



Clinical Outcome Of Low Birth Weight Neonates With Early Stoppage Of Antibiotics After A Negative Blood Culture Diagnosed With Early Onset Neonatal Sepsis In A Tertiary Care Hospital.

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Type of Publication: Original Research Paper

Conflicts of Interest: Nil

Abstract

Introduction:- New born mortality represents 40% of all deaths of children <5 years of age in developing countries. Out of the several contributors to neonatal mortality, sepsis forms the single largest cause of death. . Over all culture positive sepsis in developing countries is 9.5%. So almost in all suspected sepsis , antimicrobial therapy is initiated empirically before results of blood cultures are available . Treating an un infected neonate for 5 to 7 days means disrupting maternal bonding and breastfeeding for extended period of time.

Aims & Objectives:- 1.To study the prevalence and distribution of risk factors in low birth weight neonates associated with early onset neonatal sepsis 2.Safety of discontinuation of antibiotics after 48hr of culture negativity in suspected early onset neonatal sepsis in LBW neonates. 3.To study the Incidence of culture positivity in symptomatic LBW neonates with or without risk factors in suspected early onset sepsis.

Materials And Methods: - This a Prospective study , The source of data were the LBW neonates admitted in NICU with suspected sepsis . The neonates included in this study should have-1.Clinical features of sepsis in LBW neonates with or without maternal risk factors 2.SEPSIS SCREEN MARKERS Of neonates positive initially (within 12 hrs of delivery). Neonates fulfilling the above said criteria were investigated with necessary investigations .If asymptomatic and 48 hours blood culture is negative and repeat screening test (CRP) negative then antibiotics were stopped.& continuous monitoring was done at least for 72 hours before return to ‘rooming in’ with mother.

Result:- Out of 135 cases 68 were continued with antibiotic for >2 days and 65 given antibiotic ≤2 days & 2 deaths within 48 hours. Out of 68 cases (antibiotic >2 days), 32(23.7%) were blood culture positive (most of them are klebsiella& pseudomonas) and 10(7.4%) were CSF culture positive. 11 babies succumbed to death.

Conclusion:-With the present study, it was observed that along with evaluation of clinical condition of the baby and 48 hour BacTec/Alert blood culture report, antibiotics can be safely discontinued in those babies who are clinically asymptomatic and 48 hour blood culture negative i.e 52 out of 65 cases (85.4%) in the present study.

Keywords: SEPSIS, LBW, PRE TERM, CRP, BLOOD CULTURE

Introduction

According to the World Health Organization (WHO) estimates there are about 5 million neonatal deaths in a year globally, out of which 98% occur in developing countries, that contributes 26-34% of total deaths each year^[1]. Among the commonest cause of neonatal mortality; Sepsis contributes about 30-50% of the total neonatal deaths in developing countries. The term, neonatal sepsis, has been traditionally defined as bacteraemia accompanied by hemodynamic compromise and systemic signs of infection.^[2] In resource poor countries, the diagnosis of neonatal sepsis is often based solely on clinical signs as blood culture and adjunct laboratory investigations are often not possible.^[3] About 2-3% of term and 20-30% of preterm infants die from EONS despite receiving extensive care in hospitals in the form of ventilator and inotropic support in intensive care set up^[4]. In an untreated or inadequately treated case often leads to prolonged dependence on health care and this aggravates the

Aims And Objectives-

Objectives:- 1.To study the prevalence and distribution of risk factors in low birth weight neonates associated with early onset neonatal sepsis. 2. Safety of discontinuation of antibiotics after 48hr of culture negativity in suspected early onset neonatal sepsis in LBW neonates. 3.To study the Incidence of culture positivity in symptomatic LBW neonates with or without risk factors in suspected early onset sepsis.

Materials And Methods-

Study Type: - Prospective observational study.

Study Area And Setting:- All LBW neonates admitted in NICU with suspected sepsis in HI-TECH MEDICAL COLLEGE AND HOSPITAL, BHUBANESWAR, from 1st October 2020 – 30th September 2022 (2 YEARS). Approval from Hi-Tech medical college Institutional Ethics committee was taken before the study.

Inclusion Criteria:- 1.LBW 1.5 kg to <2.5 kg neonates on admission to NICU with risk factors of sepsis 2.LBW neonates with clinical features of sepsis 3.Markers of sepsis screen positive within 12 hrs of birth.4.Parents given consent.

Exclusion Criteria: - 1.Neonates with suspected TORCH group of infection.2.Any congenital anomaly. 3.Any surgical conditions. 4.Neonates who

situation especially in developing countries. As there is very non-specific signs and symptoms of sepsis, so “Suspected sepsis” is one of the common diagnosis made in neonatal care^[5]. Clinical suspicion therefore frequently leads to initiation of empirical antibiotic therapy in an uninfected infant. The incidence of culture confirmed early-onset sepsis is rather very low, in LBW infants in developed countries. Approximately 6 to 16 times the infants receive overtreatment for culture negative sepsis^[6]. However, treating an uninfected infant for 5 to 7 days in a case of suspected sepsis means disturbing & disrupting the maternal bonding and breast feeding for an extended period of time, pain and distress from starting IVs, exposing the infant to drugs with potential toxicities, fostering the development of antibiotic resistant flora and increasing the probability that the infant will experience a more serious morbidity later in the course of hospitalization^[7]

have received antibiotics prior to hospitalisation.5.Parents not given consent.

A total number of 135 cases were included in the present study who had fulfilled the above criteria.

Method:- The neonates included in this study should have-

1.Clinical features of sepsis in LBW neonates with or without maternal risk factors^[8] Risk factors are-a. Foul smelling liquor, b. Spontaneous pre maturity, c. Rupture of membranes >24 hrs, d. Prolonged labour>24 hrs, e. Perinatal asphyxia, f. Single unclean or >3 sterile prevaginal examination, g. Maternal pyrexia, h. Maternal UTI.

2. Markers Of Sepsis Screen neonates positive initially (within 12 hrs of delivery) i.e. ^[8]- a. Total leukocyte count <5000/cumm, b. Absolute neutrophil count: low as per Monroe chart for term, Mouzinho chart for very low birth weight neonates. c. Immature neutrophils: Total neutrophils > 0.2, d. micro ESR >15 mm in 1st hr, e.CRP positive >10 mg/dl.

If 2 or more parameters abnormal, it should be considered as a positive sepsis screen, these neonates were included in this study. All the 135 enrolled neonates were evaluated at 30 mins of life for ESN score^[9]. Cut off ESN score for -preterm is- ≤12 & ≤11 for term neonate was taken in our study.^[9] Neonates fulfilling the above said criteria were

investigated with necessary tests like blood culture, urine culture, CSF culture and those found positive for any microorganism growth were studied further for relevant antimicrobial sensitivity pattern(s). If asymptomatic and 48 hours blood culture is negative

and repeat screening test (CRP) negative then antibiotics was stopped.& continued monitoring at least 72 hours before return to ‘rooming in’ with mother.

Results-

1.1 Gender distribution

Out of 135 neonates, 88(65.2%) cases were males and 47(34.8%) females

Gender	No.	%
Male	88	65.2
Female	47	34.8
Total	135	100

1.2 Gestational Age and mode of delivery

Gestational Age in weeks	No.	%
<34 weeks	24	17.8
34 week – <37 weeks	61	45.2
≥37 weeks	50	37
Mode of Delivery		
NVD	16	11.9
LSCS	119	88.1
Total	135	100

1.3 Mode of delivery according to the POG

Gestational Age	Mode of Delivery				Total		c2, p
	NVD		LSCS				
	No.	%	No.	%	No.	%	
<34 Weeks	0	0	24	100	24	100	c2=3.940 p=0.139
34- <37 weeks	9	14.8	52	85.2	61	100	
≥37 weeks	7	14	43	86	50	100	

Total	16	11.9	119	88.1	135	100	
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Majority of the neonates delivered by LSCS as it is a tertiary care setup & majority of them referred from other institutions.

Out of 135 cases, 24 were <34 weeks in which all of the cases were LSCS, similarly 61 cases were 34-<37 weeks in which 9(14.8%) were NVD and 52(85.2%) LSCS, out of 50 cases were ≥37 weeks in which 7 (14%) were NVD and 43(86%) LSCS. There was no significant association between mode of delivery and gestational age with p=0.139.

1.5 Sepsis Screening and 48 hrs.blood culture

Sepsis screening revealed that 11 (8.1%) had low ANC, 92 (68.1%) sepsis positive and 32 (23.7%) CRP-positive. Blood culture revealed that 32.37% cases had growth.

1.4 Prevalence and distribution of Maternal risk factors in LBW Neonates.

Most common maternal risk factors i.e. 50.4% had prom >12 hrs followed by 31.1% Prolonged Labour, 17.0% Perinatal Asphyxia, 10.4% IDM.

Maternal Risk Factors	No.	%
HTN	3	2.2
Prom >12 Hours	68	50.4
Gravida ->5	3	2.2
Prolonged Labour	42	31.1
MSL	6	4.4
GDM	10	7.4
Pre Eclampsia	13	9.6
Perinatal Asphyxia	23	17
Foul Smelling Liquor	2	1.5
Unclean P/V Examination	3	2.2
Fever	9	6.7
IDM	14	10.4

Sepsis Screening (N=135)	No.	%
LOW ANC	11	8.1
POSITIVE	92	68.1
CRP -POSITIVE	32	23.7
48 Hour Blood Culture (N=135)		

NO GROWTH	103	76.3
GROWTH	32	23.7
GROWTH (N=32)		
KLEBSILLA	9	28.1
E.COLI	6	18.8
PSEUDOMONAS	9	28.1
STAPH AUREUS	8	25.0

1.6 Association of 48 hrs blood culture

Out of 135 cases, 11 were low ANC in which 9 (81.8%) had no growth and 2(18.2%) growth, Out of 92 cases of sepsis positive 70(76.1%) had no growth and 22(23.9%) growth. Out of 32 cases of CRP-positive, 24(75%) had no growth and 8(25%) growth. There was no significant association between 48 hrs. blood culture and sepsis screening with p=0.897.

1.7 Complications With Sepsis Screening

Most common complications i.e 11.1% cases had AKI followed by 8.1% each had VAP & NEC, 7.4% each BPD & culture positive meningitis.

Table 1.6 Association of 48 hrs blood culture with sepsis screening							
Sepsis Screening	48 Hour Blood Culture				Total		c2, p
	NO GROWTH		GROWTH				
	No.	%	No.	%	No.	%	
LOW ANC	9	81.8	2	18.2	11	100	c2=0.217 p=0.897
POSITIVE	70	76.1	22	23.9	92	100	
CRP -POSITIVE	24	75	8	25	32	100	
Total	103	76.3	32	23.7	135	100	

Table 1.7 Complications (N=135)		
Complications	No.	%
VAP	11	8.1
BPD	10	7.4
PPHN	6	4.4

PNEUMOTHORAX	2	1.5
AKI	15	11.1
NEC	11	8.1
IVH	4	3
DIC	4	3
CULTURE POSITIVE MENINGITIS	10	7.4

1.8 Comparison of ESN score at 30 min, use of inotropes and mechanical ventilation among days of NICU stay

Table 1.8 Comparison of ESN score at 30 min, use of inotropes and mechanical ventilation among days of NICU stay

Variables	Days of NICU Stay						Total		ANOVA 'p' value
	≤3		4-10		>10		N	Mean ± SD	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD			
ESN Score at 30 min	70	13.23 ± 2.16	22	10.68 ± 1.29	43	9.47 ± 1.58	135	11.61 ± 2.53	0.000
Use of Inotropes in day	15	1.53 ± 1.55	20	2.05 ± 1.05	43	4.40 ± 3.06	78	3.24 ± 2.74	0.000
Mechanical Ventilation	4	6.75 ± 10.18	5	3.60 ± 2.30	27	10.26 ± 17.41	36	8.94 ± 15.51	0.661

The mean ± SD of ESN score at 30 minutes was 13.23 ± 2.16 in ≤3 days of NICU stay, 10.68 ± 6.8 in 4-10 days and 9.47 ± 1.58 in >10 days and the difference was significant with p=0.000. The mean ± SD of ESN score at 30 min was significantly higher in ≤3 days of NICU stay as compared to 4-10 & >10 days.

The mean ± SD of use of ionotropes was significantly higher in >10 days of NICU stay i.e. 4.40 ± 3.06 days as compared to ≤3 days (1.53 ± 1.55 days) and 4-10 days (2.05 ± 1.05) with p=0.000.

The mean ± SD of mechanical ventilation was 6.75 ± 10.18 in ≤3 days of NICU stay, 3.60 ± 2.30 in 4-10 days and 10.26 ± 17.41 in >10 days and the difference was not significant (p=0.661).

1.9 Association of clinical feature of sepsis, sepsis screening, 48 hrs blood culture and days of NICU stay with maternal risk factor

Table 1.9 Association of clinical feature of sepsis, sepsis screening, 48 hrs blood culture and days of NICU stay with maternal risk factor

Clinical feature of sepsis	Maternal Risk Factor						Total (N=135)		c2, p
	No risk factor (N=10)		≤2 (N=110)		>2 (N=15)		No.	%	
	No.	%	No.	%	No.	%			

No symptoms	0	0	2	1.8	0	0	2	1.5	c2=4.199 p=0.380
≤2	5	50	49	44.5	3	20	57	42.2	
>2	5	50	59	53.6	12	80	76	56.3	
Sepsis Screening									
Low ANC	2	20	9	8.2	0	0	11	8.1	c2=13.833 p=0.008
Positive	3	30	74	67.3	15	100	92	68.1	
CRP – positive	5	50	27	24.5	0	0	32	23.7	
48 Hour Blood Culture									
No Growth	7	70	85	77.3	11	73.3	103	76.3	c2=0.350 p=0.839
Growth	3	30	25	22.7	4	26.7	32	23.7	
Days of NICU Stay									
≤3	5	50	57	51.8	8	53.3	70	51.9	c2=1.989 p=0.738
4-10	1	10	20	18.2	1	6.7	22	16.3	
>10	4	40	33	30	6	40	43	31.9	

Out of 135 cases, 10 cases were having no maternal risk factor, 110 cases having ≤2 maternal risk factor and 15 cases having >2 maternal risk factor. Among those having no maternal risk factor cases, 2 (20%) cases having low ANC sepsis screening, 3 (30%) having positive and 5(50%) CRP-positivity. Similarly those having ≤2 maternal risk factor cases, 9(8.2%) cases having low ANC sepsis screening, 74(67.3%) positive and 27(24.5%) CRP-positive. Among those having >2 maternal risk factor, all of the cases having positive sepsis screening and none of the cases were low ANC and CRP-positive. There was a significant association of sepsis screening and maternal risk factors with p=0.008.

1.10 Descriptive statistics of clinical profile of neonates

The mean ± SD and median(IQR) of birth weight of neonates was 1.96 ± 0.31 kg and 1.99(1.67-2.20) kg. Mean ± SD and median(IQR) of APGAR score at 5 min was 7.77 ± 0.63 & 8.00(7.00-8.00). Mean ± SD and median(IQR) of ESN score at 30 min was 11.61 ± 2.53 & 12.00(9.00-14.00). Mean ± SD and median(IQR) of repeat CRP(Q) was 29.77 ± 28.89 mg/dl & 12.80(9.00-50.30) mg/dl. Mean ± SD and median(IQR) of use of inotropes was 3.24 ± 2.74 days & 2.00(1.00-5.00) day. Mean ± SD and median(IQR) of need of ventilation was 7.47 ± 13.09 & 4.00(1.00-7.00). Mean ± SD and median(IQR) of C-PAP was 3.46 ± 3.65 & 2.00(1.00-5.00). Mean ± SD and median(IQR) of mechanical ventilation was 8.94 ± 15.51 & 6.00(3.00-8.00). Mean ± SD and median(IQR) of duration of antibiotics was 10.90 ± 11.96 & 2.00(2.00-15.50).

Table 1.10
Descriptive statistics of clinical profile of neonates

Variables	N	Mean ± SD	Median(IQR)	Range
Birth Weight In Kg	135	1.96 ± 0.31	1.99(1.67-2.20)	(1.51-2.45)
APGAR Score at 5 Min	135	7.77 ± 0.63	8.00(7.00-8.00)	(6.00-9.00)
ESN Score at 30 min of life	135	11.61 ± 2.53	12.00(9.00-14.00)	(4.00-15.00)

Repeat CRP(Q) Mg/Dl	135	29.77 ± 28.89	12.80(9.00-50.30)	(3.90-109.80)
Use of Inotropes in day	78	3.24 ± 2.74	2.00(1.00-5.00)	(1.00-15.00)
Need of Ventilation	71	7.47 ± 13.09	4.00(1.00-7.00)	(0.50-97.00)
C-PAP	60	3.46 ± 3.65	2.00(1.00-5.00)	(0.50-23.00)
Mechanical Ventilation	36	8.94 ± 15.51	6.00(3.00-8.00)	(1.00-95.00)
Duration of Antibiotics	133	10.90 ± 11.96	2.00(2.00-15.50)	(1.00-49.00)

Discussion-

The given study is a single-centre prospective study conducted in the tertiary care hospital setting in Bhubaneswar, Odisha, and studied the demographic profile of those neonates identified as suspected sepsis, their associated risk factors, and the further attempted to assess the need to continue antibiotics based on the results of blood culture. However, there is no data available earlier regarding the safety of such practice.

Male babies were predominant in the present study, the male to female Ratio being 1.87:1. Similar finding was seen in the study done by Rajarshi Basu et al ^[19], where Male to Female ratio was 1.5: 1. Morven S and colleagues ^[10] observed male to female ratio of 2:1, which again is consistent with the present study. In the present study, Early onset culture positive neonatal sepsis was more common among male babies as well (male: female ratio 1.87:1). In the study done by Chandra ^[12] in 1998, he mentioned that the factors regulating the synthesis of gamma globulin are situated on X-chromosome, which makes male inherently more prone for sepsis.

Out of 135 LBW cases, who were suspected to have sepsis in the present study, 45% are late preterm, 17% is very preterm deliveries (62%-Preterm Deliveries) & 38% term. Out of this 68% cases are sepsis screen positive, 23.7% cases were positive for blood culture at 48 hours of life & around 7.4% cases were positive for CSF culture. This shows LBW babies are at increased risk of sepsis and other neonatal illness with clinical symptoms similar to sepsis. Rajarshi Basu et al 2014^[10] and Heena et al^[13] 2016 showed majority of cases of proven sepsis to be in premature and low birth weight (65%).

Maternal risk factors were sub classified into 3 categories, GROUP-A-no maternal risk factors

(n=10), both sepsis screen & blood culture was positive in 30% cases, around 40% of cases required NICU stay >10 days. GROUP-B- ≤2 risk factors (n=110) sepsis screen & blood culture was positive in 67% & 23% cases respectively, around 30% of cases required NICU stay >10 days. GROUP-C->2 risk factors (n=15) sepsis screen & blood culture was positive in 100% & 32% cases respectively, around 32% of cases required NICU stay >10 days. In a study done by Vamsi Krishna kondle et al ^[14] on septicemia in neonates, around 14% of cases had no risk factors, as compared to 7.4% in the present study.

Out of 135 suspected EOS cases. Overall 64.16% symptomatic babies were screen positive. However, 16.30% of asymptomatic babies (n=15) were also sepsis screen positive. 32 (23.7%) showed growth in blood culture media, in which blood was drawn prior to starting antibiotics. The finding was consistent with the result obtained by Dr. G. Vandana 2017 [15] and Mamtajoo et al 2018 [14] where the culture positivity was 22% and 18% respectively.

Among the 11 babies who died, 5 (45.45%) were blood culture positive. 2 deaths (18.2%) death occurred within 48 hours of birth. There were 4 (36.36%) deaths whose blood culture were negative due to acquired complications like severe sepsis, pneumothorax, NEC, AKI. This high mortality in culture positive babies could be due to delay & in appropriate antibiotic initiation, presence of >3 maternal risk factors at birth and development of complications. Mathur et al ^[17], who observed mortality of 64.5% when the onset of illness was early.

Laboratory markers, although consistently obtained and discussed, do not appear to influence decision-making, as out of 10 cases in whom antibiotics were stopped on the basis of negative CRP report, 5 (50%)

cases were re admitted to NICU. This shows sepsis screen is neither 100% sensitive or specific. Hence, recent guidelines do not advise continuation of antibiotic therapy based on serial abnormal values in the absence of culture confirmed infection [16].

Each case of culture-proven or culture-negative sepsis was also re-analyzed; in fact, one of the major concerns of clinicians regarding Antibiotic stewardship is that giving shorter antibiotic treatments at birth or narrowing the antibiotic spectrum may be associated with an increased risk of infectious relapses (20%) cases and neonatal deaths (8.1%) cases.

What This Study Adds? - The Extended Sick Neonate Score (ESNS) can predict 'in-hospital mortality' outcome with good sensitivity and specificity at admission in all gestational ages. In the present study ESNS had a strong correlation to predict mortality in sick hospitalized neonates even when stratified by gestation. From the feasibility point of view our score is simple to apply for a trained healthcare worker with access to equipment that would be considered routine for any specialized new born care unit. The mean \pm SD of ESN score increases with the increase of birth weight ($p=0.000$) in our study which is statically significant. A low ESN Score <11 was found in critically ill baby who are requiring inotropes 78 cases (57.7%) & a score of <9 in whom ventilatory support was required i.e. 36 cases (26.6%). A high ESN score is inversely proportional to the days of NICU stay & adverse clinical outcomes.

Summary And Conclusion-

During the period of study, 228 number of LBW babies were born in the O & G Dept. of the Hi-Tech medical college and hospital. On the basis of exclusion criteria, 94 neonates were excluded from the study and the remaining 135 included in the observations. Two number of death occurred within 48 hrs. of born. Treatment and observations were taken on 133 neonates with LBW. Out of 133 cases 68 were continued with antibiotic for >2 days and 65 given antibiotic ≤ 2 days. Out of 68 cases (antibiotic >2 days), 32 (23.7%) were blood culture positive (most of them are klebsiella & pseudomonas) and 10 (7.4%) were CSF culture positive. Average days of antibiotic was 20.08 ± 11.14 . Average days of NICU stay was 17.51 ± 12.43 . Complications were noticed

for 37 cases. 11 babies succumbed to death. Out of 65 cases (antibiotic ≤ 2 days), 55 were asymptomatic (no features of sepsis) and 10 symptomatic (but CRP negative). After 3 days of closed observations, 8 (14.5%) cases were re-admission from asymptomatic cases and 5 (50%) cases were re-admission from symptomatic cases, there was no cases of death.

With the present study, it was observed that along with evaluation of clinical condition of the baby and 48 hour BacTec/Alert blood culture report, antibiotics can be safely discontinued in those babies who are clinically asymptomatic and 48 hour blood culture negative i.e. 52 out of 65 cases (85.4%) in the present study. Early onset sepsis has vague clinical presentation for which empirical antibiotics is practiced universally without knowing the blood culture status.

What the present study adds to the existing knowledge?

This study provides a means to reduce the burden and antibiotic misuse by establishing safety in discontinuing antibiotics in term neonates with suspected early onset sepsis with negative blood culture at 48 hours and clinically asymptomatic neonates. The inclusion of ESN score which was easy to carry out & it strongly correlates with the days of NICU stay (including the requirement of inotropes and ventilation).

The limitation of the present study- was smaller sample size with male baby predominance, Majority of the cases were preterm deliveries and the study was a single center study. Our results may not be generalizable to other settings with different personnel, structures, and patient mixes (e.g., settings where all neonates were in-born).

Ethics Committee : Approval from Hi-Tech medical college Institutional Ethics Committee , Bhubaneswar

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