JOURNAL Of Medical Science And Clinical Research

IGM Publication   An Official Publication Of IGM Publication

Risk Factors and Immediate Outcome of Early Onset Neonatal Sepsis

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ABSTRACT
Background - *Neonatal septicemia remains one of the main causes of mortality and morbidity despite the progress in hygiene, introduction of new and potent antimicrobial agents for treatment and advanced measures for diagnosis. Estimates of direct causes of death indicate that severe infections account for 36% of neonatal deaths (sepsis/pneumonia 26%; tetanus 7%; diarrhoea 3%). Three-fourths of neonatal deaths occur in the first week of life.*
Aims of the study-*1. To identify the maternal and neonatal risk factors associated with early onset neonatal sepsis. 2. To recognize the common clinical features with which the newborn are most likely to present with early onset neonatal sepsis. 3. To determine the various factors associated with increased risk of mortality in early onset neonatal sepsis. 4. To evaluate immediate outcome of early onset neonatal sepsis.*
Study design- *A descriptive study. Material and methods- The study was carried out in the Department of Pediatrics, RIMS, Imphal for a period of 2 years from October 2011 to September 2013 in neonates admitted with history, clinical features and laboratory parameters / cultures suggestive of sepsis within first 7 days of life. Neonates included in the study were followed up till they were admitted in this hospital and immediate outcome was evaluated.*
Results- *Out of 120 eligible cases, 75.8% presented within first 3 days of life. Male to female ratio was found to be 1.22:1. Hindus accounted for 68.3% while 59.2% were delivered preterm. Maternal fever was the most common maternal risk factor present in 67.5% cases. Amongst culture positive cases, E. coli was the predominant organism. 84.2% were discharged with advice, 4.2% left against medical advice and 11.7% babies expired (mortality).*
Conclusion- *Early onset neonatal sepsis is to be strongly suspected when risk factors associated with it are present or when newborns present with clinical features suggestive of it. Thorough history taking about risk factors and detailed clinical evaluation needs to be done followed by laboratory analysis and blood culture for confirmation of the diagnosis.*
Keywords: *Neonatal sepsis, risk factors, prematurity, sepsis screen.*

Background

Neonatal septicemia remains one of the main causes of morbidity and mortality despite the progress in hygiene, introduction of new and potent antimicrobial agents for treatment and advanced measures for diagnosis. Neonatal Sepsis can be defined as any systemic bacterial infection confirmed by a positive blood culture in the first month of life.[1] Newborns are immunologically immature and are ill-suited to defend themselves against the polymicrobial flora to which they are exposed during and after parturition.[2] Early onset

neonatal bacterial sepsis is defined as sepsis in neonates less than 7 days old.[3]

Clinically, sepsis in the newborn may present as lethargy, hypothermia, hever, poor feeding, abnormal cry, vomiting diarrhoea, respiratory distress, bleeding tendencies, seizures, pallor, shock etc. But the gold standard for diagnosing early onset sepsis is the isolation of causative organism from blood.[4] Worldwide, the neonatal mortality rate varies from 2.8 to 4 million deaths each year with 95% of the deaths occurring indeveloping countries[5] India accounts for 27% of the global burden of neonatal deaths each year. Nearly two-thirds of the infant mortality and 46% of the under five mortality occur in the neonatal period in India. Estimates of direct causes of death indicate that severe infections account for 36% of neonatal deaths (sepsis/pneumonia - 26%, tetanus - 7% and diarrhoea - 3%). The most common organisms found in the amniotic fluid and vagina are Escherichia coli, Enterococcus faecalis, Staphylococcus aureus, and Group B beta haemolytic Streptococcus is also occasionally present in the vaginal flora.[1]

Aims of the study

1. To identify the maternal and neonatal risk factors associated with early onset neonatal sepsis.
2. To recognize the common clinical features with which the newborn are most likely to present with early onset neonatal sepsis.
3. To determine the various factors associated with increased risk of mortality in early onset neonatal sepsis.
4. To evaluate immediate outcome of early onset neonatal sepsis.

Material and Methods

The present study was carried out in the Department of Pediatrics, Regional Institute of Medical Sciences, Imphal, Manipur, during the period from October 2011 to September 2013 in neonates admitted with history, clinical features and laboratory parameters / cultures suggestive of

sepsis within first 7 days of life. Ethical approval was obtained from the Institute Ethics Committee, RIMS, Imphal prior to initiation of the study. Consent from the parents was also obtained before starting of the study. It was a hospital based descriptive study with a sample size of 120 eligible cases. Babies born to human immunodeficiency virus (HIV) positive mothers, with external congenital anomalies and parents/guardians declining consent were excluded from the study.

Detailed history with regards to patient's epidemiological factors, presenting complaints, maternal and neonatal risk factors was noted as per pretext proforma. Detailed physical examination and laboratory evaluation were carried out. A sample of at least 2ml of blood was taken under strict asepsis and cultured aerobically and anaerobically.

After initial assessment, all neonates included in the study were given intravenous fluids and parenteral antibiotics as per protocol. All the cases were closely monitored and their clinical progress recorded daily. Neonates included in the study were followed up till during their stay in the hospital and immediate outcomes were evaluated.

Statistical Analysis

The information about various demographical factors, maternal and neonatal risk factors, clinical features and lab parameters was collected and it was analyzed using the Statistical package for social sciences (SPSS) version 16 with Fisher's exact and Chi-square test for comparison of proportion.

Results and Observation

Out of 120 enrolled cases, 91(75.8%) neonates presented in first 3 days of life. 10(8.3%), 9(7.5%) and 5(4.2%) newborns presented on the 4th,5th and 6th day of life respectively. There were 66 males to 54 female neonates (M:F=1.22:1). Hindus accounted for 68.3% cases; Christians 15.8%, Muslims 11.7% and others 4.2% constituted the rest. 105(87.5%) babies were delivered in the hospital and vaginal delivery was the commonest

mode of delivery in 62(51.7%) cases; cesarean section and assisted vaginalprocedures comprised of 53(44.2%) and 5(4.2%) deliveries respectively. Majority of neonates 71(59.2%) were delivered preterm and 45(37.5%) were term deliveries. Maternal fever was found to be the most frequent maternal risk factor present in 67.5% (Table - 1). Other significant risk factors were : primipara 77(64.2%), prolonged rupture of membranes >18 hrs – 49(40.8%), meconium stained amniotic fluid – 29(24.2%), maternal age <20 yrs – 18(15.0%) and foul smelling liquor – 14(11.7%).

Table – 1 : Distribution of maternal risk factors

Risk factor	Total number of cases (n = 120)	
	Yes n (%).	No n (%)
Maternal fever	81(67.5)	39(32.5)
Primipara	77(64.2)	43(35.8)
PROM > 18 hours	49(40.8)	71(59.2)
MSAF	29(24.2)	91(75.8)
Maternal age < 20 years	18(15.0)	102(85.0)
Foul smelling liquor	14(11.7)	106(88.3)
PIH	10(8.3)	110(91.7)
UTI	5(4.2)	115(95.8)
APH	5(4.2)	115(95.8)

PROM prolonged rupture of membranes
MSAF – meconium stained amniotic fluid

73(60.8%) newborns were weighing less than 2.5 Kg at birth. (Table - 2). Prematurity – 71(59.1%) and APGAR score <5 at 1 min – 62(51.7%) were other neonatal risk factors.

Table 2 : Distribution of neonatal risk factors

Risk factor	Total no. of cases (n=120)	
	Yes n (%)	No n (%)
LBW	73 (60.83)	47 (39.17)
Preterm	71 (59.16)	49 (40.84)
APGAR score less than 5 at 1 min	62 (51.7)	58 (48.3)
Product of multiple pregnancy	8 (6.7)	112 (93.3)

LBW – low birth weight

Refusal to feed and jaundice were the most common findings, being present in 77(64.2%) each of the studied cases (Table – 3). Respiratory distress syndrome -51(42.5%), seizures- 48(40%), bleeding diathesis - 44(36.7%), fever and sclerema - 34(28.3%), hypothermia-29(24.2%), abdominal distension-28(23.3%),diarrhea-24

(20%), apnoea- 9(15.8%),vomiting-9(15.8%) and cyanosis-19(15.8%) were the other presenting features. C-reactive protein level >1 mg/dl was found in 92(76.7%) of the neonates. 77(64.2%) babies had raised micro-erythrocyte sedimentation rate (>10 mm/1st hr). Ratio of immature to total neutrophils (> 0.2) was observed in 62(51.7%) of the cases.

Table – 3: Presenting clinical features of the neonates

Clinical features	Yes n(%)	No n(%)
Refusal to feed	77(64.2)	43(35.8)
Jaundice	77(64.2)	43(35.8)
Respiratory distress syndrome	51(42.5)	69(57.5)
Seizures	48(40.0)	72(60.0)
Bleeding tendency	44(36.7)	76(63.3)
Fever	34(28.3)	86(71.7)
Sclerema	34(28.3)	86(71.7)
Hypothermia	29(24.2)	91(75.8)
Abdominal distension	28(23.3)	92(76.7)
Diarrhoea	24(20.0)	96(80.0)
Apnoea	19(15.8)	101(84.2)
Vomiting	19(15.8)	101(84.2)
Cyanosis	19(15.8)	101(84.2)
Bulging fontanel	14(11.7)	106(88.3)

Blood culture, which was done in all the cases, was found to be sterile in 91 (75.8%) cases. Out of the remaining 29 (24.2%) culture positive cases, E. coli was the commonest organism, being found in 13(45%) cases; Klebsiella and Group B Streptococci were recovered in 6(21%) and 5(17%) cases respectively. Staph. aureus and coagulase negative staphylococci were grown in 2(7%) babies each. Pseudomonas was grown in 1(3%) case only. Mean birth weight of the newborns included in the study was 2.502 Kg (SD± 0.60). Median gestational age in days amongst all the cases was 255 days with SD± 20.
Out of 120 newborns in the study, 101 (84.2%) were discharged with advice, 5 (4.2%) left against medical advice and 14 (11.7%) babies expired.

Table – 4 : Maternal risk factors in alive and expired newborns

Maternal risk factor	Observation	Alive	Expired	Total	*p*-value
Maternal fever	+	63(82.9)	13(17.1)	76	0.032
	-	38(97.4)	1(2.6)	39	
Primiparity	+	59(81.9)	13(18.1)	72	0.013
	-	42(97.7)	1(2.3)	43	
PROM > 18 hours	+	67(94.4)	4(5.6)	44	0.006
	-	67(94.4)	4(5.6)	71	
MSAF	+	21(72.4)	8(27.6)	29	0.007
	-	80(93.0)	6(7.0)	86	
Maternal age < 20 years	+	10(55.6)	8(44.4)	18	0.000
	-	91(93.8)	6(6.2)	97	
Foul smelling liquor	+	5(35.7)	9(64.3)	14	0.000
	-	96(95.0)	5(5.0)	101	
PIH	+	9(100)	0(0)	9	0.598
	-	92(86.8)	14(13.2)	106	
UTI	+	5(100)	0(0)	5	1.000
	-	96(87.3)	14(12.7)	110	
APH	+	5(100)	0(0)	5	1.000
	-	96(87.3)	14(12.7)	110	

(+) - present; (-)- absent; PROM – prolonged rupture of membranes; MSAF – meconium stained amniotic fluid; PIH – pregnancy induced hypertension; UTI-urinary tract infection; APH – ante-partum hemorrhage.

Table – 5 : Neonatal risk factors in alive and expired newborns

Neonatal risk factor	Observation	Alive	Expired	Total	*p*-value
Prematurity	+	56(84.8)	10(15.2)	66	0.257
	-	45(91.8)	4(8.2)	49	
Birth weight <2.5 kg	+	54(79.4)	14(20.6)	68	0.001
	-	47(100)	0(0)	47	
Apgar score < 5 at 1 min	+	50(80.6)	12(19.4)	62	0.011
	-	51(96.2)	2(3.8)	53	
Product of multiple pregnancy	+	8(100)	0(0)	8	0.593
	-	93(86.9)	14(13.1)	107	

(+) - present; (-)- absent

Table – 6 : Clinical features in alive and expired newborns

Clinical features	Observation	Alive n(%)	Expired n(%)	Total	*p*-value
Diarrhoea	+	22(91.7)	2(8.3)	24	0.731
	-	79(86.8)	12(13.2)	91	
Apnoea	+	19(100)	1(0)	19	0.122
	-	82(85.4)	14(14.6)	96	
Vomiting	+	15(100)	0(0)	15	0.209
	-	86(86.0)	14(14.0)	100	
Abdominal distension	+	23(85.2)	4(14.8)	27	0.737
	-	78(88.6)	10(11.4)	88	
Cyanosis	+	15(100)	0(0)	15	0.209
	-	86(86.0)	14(14.0)	100	
Seizures	+	44(91.7)	4(8.3)	48	0.286
	-	57(85.1)	10(14.9)	67	
Hypothermia	+	21(72.4)	8(27.6)	29	0.007
	-	80(93.0)	6(7.0)	86	
Bulging fontanel	+	10(71.4)	4(28.6)	14	0.068
	-	91(90.1)	10(9.9)	101	
Bleeding tendency	+	42(95.0)	2(5.0)	44	0.049
	-	59(83.1)	12(16.9)	71	
Respiratory distress syndrome	+	38(76.0)	12(24.0)	50	0.001
	-	63(96.9)	2(3.1)	65	
Sclerema	+	17(58.6)	12(41.4)	29	0.000
	-	84(97.7)	2(2.3)	86	
Refusal to feed	+	64(87.7)	9(12.3)	73	0.947
	-	37(88.1)	5(11.9)	42	
Fever	+	29(85.3)	5(14.7)	34	0.755
	-	72(88.9)	9(11.1)	81	
Jaundice	+	62(81.6)	14(18.4)	76	0.002
	-	39(100)	090(0)	39	

Various maternal factors which showed statistical significance with mortality were maternal fever (*p*= 0.032), primiparity (*p*= 0.013), prolonged rupture of membrane (PROM) >18 hours (*p*=0.006), meconium stained amniotic fluid (*p*=0.007), maternal age< 20yrs (*p*= 0.000), foul smelling liquor (P= 0.000)[Table-5]. Among the neonatal factors - birth weight less than 2.5 Kg (*p*=0.001), APGAR score <5 at one minute (*p*=0.011), hypothermia (*p*=0.007), bleeding tendency (p=0.049), respiratory distress syndrome (*p*=0.001), sclerema (*p*= 0.00) and jaundice (*p*= 0.002) were the important clinical features[Table - 6].

Laboratory parameters which showed high statistical significance (*p*<0.01) were raised microerythrocyte sedimentation rate (> 10mm/1st hour), immature to total neutrophils ratio >0.2 and blood culture positivity (*p*=0.007).

Table – 7 : Laboratory parameters in alive and expired newborns

Laboratory parameter	Observation	Alive n(%)	Expired n(%)	Total	p-value
I/T ratio > 2	+	49(79.0)	13(21.0)	62	0.002
	-	52(98.1)	1(1.9)	53	
CRP	+	74(85.1)	13(14.9)	87	0.182
	-	27(96.4)	1(3.6)	28	
Raised micro ESR	+	58(80.6)	14(19.4)	72	0.002
	-	43(100)	0(0)	43	
Blood culture	+	21(72.4)	8(27.6)	29	0.007
	-	80(93.0)	6(7.0)	86	

I/T ratio – immature to total neutrophil ratio; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate

Discussion

Neonatal septicaemia is one of the major contributors of neonatal morbidity and mortality in India. The present study was undertaken to assess the various risk factors for neonatal sepsis and determine the immediate outcomes.

Most of the cases (75.8%) presented within the first 3 days of life (mean age of presentation of all these cases of EOS being 2.6 days). Sheikh AM *et al*[4] also found similar results with majority of cases (61%) presenting within 48 hours and a mean age of presentation at 2.73 days. Varsha *et al* [7] also reported in their study that 74.6% of neonates evaluated for sepsis were less than 3 days of age. Though early onset sepsis is generally taken as infections occurring in the first 7 days of life, the current trend is being focused in the first 72 hours.

Prematurity and low birth weight are usually associated with neonatal sepsis and mortality, which may be related to the fact that these neonates require prolonged hospitalization and interventions which predispose them to increased risk of hospital acquired infection or related to innate immunological deficiency.[8,9,10] In this study,59.16% were preterm deliveries. Dasoky HA *et al*[2], Zakariya BP *et al*[11] Jain NK *et al*[12] also found comparable results with prematurity being present in 53.3%, 60.6% and 58.49% respectively. 60.8% were weighing less than 2.5 Kg at birth which was comparable with the results of study by Dasoky HA *et a*l[2] in which low birth weight

contributed 63.3% of the study population. Low APGAR score at 5 min <1 was observed in 51.9% cases. Significant association with neonatal sepsis and birth asphyxia have been reported by others also.[7,13,14,15] Perinatal asphyxia is believed to cause immunological insult and subsequent interventions for resuscitation frequently render the newborns prone to infection.[13,15] Low birth weight and APGAR score <1 at 5 min. were statistically important risk factors of neonatal mortality in the present study (Table -5), which was also reported by others.[8,9,10]

Maternal fever was the most common maternal risk factor (67.5%) in our study. Hasan MS *et al* [13] also reported the finding of maternal fever (78.6%) as an important independent factor in their studied subjects. Maternal fever is indicative of maternal infections which may be transmitted to fetuses in utero or during passage through birth canal resulting in early onset sepsis.[13,14] Next most common maternal factor was prolonged rupture of membranes (PROM) ≥18 hours, being found 40.8% of the studied cases. Prolonged rupture of membranes (≥18 hours) has strong relations to early onset neonatal sepsis.[16] Early rupture of membranes together with prolonged labor increases the risk of acquiring ascending infections from the maternal tract into the amniotic sac.[13] Prolonged rupture of membranes (≥18 hours), fever or infection during were associated with significant neonatal mortality by others also.[4,17] However, in the present study, foul smelling liquor and maternal UTI were lesser contributors. As observed in this study, maternal fever, PROM>18 hours, meconium stained amniotic fluid, maternal age <20 years, primiparity and foul smelling liquor had significant associations with neonatal mortality.

A neonate with sepsis can present with manifold features of multiple systemic involvement, but many of them may be non-specific. [18,19] In the present study, hypothermia, respiratory distress syndrome, bleeding tendency, sclerema and jaundice were found to have statistically significant relations with neonatal mortality.

The isolation of bacteria and antimicrobial susceptibility report by blood culture remains the gold standard in the diagnosis of neonatal sepsis. But in a large number of cases the blood culture may be sterile despite the presence of clinical and laboratory signs which may be attributed to small inoculums or prior antibiotic use. In the West, Group B streptococcus is the most commonly isolated organism[16] In this study, E. coli was the commonest organism isolated in 13 (45%) out of 29 culture positive cases. Other authors had also observed E.coli as the commonest organism grown in blood culture.[1,20] The mortality rate in this study was 11.7% which is lower as compared to other studies.[13,14,15] The differences in mortality rates in neonatal sepsis may be attributed to sample sizes, socio-economic and racial factors, various microbial strains and choice of antibiotics.

Conclusion

Early onset neonatal sepsis is to be strongly suspected when risk factors associated with it are present or when newborns present with clinical features suggestive of it. A high index of suspicion is needed as clinical presentations vary widely. Once sepsis is suspected, thorough history taking about risk factors and detailed clinical evaluation need to be performed followed by appropriate laboratory analysis and blood culture for confirmation of the diagnosis. Parents should also be made aware of the common clinical presentations of sepsis.

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