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Original Research Article

Early Discontinuation of Antibiotics in Patients with Suspected Early Onset Sepsis Based on A Negative Blood Culture and Their 7-Day Outcome

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Abstract

Aim: the aim of this study to evaluate the early stoppage of antibiotics in blood culture negative term suspected early onset sepsis and their 7 days outcome.

Materials and methods: A cross-sectional study were conducted in the Department of Paediatrics, Patna Medical College and Hospital, Patna, Bihar India for 12 months. Symptomatic babies >37 weeks of gestation with possible EOS and Gestational age ≥37 weeks with suspected early onset sepsis were included in this study.

Results: Out of 186, 178 (95.7%) were symptomatic and 8 (4.3%) were asymptomatic at the time of admission. Maximum death occurred on day 1 of life i.e., 19 (67.8%), on day 2 6 (21.4%) and on day 3, 3 (10.7%). Mortality of culture positive sepsis was found to be 58.4 % (28 deaths out of 48 cultures positive). Among various risk factors studied in relation to suspected early onset sepsis, low birth weight led the list in the present study with 80 (43%) cases, followed by perinatal asphyxia 45(24.2%) and prolonged rupture of membranes 37 (19.9%).A significant association was noted between the incidence of blood culture positivity with 2 risk factors namely, low birth weight and prolonged rupture of membranes ($p<0.05$).Among 186 cases, 64 (34.4%) had no perinatal risk factors at the time of admission whereas 77(41.3%) had single risk factor. 2 risk factors were noted in 34 (18.3%) of the study population, >2 risk factor 44 (23.7%), ≥ 3 risk factors were seen in 11 (5.9%) of the cases. However, 16 (8.6%) babies had foul smelling liquor. Out of the 64 cases which had nil perinatal risk factor, all were symptomatic at admission.

Conclusion: it was observed that along with evaluation of clinical condition of the baby and 48-hour BacT/Alert blood culture report, antibiotics can be safely discontinued in those babies who are clinically asymptomatic and 48-hour blood culture negative.

Keywords: antibiotics, sepsis, neoanates.

Introduction

Early-onset sepsis (EOS) is a major concern for neonatologists. The most frequent causative pathogens are *group B streptococci* (GBS) and *Escherichia coli.*[1] Currently, neonates with one or more risk factors for EOS, as maternal fever or premature rupture of membranes, undergo sepsis screening, according to the unit protocols, and empirically start antibiotics. Clinicians prolong the therapy even in the absence of clinical signs of infection, while awaiting the results of blood cultures (BC), often on the plasmatic trend of conventional infection biomarkers. New biomarkers such as presepsin (PSEP) seem to be promising to predict EOS[2], but it has not yet entered current clinical practice. Conversely, C-reactive protein (CRP) and procalcitonin (PCT) are the most widely used markers to guide antibiotic therapy, although their early increase after birth is not always related to the onset of infections[3,4]. Recent studies have shown that in cases of suspected EOS, when the neonate has no uncertain symptoms and the blood culture is negative at 36–48 h, the discontinuation of empiric antibiotics, guided by the negativity or reduction of the biomarkers of infection (CRP, PCT, and/or PSEP) is a safe practice and saves improperly used antibiotics and costs, with a low rate of suspected re-infections (less than 1%) but no culture-proven bacterial re-infections[5], and above all, without study-related mortality[5-7].

Materials and methods:

A cross-sectional study was conducted in the Department of Paediatrics, Patna Medical College and Hospital, Patna, Bihar India for 12 months. after taking the approval of the protocol review committee and institutional ethics committee. Symptomatic babies >37 weeks of gestation with possible EOS and Gestational age ≥37 weeks with suspected early onset sepsis were included in this study. Neonates with suspected TORCH group of infection, any congenital anomaly, Congenital heart disease, Syndromic baby and any surgical conditions were excluded from this study. A total number of 186 cases were included in the present study that had fulfilled the criteria.

Method:

All the investigation was done in the central laboratory. Using all aseptic precautions blood was collected from peripheral vein prior to starting antibiotic treatment.

Statistical analysis:

Statistical analysis was done by statistical software SPSS for windows version 23. P values were calculated using chi-square test. $P< 0.05$ was considered as significant and $P< 0.01$ as highly significant.

Results:

Table 1: Age distribution in the study group (n=186).

Age in hours	No. of cases	Symptomatic
<24 hours	75 (40.3%)	70 (93.3%)
24-48 hours	52 (28%)	50 (96%)
48-72 hours	39 (21%)	38 (97.5%)
72-96 hours	20 (10.8%)	20 (100%)
Total	**186 (100%)**	

All babies who were subsequently culture positive presented within 24 hours of life.

Out of 186 cases 75 (40.3%) presented within <24 hours of age, out of which, 93.3% were symptomatic; 52 (28%) cases presented within 24 to 48 hours of age, of which 96% were symptomatic, and 39 (21%) presented to 48 to 72 hours of life and rest 20 (10.8%) were 72 to 96 hours of age at the time of presentation.

Table 2: Sex distribution in the study group (n=186)

Sex	No. of cases	Growth on blood culture
Female	67 (36%)	22 (32.8%)
Male	119 (64%)	26(21.8%)
Total	**186 (100%)**	**48 (25.8%)**

Out of 186 cases, the majority i.e. 119 (64%) were male and 67 (36%) were female. The male to female ratio in the present study was 1.8:1. Also, culture positive sepsis was seen more in males with the male to female ratio being 1.2:1.

Table 3: Distribution of cases with respect to birth weight

Birth weight	No of cases	Symptomatic	Growth on blood culture (n=48)
<2.5kg	80 (43%)	75 (93.7%)	29 (60%)
≥2.5kg	106 (57%)	103 (97%)	19 (39.5%)
Total	**186 (100%)**	**178**	**48 (100%)**

Out of 186 cases, 106 (57%) were normal birth weight (≥2.5kg) and 80 (43.2%) were low birth weight. 75 (93.7%) babies out of 80 cases of the LBW babies were symptomatic .19 (67.8%) of 28 died subsequently.

Among the 48 culture positive babies, 29 (60%) were Low birth weight.

Table 4: Initial assessment at the time of admission (n=186)

Initial assessment	No of cases
Symptomatic	178 (95.7%)
Asymptomatic	8 (4.3%)
Total	**186 (100%)**

Out of 186, 178 (95.7%) were symptomatic and 8 (4.3%) were asymptomatic at the time of admission.

Table 5: Relation of death rate with day of hospitalisation

Day of hospitalization	Death (n=28)
Day 1	19 (67.8%)
Day 2	6 (21.4%)
Day 3	3 (10.7%)
Total	**28 (100%)**

Maximum death occurred on day 1 of life i.e., 19 (67.8%), on day 2 6 (21.4%) and on day 3, 3 (10.7%). Mortality of culture positive sepsis was found to be 58.4% (28 deaths out of 48 cultures positive).

Table 6: Incidence of perinatal risk factor among suspected case of early onset sepsis (n=186)

Risk factors	No of cases	P value
Low birth weight	80 (43%)	0.004
Prolonged rupture of membrane	37 (19.9%)	0.002
Foul smelling liquor	16 (8.6%)	0.086
Unclean vaginal examination	8 (4.3%)	0.112
Prolonged labour	9 (4.8%)	1.71
Maternal fever	2 (1.1%)	0.43
Perinatal asphyxia	45 (24.2%)	3.65

P value <.05, chi-square test applied

Among various risk factors studied in relation to suspected early onset sepsis, low birth weight led the list in the present study with 80 (43%) cases, followed by perinatal asphyxia 45(24.2%) and prolonged rupture of membranes 37 (19.9%).
A significant association was noted between the incidence of blood culture positivity with 2 risk factors namely, low birth weight and prolonged rupture of membranes ($p<0.05$).

Table 7: Number of perinatal risk factors present at the time of admission (n=186)

No of risk factor	No of cases	Growth on blood culture
0	64 (34.4%)	11 (17.2%)
1	77 (41.3%)	15 (19.5%)
2	34 (18.3%)	14 (41.2%)
≥3	11 (5.9%)	8 (72.7%)
Foul smelling liquor	16 (8.6%)	7 (43.8%)
Total	**186 (100%)**	

Among 186 cases, 64 (34.4%) had no perinatal risk factors at the time of admission whereas 77(41.3%) had single risk factor. 2 risk factors were noted in 34 (18.3%) of the study population, >2 risk factor 44 (23.7%), ≥ 3 risk factors were seen in 11 (5.9%) of the cases. However, 16 (8.6%) babies had foul smelling liquor.

Table 8: Assessment of risk factors at the time of admission (n=186)

No. of risk factor	Asymptomatic	Symptomatic
0 (n=64)	0	64 (100%)
1 (n=77)	0	77 (100%)
2 (n=34)	5 (14.7%)	29 (85.3%)
≥3 (n=11) or FSL	3(27.3%)	8 (72.7%)
Total (n=186)	**8 (4.3%)**	**178 (95.7%)**

Out of the 64 cases which had nil perinatal risk factor, all were symptomatic at admission. Similarly, among 77 cases with single risk factor, all were symptomatic. Also, among 34 cases with 2 risk factor, 29 (85.3%) were symptomatic and 5 (14.7%) were asymptomatic but sepsis screen positive. Further, 8 (72.7%) out of 11 cases which had ≥3 risk factors, were symptomatic

Table 9: Perinatal risk factors at admission versus sepsis screen result.

Risk factors	Sepsis screen				P Value
	Result	Initial	p value	After 48 hours	
<2 Risk factor (n=141)	No growth	106 (75.2%)		115 (81.5%)	
	Growth	35 (24.8%)		26 (18.5%)	
≥2 Risk factors (n=45)	No growth	27 (60%)	0.05	23 (51%)	0.001
	Growth	18 (40%)		22 (49%)	

Out of 141 cases with <2 risk factors, 35 (24.8%) had positive initial sepsis screen and all were symptomatic at the time of admission. After 48 hours 26 (18.5%) showed growth on blood culture. All were symptomatic at the time of admission.

Table 10: Assessment of sepsis screen prior to starting antibiotics (n=186) and after 48hours.

Assessment	Sepsis screen				
	Result	Initial (178/8)	P Value	After 48 hours (22/139)	P Value
Symptomatic	No growth	50 (28%)		17 (77.2%)	
	Growth	128 (72%)		5 (22.7%)	
Asymptomatic	No growth	3 (37.5%)	0.51	6 (4.4%)	0.001
	Growth	5 (62.5%)		133 (95.6%)	

Out of 186 cases, 178 (95.7%) cases were symptomatic out of which 50 (28%) cases had positive sepsis screen. Further, 8 (4.3%) cases were asymptomatic out of which 3 (37.5%) cases had positive screen.

Out of 161 cases, 22 (13.7%) cases remained symptomatic out of which 17 (77%) had growth on blood culture.However, 139 (86.3%) cases remained asymptomatic out of which 6 (4.4%) had growth on blood culture.

Discussion

The given study was conducted in the tertiary care hospital setting in Patna 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 regarding the safety of such practice.

Adding to this, the study further acts like a prototype of the situation in a developing country as ours where resources are limited as compared to the huge load of patients, and limited availability of facilities round the clock, which further complicates the diagnosis and management of neonatal sepsis. In most situations, babies presenting with symptoms or with risk factors land up getting prolonged course of antibiotics.

Many a time use of antibiotics happen without any blood culture so only the baby's symptoms guide the duration of antibiotics. The present study tried to utilize the BacT/Alert blood culture to diagnose cases of culture positive sepsis and rationalize use of antibiotics. Out of 186 cases, most of the neonates presented within 24 hours of life (40.3%) and there were significant number of babies, who presented by 48 hours, who reached the hospital late after onset of symptoms, perhaps due to distance from the tertiary centre or were referred from periphery.

Kari A et al (2014)[8] further showed that most neonates developed signs of EOS within 12 hours of life, which was also on the lines of our findings.

Male babies were predominant in the present study, the male to female Ratio being 1.8:1. Similar finding was seen in the study done by A.c. Buch et al.[9], where Male to Female ratio was 1.8: 1. Morven S and colleagues[10] observed male to female ratio of 2:1, which again is consistent with the present study. Males outnumbered females in numerous studies, in terms of EOS cases, including those done by Chandra 1988[11], Antoniette 2005[12], Rajarshi Basu et al (1.5:1)[13] and Heena Rihan et al (1.63:1)[14]. In the present study, Early onset culture positive neonatal sepsis was more common among male babies as well (male: female ratio 1.2:1). The increased incidence of sepsis in male newborns could been due to presence of only single X-chromosome in them, as opposed to two in female. In the study done by Chandra[11] 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.

Study conducted by K. Padma Malini et al (2016)[15], 112 male babies (56%) and 88 female babies (44%) were affected by neonatal septicemia. Preponderance was also seen in several other studies by Piyush Gupta et al.[16], Sumon et al.[17], Philip et al.[18], Khatua, et al.[19], Sinha, et al.[20] observed that the male to female ratio was 1.7. The situation in developing countries is however more complex and influenced by a multitude of factors, ranging from cultural beliefs and traditions to availability of nearby health facility. There still exists an unspoken bias to towards the male child, thus causing more males to be brought to focus of medical care, and more so in a higher centre. On the other hand, there is delayed health seeking for female babies. These inequalities further add to the final male to female ratio of neonatal sepsis.

Out of 186 cases, who were suspected to have sepsis in the present study, 80 (43.2%)

were low birth weight and 60% babies who are culture positive were LBW and both the above incidences are higher than the incidence of LBW in general population. This shows LBW babies are at increased risk of sepsis and other neonatal illness with clinical symptoms similar to sepsis. Early-onset septicemia was present in 58.8% with normal birth weight ≥ 2000 gm in a study done by Jyoti Bendigeri et al (2015)[21], which is consistent with result of the present study.

However, various studies done by Rajarshi Basu et al. 2014[13]and Heena et al.[14] 2016 showed majority of cases of proven sepsis to be in premature and low birth weight (65%). A.C. Buch et al (2011)[9] also reported that the 80.8% neonates affected with sepsis were low birth weight. This was attributed to immature cellular and humoral immune system at birth, including phagocytic activity, decrease response to localize infection etc., making them vulnerable to infections[12]. The difference in the present study could probably be due to consideration of suspected sepsis cases that are exclusively term, in contrast to other studies where sepsis has been studied in both low birth weight and premature babies, suggesting that preterm may act as a confounding factor, for early onset sepsis. 178 (95.7%) were symptomatic at presentation and 8 (4.3%) were asymptomatic. Out of total number of deaths maximum death happened on day 1 of hospitalisation i.e. 19 (67.8%); on day 2, 6 deaths (21.4%) and on day 3, 3 deaths (10.7%). This is because the babies may be very sick at the time of admission and that could be due to delayed initiation of treatment due to poor health seeking behaviour by parents or delay in referral.

Mortality rate of culture positive sepsis was found to be 58.4% and 67.8% death happened within 24 hours of hospitalisation. There was no single death on blood culture negative babies. This high mortality in culture positive babies could be due to delay in referral, antibiotic initiation and poor transport. Mathur et al.[22] who observed mortality of 64.5% when the onset of illness was early.

However, A. C. Buch.[9] reported that the mortality rate of 24.61 % in culture positive cases, which is quite less than ours and 18.18 % death in culture negative cases which is higher than the present study. As per DeNIS[23] reported a lesser mortality rate of 8.6% in culture positive sepsis in inborn babies. The difference of the mortality is because all the babies were inborn, and diagnosis and initiation of antibiotic was quick.

Among various risk factors studied in relation to suspected early onset sepsis, low birth weight led the list in the present study, with 80(43%) cases, followed by perinatal asphyxia 45(24.2%) and prolonged rupture of membranes 37 (19.9%). Other risk factors noted included foul-smelling liquor 8.6%, unclean vaginal examination 4.3%, prolonged labour 4.8%, and maternal fever 1.1%. The above results were similar to those seen in study conducted by Meenusingh et al[24] where majority of suspected sepsis cases had prolonged rupture of membrane (45%), birth asphyxia (34%), and low birth weight (60%) as their risk factors. Further foul-smelling liquor, maternal fever, unclean vaginal examination and birth asphyxia were proven to be independent, and PROM and prolonged labour as dependent factors. The study further mentioned few combinations of risk factors such as LBW (32%), PROM+PL (14%), PROM+BA (35%) and PROM+FSL (70%) to contribute to EOS, rather than each factor individually. Study done by Mamta Jajoo et al[25] [2018 reported low birth weight as most common risk factor in EOS (68.3%), followed by perinatal asphyxia and multiple vaginal examination (35.4%). A study done on risk factors in neonatal sepsis by Agarwal et al.[26] showed birth asphyxia as one of the most common risk factors associated with EOS.

Kishore et al.[27] reported 19.2% of vertical transmission and sepsis in babies born to mothers with prolonged rupture of membrane. Anand et al.[28] observed 29.3% of EOS can be attributed to prolonged rupture of membrane. These findings are consistent with the present study. Further, N. Mehrotra[29] noted threefold increase in incidence of sepsis after PROM. Investigators of the Delhi Neonatal Infection Study (DeNIS 2016) collaboration[30] reported that Maternal fever within 7 days before delivery (7.8%), Per-vaginal examination (≥3) (38.5%), Prolonged rupture of membranes (18 h or more) (14.5%), Prolonged labour (24 h or more) (1.3%), Foul-smelling liquor (2.8%) are the major risk factors contributing to neonatal EOS, the findings of which are in contrast to the present study.64 (34.4%) had no perinatal risk factors at the time of admission whereas 77 (41.3%) had single risk factor. 2 risk factors were noted in 34 (18.3%) of the study population, ≥ 3 risk factors were seen in 11 (5.9%) of the cases, however 16 (8.6%) babies had foul smelling liquor.

In a study done by Vamsi Krishna kondle et al.[31] on septicaemia in neonates, around 14% of cases had no risk factors, as compared to 34% in the present study. The difference could be due to difference in the type of population group. Single risk factor was present in 41% of our cases, which was much higher than that observed by Meenu Singh et al.[24], where 15% of babies had single risk factor. Foul smelling liquor was present in 8.6% of our population as compared to Meenu singh et al.[24], where it was 13%.

Unlike the study done by Meenu Singh et al.[24] where the incidence of 2 or more risk factors is as high as 85%, in the present study it formed only 24% of the population. Among those, 2 risk factors were seen in 18% and three or more than three was present in 6% of the Suspected EOS. The difference could probably be because of the difference in the structure of the former study, which was a case control study and perinatal history was obtained from the obstetric team rather than mothers. On comparing the number of risk factors present at the time of admission with the presence or absence of symptoms at admission, showed that the number of risk factors did not correlate with presence of symptoms at admission. In fact, all those babies with nil or singe risk factor were symptomatic [Table 10]. Thus, presence of symptoms should be assessed independently than the number of risk factors.

In the present study, the above sepsis screen was performed at admission and repeat screen was done in those patients in whom first screen was negative, but baby clinically symptomatic, or first screen obtained before 12 hours of life (10 babies had repeat screen positive) prior to starting antibiotics in all 186 suspected EOS cases. Overall, 34% symptomatic babies were screen positive. However, 37% of asymptomatic babies were also sepsis screen positive.

Conclusion

Sepsis is one of the major causes of neonatal mortality. So, there is an inherent urgency in initiating antibiotics in babies born with multiple perinatal risk factors for sepsis, with or without clinical symptoms. However, the signs and symptoms of sepsis are very nonspecific. Thus, many babies who are not having infection or symptomatic because of noninfectious causes, receive antibiotics for a long duration. This increases the length and cost of hospitalisation, increases parental anxiety, creates an unnecessary burden to the overburdened health system and overall, increases antibiotic resistance with its consequences.

With the present study, it was observed that along with evaluation of clinical condition of the baby and 48-hour BacT/Alert blood culture report, antibiotics can be safely discontinued in those babies who are clinically asymptomatic and 48-hour blood culture negative. Early onset sepsis has

vague clinical presentation for which empirical antibiotics is practiced universally without knowing the blood culture status.

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