(12.5%)	6(16.21%)
Meconium aspiration pneumonitis	6(8.3%)	5(14%)
Neonatal hyperbilirubinemia	8(11.1%)	5(14%)
Bronchopulmonary dysplasia	5(6.94%)	3(8%)

***p<0.001

The co-morbidities seen among infant with EOS were pneumonia in 68%, necrotizing enterocolitis in 15.3% and meningitis in 8.3%,culture positivity had no significant influence on rate of occurrence of various co-morbidities except for pneumonia which was more common in culture negative than culture positive cases(76%vs33.3,p<.001).

The majority of blood culture isolates i.e. out of 37 culture positive cases, 21(56.75%) were Gram negative and klebsiella pneumoniae being commonest in 18(48.6%), followed by E.coli 5(13.5%),Gram positive organism isolated in 16(43%) of cases commonest organism being staphylococcus aureus in 14(38%) followed by staphylococcus epidermidis in 2(5.4%) cases.

Figure 4

Table 4: Co-relation of sepsis screen parameter with the blood culture status

Sepsis screen parameter	Culture positive (n=37)	Culture negative (n=35)	Total (n=72)	P-value
A. single test				
C-reactive protein	33(89.2%)	30(85.7%)	63(87.5%)	.356
Leucopenia	4(10.8%)	2(5.7%)	6(8.3%)	.054
Neutropenia	1(2.7%)	1(2.8%)	2(2.8%)	.676
I/T ratio \geq 2	30(81%)	27(77%)	57(79.16%)	.456
Thrombocytopenia	15(40.5%)	10(28.5%)	25(34.7%)	.266
M-ESR>15mm in 1 st hr	11(29.7%)	4(11.4%)	15(21%)	.009
Buffy coat smear	32(86.4%)	11(31.4%)	44(61%)	<.0001
B. Two or more test +				
	36(97.2%)	28(80%)	64(89%)	.002
C. Three or more test +				
	32(86.4%)	16(45.7%)	48(67%)	<.0001

Of 37 culture positive cases CRP (89.2%), Buffy coat smear (86.4%) and I/T ratio \geq 2 (81%) were the most common positive single test.

Figure 5

Table 5- Shows the sensitivity, specificity, Positive predictive value and Negative predictive value of sepsis screen parameters

Sepsis screen parameter	sensitivity	specificity	Positive predictive value	Negative predictive value
A. single test				
C-reactive protein	52.3%	56%	89%	14.3%
Leucopenia	66.6%	50%	10.8%	94%
Neutropenia (ANC <1800 CELLS/mm ³)	50%	48.27%	2.7%	97%
I/T ratio \geq 2	52.63%	53.3%	81%	22.8%
Thrombocytopenia	60%	53.19%	40.5%	71.4%
M-ESR>15mm in 1 st hr	73%	54%	29.7%	88.5%
Buffy coat smear	74.4%	82.7%	86.4%	68.5%
B. Two or more test +				
	56%	87.5%	97%	20%
C. Three or more test +				
	66.7%	79%	86.5%	54%

A positive Buffy coat smear study was the single best reliable septic screen test to diagnose sepsis and positive predictive value and specificity was high when two or more sepsis screen were combined. 14 neonates with EOS died with case fatality rate of 19.4% while among culture positive cases 6 died, the mortality rate being 16.2%.

DISCUSSION

An overall incidence of neonatal sepsis of 52.88/1000 LB in the present study is comparable to other studies studies.(16, 17) The incidence of culture proven EOS of 10.35/1000 LB is comparable to 9.8/1000 LB and 8.6/1000 reported from South and North India.(18, 19) Male constitute 42(58%) and females were 30(42%), ratio being 1.4:1, these results are comparable with the observations made by other authors.(16, 20) The male preponderance in neonatal septicemia may be linked to the X- linked immunoregulatory gene factor contributing to the host's susceptibility to infections in males.(21) Among the infant with EOS, 64(88.8%) were LBW, 26(36%) were VLBW and 63(87.5%) were Pre-term. The incidence of EOS in various categories of babies as shown in table.1 is significantly higher in preterm and LBW infants. Similar observations were reported by previous studies.(19, 20, 22, 23) The rate of infection is inversely proportional to the birth weight, and low IgG levels due to impaired cellular immunity in the low birth weight neonates contributes to the increased susceptibility to infections in these neonates.(5) Sepsis is generally considered to be the result of various risk factors both maternal (Table 2) and neonatal such as prematurity, low birth weight and asphyxia. There are no uniform criteria for performing sepsis screen for infants at risk of EOS. The cut off values for prolonged rupture of amniotic membranes have varied between 12 to 24 hours. At certain centers, birth weight is also taken into consideration for screening. Among a total of 292 neonates with underlying potential neonatal risk factor for sepsis 20.9% developed sepsis, while in those without risk factor EOS occurred in only 0.32% cases (p=.0000). Among the various high risk group of infants such as VLBW,Pre-term and SGA, the incidence of sepsis was negligible if maternal risk factor were absent(.67-4%) but in those cases where risk factor were present the incidence varied from 0.31-38.46%.(19). PROM and foul smelling liquor were significant Perinatal risk factor associated with sepsis (p<.001). (19, 24) There was no significant association of maternal diabetes, multiple pregnancy and meconium staining of liquor with EOS. Asphyxiated infants were more likely to have EOS (p<.0001).(22) In the absence of maternal risk factors, even if the infant is at high risk for sepsis due to prematurity, very low birth weight, small for gestational age, or neonatal asphyxia, the incidence of EOS is negligible (Table 1). Hence neonatal factors by themselves do not deserve consideration for performing sepsis screen in an asymptomatic infant. However, these very same factors have an important and significant role in late onset sepsis in

which instance screening is done only when infant becomes symptomatic. The usual presentation of EOS is with respiratory distress and pneumonia within 72 hours of age according to the National Neonatal Perinatal Database (NNPD) 2000 report.(6) Pneumonia was the commonest (68%) presentation in the present study too. Culture proven sepsis occurred in 51.38% of overall EOS. The most common organism isolated was klebsiella pneumoniae (48.6%), followed by staphylococcus aureus in (38%).(6, 20, 23) The CRP test was least sensitive of the sepsis screen parameters, but had the highest positive predictive value in diagnosing septicemia. Various studies by other authors show variable results to this test.(25-28) The differences in the results of this parameter shown by the different studies is due to variations in the diagnostic criteria, the time of onset of infection (early or late) and different methods of CRP estimation. Neonatal septicemia is associated with leucopenia.(15) In the present study, Leucopenia i.e. total WBC counts <5000 cells/ cu.mm was taken as the diagnostic criteria for detecting neonatal septicemia. Leucopenia had a low sensitivity, specificity and positive predictive value but, a very high negative predictive value similar to the observation made by another study.(29) The differences in the results of this parameter in different studies may be due to variations in the blood sampling time, the severity of infection, the diagnostic criteria followed, the age of the neonates, and the reduced sensitivity of this test after the first week of life. ANC had the highest negative predictive value of 97% among the sepsis screen tests studied, which was similar to the observations seen in another study.(27) ANC varies considerably in the immediate neonatal period and normal reference ranges are available from Monroe's chart (30). ANC below 1800 per cubic mm is believed to be the best predictor of sepsis, while neutrophilia does not correlate well(15). I/T ratio is 0.16 at birth and declines to a peak value of 0.12 after 72 hours of age (7). A ratio of 0.2 is a highly sensitive marker of neonatal septicemia.(15) In this study, I/T ratio had a very low sensitivity, specificity and the negative predictive values of 52.63%, 53.3% and 22.8% respectively while, the positive predictive value was comparatively high at 81%. Different studies have shown variable results in this parameter which may be due to the variations in the blood sampling time, the severity of infection, the age of the neonates, the diagnostic criteria followed and the reduced sensitivity of this test after the first week of life.(26, 27, 31) Thrombocytopenia was a poor predictor of neonatal septicemia in this study compared to the studies conducted by different authors.(27, 31) This is

because the platelet counts are significantly low in all neonates in the first week of life and only rise after this period.(27, 32) Micro-ESR had very low specificity and positive predictive value, but a higher specificity and negative predictive value in detecting septicemia in the study. Similar observations were made by the other authors. Micro-ESR was a poor predictor of neonatal septicemia in our study compared to the studies conducted by other authors.(26, 27, 33) These variations are due to the fact that at least four hours are required for hematological response to develop after the onset of infection and blood samples collected and analyzed before this will yield normal results.(27) High micro-ESR is a specific test but it has only moderate sensitivity. The value is spuriously high in neonates with haemolysis and low in babies with disseminated consumptive coagulopathy.(15) Positive Buffy coat smear was the most sensitive (74.4%) and specific (82.7%) parameter for screening septicemia which was comparable with the observations made by other authors in their study (31, 34). A positive Buffy coat smear study, micro-ESR >15 mm min the 1st hour and leucopenia were the Sepsis screen tests in the decreasing order of significance in diagnosing neonatal septicemia in the present study. When two or more sepsis screen tests were combined together, the sensitivity and the negative predictive values decreased to 56% and 20% respectively, while the specificity and the positive predictive values increased to 87.5 and 97% respectively and was found to be statistically significant in detecting septicemia compared to the individual sepsis screen tests in this study. Similar observations were made by the other authors (26, 27, 35). When three or more tests were considered together, the sensitivity and the negative predictive value increased to 66.7% and 54% respectively, but, the specificity and the positive predictive value decreased to 79% and 86.5% respectively; compared to two or more tests being positive. From this study it can be derived that among the sepsis screen parameters studied, when single tests were considered, a positive Buffy coat smear study was the most sensitive (74.4%) and specific (82.7%) test, CRP had the highest positive predictive value (89%), while Neutropenia had the highest negative predictive value (97%).

CONCLUSION

An accurate and timely diagnosis of early onset neonatal sepsis remains challenging to the clinician and the laboratory. A test with a rapid turnaround time, with 100% sensitivity which allows accurate diagnosis and appropriate

antimicrobial treatment, is desirable. A reasonable specificity is also required to allow the antibiotics to be safely withheld in noninfected infants. Recently, measures of acute phase proteins, cytokines, cell surface antigens, and bacterial genomes have been used alone or in combination to improve the diagnosis of neonatal sepsis.(36) The value of the sepsis screen is more for excluding the diagnosis of neonatal septicemia which can be done reasonably if two screens 12-24 hours apart are negative. In a neonate who is stable otherwise or suspected of sepsis because of maternal risk factors, it is desirable to await results of sepsis screen before initiation of antibiotics. Since symptoms suggestive of sepsis may be caused by a variety of other illnesses, confirmation of sepsis by the sepsis screen tests may help in avoiding unnecessary antibiotic therapy.(15) Blood culture is still the "Gold standard" for the diagnosis of septicemia in neonates and should be done in all cases of suspected septicemia. In view of the changing spectrum of the causative agents of neonatal septicemia and their antibiotic susceptibility patterns from time to time and from one hospital to another, a positive blood culture and the antibiotic susceptibility testing of the isolates are the best guide in choosing the appropriate antimicrobial therapy in treating neonatal septicemia.

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