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### Original Article

# Profile of sepsis in extramural neonates admitted to a tertiary level NICU in a rural hospital

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#### ABSTRACT

**Objectives:** 1)To study the causative organisms and profile of sepsis in outborn newborns admitted to NICU in a rural hospital.2)To study the usefulness of S.CRP as a tool in rural and resource limited settings for diagnosis of Early and Late onset sepsis as well as in suspected & proven sepsis cases. Setting: The prospective study was undertaken in the tertiary level NICU of MVJ Medical College & Research hospital located in rural Bangalore, India. Extramural neonates admitted with clinical features suggestive of sepsis were included. Results: A total of 90 neonates were included in the study. Neonates were divided into early onset sepsis (EOS, n=49) and late onset sepsis (LOS, n=41) groups. Depending on the blood culture positivity the neonates were categorized into proven (culture positive, n=36) and suspected (culture negative, n=54) sepsis groups. The blood culture positivity was 40% and EOS was seen in 54.44% and LOS in 45.56%. The blood culture positivity in LOS group was 48.78%, much higher than in EOS group. Gram negative organisms formed majority of the isolates. Klebsiella was the predominant isolate in both EOS (25%) and in LOS (40%) groups followed by CONS and E coli respectively in EOS and LOS. Serum CRP had a specificity of 75.92%, with a positive predictive value of 50% and a negative predictive value of 64.06% in the proven and suspected sepsis groups. The specificity of Serum CRP in EOS was 81.82%, higher than in LOS group of 66.67%.

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### 1. Introduction

One of the major causes of morbidity and mortality in the newborn is Septicemia. Approximately 1 million annual neonatal deaths occur from life-threatening invasive bacterial infections. 99% of these deaths occur in developing countries, and at least 50% of them are from home births or community settings(1,2). There is limited data about aetiology of sepsis in these rural settings. The bacterial aetiology of life-threatening, community-acquired neonatal sepsis (CANS) are helpful in devising management guidelines for combating neonatal sepsis at the community level. Variations in CANS are observed both between global regions and age-of-onset categories. Staphylococcus aureus and Streptococcus pneumoniae were most prevalent in Africa, while Klebsiella was highly prevalent in South-East Asia(3)

Early diagnosis of Neonatal sepsis is of paramount importance in reducing neonatal mortality. Blood culture is the gold standard in diagnosing neonatal sepsis, but it is hampered by poor levels of positivity and non availability at most community level centers. There is great emphasis on effective low-cost pathogen detection techniques to combat neonatal mortality (3)

Neonatal septicemia can be divided into two types depending on whether the onset was during the first 72 hours of life or later(4)

1. Early Onset Septicemia (EOS) occurring within 72 hours of birth
2. Late Onset Septicemia (LOS) occurring after 72 hours of birth.

Typically, early-onset sepsis is considered maternally-acquired, usually from the maternal genital tract, and late-onset sepsis is generally regarded to originate from the care-giving environment - either a healthcare or community setting. Consequently early- and late-onset sepsis are also associated with

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The incidence of neonatal sepsis among intramural babies was 38 per 1000 live births as per the report of National Neonatal Perinatal Database (NNPD) (4) in 16 major hospitals in India. The current study was undertaken to determine the bacteriological profile of neonatal septicemia in rural Bangalore.

**2. Material and Methods**

Prospective study was conducted in Neonatal Intensive care unit of MVJ Medical College and Research Hospital, Hoskote, Bangalore. This is a tertiary level NICU located in rural Bangalore, South India. A total of 90 extramural new born infants were included in the study. All neonates with clinical features of sepsis (Lethargy, Irritability, Refusal of feeds, Hypothermia, Hyperthermia, Respiratory distress, Jaundice, Hepatomegaly, Vomiting, Abdominal distension, Diarrhoea) underwent sepsis workup including blood culture. Cultures were done as per standard protocol. The neonates with features of sepsis <72 hours of life were designated as early onset sepsis. Neonates with features of sepsis > 72 hours of life were designated late onset sepsis. The blood culture positive neonates were designated as Proven sepsis. Neonates with clinical features of sepsis/blood count abnormality ((total leucocyte>15,000 OR <5,000, a differential count with neutrophils <1,000/μL and a positive Se CRP >6mg/dl), but blood culture negative were designated as suspected sepsis and treated with antibiotics as per the neonatal unit protocol.

**3. Results**

During the study period 90 blood samples from outborn, clinically suspected cases of neonatal septicemia were obtained. The study population characteristics are shown in Table 1.

**Table 1: Study population**

Gestational age	No of cases	Males	Females
Term	59	42	17
Preterm	31	21	10
Total	90	63	27

The neonates were divided into: Early onset sepsis group (age at onset <72 Hrs): This group comprised of 49 neonates (Male =32, Female =17) i.e. 54.44% of the study population. Late onset sepsis group (age at onset >72 Hrs): This group comprised of 41 neonates (Male =31, Female =10) i.e. 45.56% of the study population. (Table 2)

**Table 2: Early and Late Onset sepsis in the study population**

Group	No of cases	Males	Females	%
Early onset	49	32	17	54.44%
Late onset	41	31	10	45.56%

Blood culture positivity was seen in 36 (40%) of the 90 neonates whereas 54 (60%) cases were blood culture negative. In the EOS group, 16 samples were blood culture positive, i.e. 32.65% of EOS cases showed blood culture positivity; whereas 33 cases did not show growth in Blood culture i.e. 67.34% of the EOS neonates belonged to the suspected sepsis group. In LOS group, 20 samples were blood culture positive, i.e. 48.78% of LOS cases showed blood culture positivity; whereas 21 cases did not show growth in Blood culture, i.e. 51.21% of the LOS neonates belonged to suspected sepsis group. The proven & suspected cases in the EOS and LOS groups are shown in Table 3.

**Table 3: Proven and suspected cases in the Early and late onset sepsis groups**

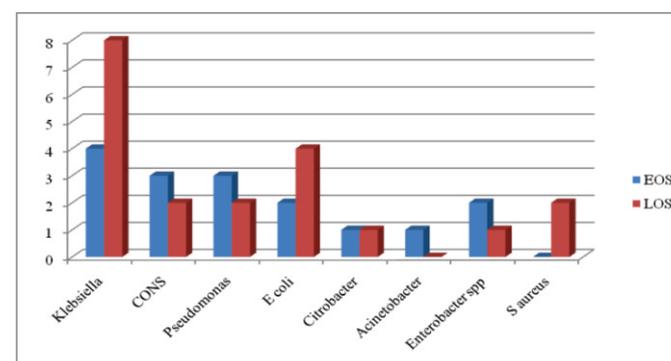
Group	EOS (32males, 17 females)	LOS (31 males, 10 females)
Proven sepsis	16	20
Suspected sepsis	33	21

Klebsiella was isolated most commonly in blood culture samples in the study (33.33%), being the predominant isolate in both the EOS (25%) and LOS (40%) groups. CONS, Pseudomonas, E coli and Enterobacter Spp were the other predominant isolates in EOS group. In the LOS group the other isolates were E coli, Staphylococcus aureus, Psedomonas and CONS. The distribution of isolates in the EOS and LOS groups are shown in Table 4.

**Table 4: Distribution of isolates in the EOS and LOS groups.**

Organism	No. of isolates in EOS	No of isolates in LOS	Total
Klebsiella	4	8	12
CONS	3	2	5
Pseudomonas	3	2	5
E coli	2	4	6
Citrobacter	1	1	2
Acinetobacter	1	-	1
Enterobacter spp	2	1	3
Staphylococcus aureus	-	2	2

**Chart 1: Distribution of organisms in the EOS and LOS groups**



The various parameters of sepsis screen especially Serum CRP were evaluated in the proven and suspected sepsis groups as well as in the EOS and LOS groups. Serum CRP was positive in 13/36 (36.11%) cases in the proven sepsis group and in 13/54 (24.07%) cases in suspected sepsis groups. Serum CRP was negative in 41/54 (75.92%) cases in the suspected sepsis group. Serum CRP had a specificity of 75.92%, with a positive predictive value of 50% and a negative predictive value of 64.06% in the proven and suspected sepsis groups.

In the EOS group, Serum CRP was positive in 4/16 (25%) blood culture positive cases and in 6/33(18.18%) of Blood culture negative cases. Serum CRP was negative in 27/33(81.81%) blood culture negative cases in the EOS group. Thus the sensitivity and specificity of Serum CRP were 25% and 81.82% respectively in the EOS group. The positive and negative predictive values of Serum CRP in the EOS group were 40% and 69.23% respectively.

In the LOS group, Serum CRP was positive in 9/20 (45%) blood culture positive cases and in 7/21 (33.33%) of blood culture negative cases. Serum CRP was negative in 14/21 (66.67%) blood culture negative cases in the LOS group. Thus the sensitivity and specificity of Serum CRP in the LOS group was 45% and 66.67% respectively. The positive and negative predictive values of Serum CRP in the LOS group were 56.25% and 56% respectively.

#### 4. Discussion

Most studies analyse the incidence of neonatal sepsis in intramural neonates in large hospitals and the various factors affecting outcome as well as bacteriological profile of neonatal sepsis in these settings. There is paucity of studies on Community acquired Neonatal sepsis (CANS). Data from developing countries about bacteriological profile of life threatening CANS are limited. In rural areas, there is significant evidence to suggest that neonates often do not receive required healthcare and that this is associated with an increase in mortality (6). There is a high prevalence of home births in rural areas due to poor health system coverage, limited or no access to referral facilities and financial constraints. Even when reasonable health care services are available, the services may be beyond the affordability of the rural poor (3,7,8).

Our study included extramural neonates admitted to our NICU in a tertiary rural hospital, with features suggestive of neonatal sepsis. There were a total of 90 such neonates who were included. Of this 36 neonates (40%) showed blood culture positivity and belonged to the proven sepsis group, while 54 neonates (60%) belonged to the suspected sepsis group. Studies have shown blood culture positivity ranging from 25.8% (Joshi et al) (9) to as high as 64.87% (Tallur et al) (10). Mane AK et al in their study in rural Nagpur reported blood culture positivity of 26.9% (11).

In the present study EOS was seen in 54.44% and LOS was seen in 45.56%. Kuruvilla et al reported an incidence of 22.9% EOS and 77.1% of LOS in their study in CMC Vellore.(12) Mane AK et al reported 81.5% EOS which was much higher than LOS in their study (11)

In our study, in the EOS neonates, 32.65% belonged to proven sepsis group and 67.34% belonged to suspected sepsis group. In the LOS neonates, 48.76% belonged to the proven sepsis group and 51.21% belonged to suspected sepsis group. The blood culture positivity was much higher in the LOS group when compared to the EOS group.

Klebsiella was the predominant organism (40%) isolated from blood in this study. Klebsiella accounted for 4 cases in EOS (25%) and for 8 cases in LOS(40%). Gram negative organisms were the predominant isolates in both EOS and LOS neonates. CONS (18.75%), Pseudomonas(18.75%), E coli(12.5%) and Enterobacter spp(12.5%) were the other isolates in EOS. In LOS E coli(20%), S aureus(10%), CONS(10%) and Citrobacter(5%) were the other predominant isolates. Klebsiella and S aureus were reported as the predominant isolates in EOS by Mane AK et al(11). Kuruvilla KA et al reported E coli and E fecalis as the most common causative organisms in EOS(12)

The review done by Waters D et al in 2011, who extensively studied the etiology of Community acquired neonatal sepsis( CANS), suggests that the majority of organisms that cause CANS in low and middle income countries are Gram negative pathogens. They found that, the most commonly isolated were, in ranked order, S. aureus, E. coli and Klebsiella species(3). These results were found to be similar to a previous review conducted by Zaidi et al, where the order of prevalence was Klebsiella species, E. coli and S. aureus (5).

Early diagnosis of neonatal sepsis helps clinicians to institute antibiotic therapy at the earliest, which greatly reduces neonatal mortality due to sepsis. This is very true in rural and community settings where there is inaccessibility to health care, delayed identification and institution of treatment. However, the diagnosis of neonatal sepsis based on clinical symptoms alone is not possible (13) Blood culture is considered as the gold standard and most specific method used to diagnose neonatal sepsis. (14) But this takes time of 24-72 hours, is complicated and has a low yield. Most importantly, blood culture requires the expertise of a trained microbiologist, the facilities for which are unavailable in many rural and

community settings. Other tests that are usually used for the diagnosis of neonatal sepsis include estimations of the white-blood cell count (WBC), the absolute neutrophil count (ANC), micro ESR and the I/T ratio. The complete blood count and the leukocyte differential assays have a relatively poor specificity for diagnosing sepsis. Though they may improve the diagnostic yield, band count and a leftward shift of neutrophils are very subjective, problematic and require thorough training and equipment. (15) For long, CRP has been one of the most analysed parameters for diagnosing neonatal sepsis(16, 17,18) In our study we found that Serum CRP was positive in 36.11% cases in the proven sepsis group and in 24.07% cases in suspected sepsis groups. Serum CRP was negative in 75.92% cases in the suspected sepsis group. Serum CRP had a specificity of 75.92%, with a positive predictive value of 50% and a negative predictive value of 64.06% in the proven and suspected sepsis groups. In their study, Sucilathangam G et al found about 43.7 % of the neonates with suspected sepsis and 20 % of the neonates with clinical sepsis had raised CRP levels. The sensitivity of CRP for predicting sepsis was 50.0 %, its specificity was 69.4 %, its positive predictive value was 38.8 % and its negative predictive value was 78.1 %.(15)

Serial serum CRP levels were evaluated by Benitz et al. They reported that serum CRP at initial evaluation had sensitivities of 39.4% and 64.6% for proven or probable sepsis and 35.0% and 61.5% for proven sepsis in early-onset and late-onset episodes, respectively (18). In the present study, in the EOS group, Serum CRP was positive in 25% of blood culture positive cases and 18.18% of Blood culture negative cases. Serum CRP was negative in 81.81% blood culture negative cases in the EOS group. Thus the sensitivity and specificity of Serum CRP were 25% and 81.82% respectively in the EOS group. The positive and negative predictive values of Serum CRP in the EOS group were 40% and 69.23% respectively.

In the LOS group, Serum CRP was positive in 45% blood culture positive cases and in 33.33% of blood culture negative cases. Serum CRP was negative in 66.67% blood culture negative cases in the LOS group. Thus the sensitivity and specificity of Serum CRP in the LOS group was 45% and 66.67% respectively. The positive and negative predictive values of Serum CRP in the LOS group were 56.25% and 56% respectively. Thus serum CRP had a high specificity in the EOS group than in the LOS group. Hence Serum CRP can be used as a simple screening marker to identify those neonates, especially in the EOS group, who do not have infection vis-a-vis those neonates who are infected and who require immediate referral for further evaluation and treatment.

The identification and treatment of newborns with infection is unsatisfactory in many developing country settings. Emphasis is being laid on promotion of strategies to reduce mortality at the community level. Hence studies are required in rural settings to evaluate simple, cost effective tools which aid in early identification and management of serious neonatal problems like sepsis. Wide acceptance is yet to be given for effective community-based interventions for management of neonatal sepsis.(8,19,20)

Data on community-acquired neonatal sepsis in developing countries are limited. The goal should be the formulation of community-based care packages, the implementation of which has significant potential to lower overall neonatal mortality. Significant differences have been shown in the aetiology of CANS between various regions of the world. This suggests the benefits of a regional, rather than global, approach to case management guidelines. Also, emphasis is on development of effective low-cost pathogen detection techniques. The case for simple and improved diagnostics is further emphasized by poor levels of culture positivity (3). Bang et al in their pioneering work in Gadchiroli on neonatal sepsis showed that hygienic birth practices with regular home visits, early detection of neonatal illness and referral to healthcare facilities, and community-based treatment using oral or parenteral antibiotic therapy, resulted in 70% reduction in neonatal mortality (21).

## 5. Conclusion

Gram Negative organisms were predominantly isolated in this study involving neonates in a rural setting. Klebsiella, Pseudomonas, E coli and CONS were common causative organisms in EOS. In LOS, Klebsiella, E coli, S aureus and Pseudomonas were predominantly isolated. Serum CRP was found to have a higher specificity and negative predictive value in EOS cases than in LOS cases. Thus Serum CRP may be used as a simple and easily available tool to identify neonates with sepsis that may require further evaluation and management. Further studies should be undertaken for community based diagnosis and treatment of neonatal sepsis.

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