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Original Research Article

Clinical profile and outcome of early onset sepsis in high risk very low birth weight neonates

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ABSTRACT

Background: Neonatal sepsis is one of the main causes of mortality and morbidity, especially in very low birth weight neonates (birth weight <1499 grams) despite the progress in hygiene, introduction of new and potent antimicrobial agents for treatment and advanced measures for diagnosis. The aim of the study was to find correlation of clinical features and risk factors of neonatal sepsis in culture positive cases.
Methods: A cross- sectional study was carried out in one hundred neonates with risk factors of septicemia after obtaining informed consent. Blood culture was done using Bactec Peds Plus/F Culture as a gold standard to diagnose septicaemia. Correlation of risk factors, clinical features with laboratory findings was obtained by using chi-square test. p-value of less than 0.05 was considered as significant.
Results: Out of 100 neonates with suspected sepsis, BACTEC culture proven sepsis was seen in 40% cases. Gram negative sepsis was seen in 62.5% cases. The most common bacteria for early onset sepsis were *Klebsiella*, *Pseudomonas* and MRSA contributing 17% each to the bacteriological profile. The most common predisposing factor and clinical feature in culture positive cases were Premature rupture of membrane >24 hours (67%) and bleeding/petechia/pupura (72%) respectively. The major cause of mortality was pulmonary hemorrhage.
Conclusions: Gram negative organism were more common and associated with higher mortality. Blood culture positivity increases with increase in number of risk factors in neonatal septicemia. A detailed history and thorough clinical examination is vital for early recognition of sepsis.

Keywords: Clinical profile, Bacteriological profile, BACTEC blood culture, Early onset sepsis, Risk factors, Very low birth weight

INTRODUCTION

Neonatal Sepsis can be defined as any systemic bacterial infection, which is confirmed by a positive blood culture in a child less than one month of age.[1]

Neonates are uniquely susceptible to infections, as the immature immune system contributes to the wide variety of organisms affecting this population. Infections during this period can have lifelong consequences even when recognized early and treated appropriately. The current Indian Neonatal Mortality rate is 28 per 1000 births and in Gujarat it is 26 per 1000 live births.[2,3] The leading cause of mortality is prematurity and its complications and second being neonatal sepsis.[3] Up to 20% of all VLBW infant deaths are caused by sepsis, and infants with sepsis are nearly three times as likely to die as those without sepsis, even after adjusting for gestational age, sex, and other co-morbidities.

Continuous monitoring blood culture systems (CMBCS), like the BACTEC currently serve as the "gold standard" for the detection of sepsis. The early diagnosis of neonatal sepsis by clinical examination is vital. Sepsis

related mortality is largely preventable with prevention of sepsis itself, timely recognition, rational antimicrobial therapy and aggressive supportive care.

METHODS

This cross sectional single centre study was carried out from February 2018 to August 2018 at a level III NICU in S.S.G Hospital, Baroda, Gujarat, India.

A written informed consent from parents was obtained, 100 neonates weighing <1499 grams, admitted in extramural NICU or delivered in the Department of Obstetrics and Gynecology S.S.G Hospital, Baroda, with one clinical feature and one risk factor for sepsis as mentioned in the inclusion criteria were recruited for the study. Inclusion criteria for risk factor and clinical features taken were as follows.

Risk factors

- Premature rupture of membranes >24 hours
- Chorioamnionitis
- Maternal fever >100°F during or within 2 weeks of delivery
- Duration of labor exceeding 24 hours
- Foul smelling liquor
- >3 per vaginal examinations during labor
- Urinary tract infection in mother
- Active resuscitation required in labor room
- Prolonged and difficult delivery with instrumentation
- Birth asphyxia (APGAR <4 at 1 minute)
- History of top feed
- Multiple pricks for blood sampling.

Clinical features

- Feed intolerance
- Jaundice (predominantly direct hyperbilirubinemia)
- Abdominal distension
- Lethargy
- Temperature instability- hypothermia /hyperthermia
- Apnoea
- Respiratory distress
- Convulsion
- Shock
- Bleeding / petechiae / purpura
- Omphalitis.

With proper consent of parents/ guardians; a detailed antenatal, natal and postnatal history followed by general and systemic examination of neonates was done in every enrolled case.

An area of approximately 5 cm over the venipuncture site was disinfected with 70% alcohol and allowed to dry, followed by application of povidone Iodine in concentric circles over the site and allowed to dry for at least 1 minute. Approximately 2 ml of blood was drawn using a sterile syringe before administration of antibiotics and inoculated aseptically into a BACTEC PEDS PLUS/F Culture Vials.

Treatment plan was modified according to blood culture reports for promoting rational antibiotic use and clinical follow up of the child till completion of hospital stay was done to study outcome of neonatal septicemia.

Correlation of risk factors, clinical features with laboratory findings was obtained by using chi-square test. p-value of less than 0.05 was considered as significant.

RESULTS

In the present study an attempt was made to study risk factors and clinical presentation of early onset sepsis. During the study period 100 preterm low birth weight neonates fulfilling the above inclusion criteria were recruited. 52 out of 100 neonates were inborn and 48 were outborn.

Table 1: Distribution of cases according to gender, gestational age, birthweight, mode of delivery and correlation with culture positivity.

Variable		Total (n=100)	BACTEC positive (n=40)	P-value (P) and Chi squared (χ^2)
Gender	Male	58	22 (38%)	P=0.6214
	Female	42	18 (42.8%)	χ^2 =0.244
Gestational age	≤30 weeks	30	11 (36.6%)	P=0.7575
	31-34 weeks	60	24 (40%)	χ^2 =0.556
	35-37 weeks	10	5 (50%)	
Birth weight (grams)	<999	19	5 (26%)	P=0.1783
	1000 to 1499	89	35 (39%)	χ^2 =1.812
Mode of delivery	Vaginal	83	34	P=0.6653
	LSCS	17	6	χ^2 =0.187

In present study group maximum neonates belonged to 31-34 week gestation age group range. A male predominance with male: female ratio of 1.4:1 was observed. In birth weight distribution the ratio of neonates with birth weight 1000-1499 grams to those with birth weight less than 1000 was 4.2:1. Normal vaginal delivery was more commonly seen as compared to lower segment caesarean section (LSCS). The correlation of above parameters with blood culture positivity is shown in Table 1.

Table 2: Correlation of risk factors of sepsis with BACTEC culture positivity.

Variable	BACTEC positive	Percentage positivity	Isolates
Premature rupture of membranes > 24 hours (N=33)	22	67	*Klebsiella*, MRSA, *Pseudomonas*, *S. aureus* *Acinetobacter*, *Enterobacter*, *Enterococcus*
Urinary tract infection in mother (N=12)	7	58	*Proteus*, *Citrobacter*, *Pseudomonas*, *Enterococcus*, *Acinetobacter*, MRSA
>3 per vaginal examinations during labor (N=33)	14	42	*Pseudomonas*, *Enterobacter*, *Acinetobacter*, *Enterococcus*, *Klebsiella*, MRSA, *S. aureus*
Active resuscitation required in labor room (N=28)	11	39	*Pseudomonas*, *Acinetobacter*, *Enterococcus*, *Klebsiella* MRSA
Chorioamnionitis (N=3)	1	33	*Klebsiella*
Maternal fever >100° F during or within 2 weeks of delivery (N=13)	4	31	*S. aureus*, *Enterococcus*, MRSA, *Klebsiella*

Table 3: BACTEC blood culture positivity according to number of risk factors present.

Number of risk factor/s present	Total cases	BACTEC positive	Bactec negative	BACTEC positivity percentage
1	78	26	52	33
2	16	9	7	56
3	6	5	1	83
Total	100	40	60	

The most common risk factors seen in the study were prolonged rupture of membrane >24 hours (33%) and ≥3 per vaginal examination during labor (33%) and maximum culture positivity was seen in was prolonged rupture of membranes (PROM) with a positivity rate of 67% followed by urinary tract in infection in mother with a culture positivity rate of 58% shown in Table 2. More the number of risk factors present enhanced the probability of culture proven sepsis as shown in Table 3.

BACTEC culture proven sepsis was seen in 40% cases and 60% were negative. Gram-negative septicemia (62.5%) was predominant than gram-positive septicaemia (37.5%). The bacteriological profile is depicted in Table 5.

The most common cause of death in our study was pulmonary hemorrhage (36%) followed by septic shock (30%), hyaline membrane disease (27%) and aspiration pneumonia (7%).

Out of all the deaths caused due to sepsis 80% were due to gram negative and 20% due to gram positive organisms. The mortality rate was significantly higher for outborn neonates (50%) as compared to inborn neonates (34%).

Table 4: Correlation between clinical features of sepsis with BACTEC culture positivity.

Presenting features	Frequency of occurrence	BACTEC positive (n=40)	BACTEC positive %
Bleeding/ petechiae/ purpura	11	8	72
Temperature instability	20	10	50
Shock	13	6	46
Respiratory distress	86	32	37
Lethargy	11	4	36
Feed intolerance	3	1	33
Apnoea	19	5	26

On correlating mortality with birth weight and gestational age; mortality rate in neonates <1000 grams were 68.4% which was significantly higher than the mortality rate in

neonates of weight range 1000-1499 which was only 34.5%. Mortality was higher in early preterm belonging to ≤30 weeks and 31-34 weeks gestational age range which was 43% each as compared to late preterm neonates with gestational age range 35-37 weeks which was only 20%.

Table 5: Bacteriological profile of early onset sepsis.

Organism	Frequency (N=40)	Percentage
Gram negative bacteria		
Klebsiella	7	17.50
Pseudomonas	7	17.50
Acinetobacter	5	12.50
Enterobacter	4	10
Proteus	1	2.50
Citrobacter	1	2.50
Gram positive bacteria		
MRSA	7	17.50
Staphylococcus aureus	5	12.50
Enterococcus	3	7.50

DISCUSSION

Sepsis occurring within 72 hours of life is labeled as early onset septicemia. It is usually acquired before or during delivery due to ascending infection following rupture of membranes or passage of the baby through an infected birth canal or at the time of resuscitation in labor room.[4,5]

A systematic analysis of global, national and regional causes of child mortality in 2013 identified preterm birth complications and infections to be the two major causes of neonatal deaths in India. The incidence of sepsis is twice as high among moderately premature infants and highest among VLBW infants with recent reports ranging from 15-23 percent per 1000 VLBW births.[6]

In present study, no statistical correlation was found when blood culture positivity was compared with variables like gender, birth weight, gestational age and mode of delivery using chi square test for statistical analysis. These results were consistent with the study conducted by Sarangi K et al, Maharaja P et al, Satyamurthi B et al.[7-9]

Out of 100 cases with suspected sepsis, culture positivity rate was 40% predominantly due to gram negative organisms. The culture positivity in various studies conducted in term and preterm neonates 29.8% by Hoque M et al, 33% by Sarangi K et al, 35.9% by Satyamurthi B et al, 34% by Kalpana KL and 47% by Kayange N et al with predominance of gram negative bacteria.[7,9-12] The most common organism isolated were *Pseudomonas*, *Klebsiella*, MRSA. Only one isolate of Citrobacter and Proteus was found in our study and both these cases had history of urinary tract infection in mother. The study done by Hoque M et al had Acinetobacter (41.2%) as the most common organism followed by *Klebsiella pneumoniae* (23.5%); study done by Lim WH et al [13] had *E. coli* (40%) and *Klebsiella* (20%) for early onset septicaemia; study done by Satyamurthi B et al had *Klebsiella* followed by *S. aureus* for early onset septicemia.[9,10,13]

Gram-negative (GN) bacteria have often been implicated in the pathogenesis of severe sepsis and septic shock, although the exact mechanism is uncertain.[14] There is evidence to support two different theories on how gram negative bacteria induce harmful systemic responses. The intravascular stimulus hypothesis states that bacteria invade through a normal or damaged epithelium and enter the bloodstream, inducing systemic inflammatory responses (for example, increased vascular permeability, leukocyte–endothelial adhesion, and activation of complement and clotting pathways) resulting in multiorgan failure. A second theory suggests that the multiorgan dysfunction and shock result from neuroendocrine dysregulation and mediators released into the bloodstream from the infected tissues; circulating bacteria or endotoxin are not needed as direct stimuli for intravascular inflammation.[15]

High culture positivity rate was seen in our study as preterm VLBW neonates are more susceptible to infection due to various reasons like lower levels of IgG which are passively transferred during the third trimester; mucous membrane defenses such as secretory immunoglobulin A (IgA), mucin, and defensins have been shown in some studies to be deficient in VLBW neonates and the first line of defense against infection is an intact epidermis and mucous membranes, which are compromised in VLBW infants.[4,16-18]

The most common risk factor associated with BACTEC blood culture positivity was prolonged rupture of membranes (PROM) with a positivity rate of 67% followed by urinary tract in infection in mother (58%). In the study done by Maharaja P et al low birth weight followed by PROM were the most common risk factors correlating to sepsis.[8] As all our enrolled case belonged to low birth weight category these results were similar to our study. In the study done by Roy P et al most common risk factors associated with blood culture positivity were urinary tract in infection in mother (100%), Fever in the mother during labour (68%), premature rupture of membranes (60%).[19] The difference of above results from our study probably reflects variations in population characteristics and in predisposing factors.

BACTEC blood culture positivity in our study was related to the number of risk factors present i.e as the number of risk factors increased, the risk of septicemia in the neonate also increased and this was also observed in the study done by Roy P et al.[19]

A remarkable feature of the clinical manifestations of neonatal septicemia is the non-specificity of symptoms evolving differently in each infant. The ability of the newborn baby to respond to an infection is limited to identical stereotyped responses to a wide range of insults, thus producing an identical clinical picture in a variety of conditions. The earliest signs of sepsis are often subtle and nonspecific and need a high index of suspicion for early diagnosis.

The most common clinical feature associated with BACTEC blood culture positivity seen in our study was Bleeding/ petechiae/purpura (72%) followed by temperature instability (50%) and shock (46%). The most common clinical features associated with blood culture positivity seen in various studies are temperature instability followed by breathlessness in the study done by Maharaja P et al; apnoea (65.8%) followed by poor activity (43%) and increased respiratory effort (36.7%) in the study done by Lim WH et al.[8,13]

Mortality rate in our study was 41%. Higher mortality rates were seen in out-born cases due to multiple factors like inadequate early intervention from the place referral, a delay in referral and transport from peripheral health facilities to referral centers and improper transportation without maintaining the warm chain. The most common cause of neonatal death in present study was pulmonary hemorrhage followed by septic shock. Preterm VLBW neonates are at high risk for respiratory complications like pulmonary haemorrhage due to surfactant deficiency and that has played a major role in mortality of VLBW neonates rather than septicaemia in our study. A study done by Lim JW et al, in VLBW neonates cardiorespiratory problems were the commonest cause of death followed by infections which was similar to our study.[20]

In our study mortality rate was found to be increasing with decreasing birth weight and gestational age. Similar findings were noted in the study done by Sohely Y et al and Gavia M et al.[21,22]

In culture positive neonatal deaths gram negative organism were seen in majority which was in concordance to study done by Lim WH et al and Kalpana KL.[11,13]

So, to conclude, neonatal sepsis is a well-recognized cause of neonatal mortality and morbidity and more pronounced in VLBW infants. Present study confirmed the presence of major concern about the high rate of sepsis among VLBW infants. A detailed antenatal, natal and postnatal history should be taken to know the risk factors of septicaemia. Clinical examination is of utmost importance for early suspicion of neonatal sepsis. Antibiotic therapy should be considered in absence of clinical features if >2 risk factors of sepsis are present. Blood culture should be done in all suspected cases of neonatal septicemia, preferably by BACTEC method which provides early confirmation of sepsis. Organisms causing neonatal sepsis and their antibiotic susceptibility vary from place to place. Antibiotics should be given according to culture and sensitivity rather than empirical treatment for better outcomes. To keep the infection rates low, strict protocol for asepsis in neonatal units must be adhered to when handling these high-risk infants as prevention is better than cure.

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