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ORIGINAL ARTICLE

# CLINICO-ETIOLOGICAL PROFILE OF NEONATAL SEPSIS AT A TERTIARY CARE HOSPITAL IN SOUTH INDIA

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**ABSTRACT**

**Introduction/Objective** Neonatal sepsis is the leading cause of morbidity and mortality among neonates. Neonates are at risk of sepsis due to several immaturities that they possess inherently. Sepsis is classified as early-onset or late-onset neonatal sepsis. Pathogenesis is different in both types. This study aims to determine the pattern of microorganisms causing sepsis and the clinical presentation of neonates admitted with suspicion of sepsis to the Government Kilpauk Medical College Hospital, a tertiary medical care centre.

**Methods** Descriptive cross-sectional study performed in Government Kilpauk Medical College and Hospital, India.

**Results** Out of 207 neonates admitted with suspected sepsis, 112 were male and 97 were female. Male to female ratio was 54.1% : 45.9 % (1.2 : 1). On categorizing the newborns based on birth weight, 11 newborns were of very low birth weight, 107 were of low birth weight, 88 had normal birth weight, and one baby weighed more than 4,000 grams. Blood culture was positive in 88 out of the 207 cases (42.51%). Klebsiella was the commonest microorganism causing sepsis (45%) in our Neonatal Intensive Care Unit. Other Gram-negative isolates included Escherichia Coli (31%), Pseudomonas (6%), Enterobacter (1%) and Acinetobacter (2%). The Gram-positive organisms grown were coagulase-positive and coagulase-negative Staphylococci (8%), Group B Beta Hemolytic Streptococcus (5%) and Enterococcus (2%). Late-onset sepsis cases were found to be 1.5 times more common than early-onset sepsis. The best overall sensitivity among Gram-negative isolates was to Imipenem (92%), followed by Amikacin (82.66%) and the best sensitivity among Gram-positive isolates was to Vancomycin (84.61%), followed by Cloxacillin and Ampicillin (61.53%). Out of 88 positive cultures, 6 were multi-drug resistant (6.8%).

**Conclusion** Acquiring knowledge about the microorganisms causing sepsis in neonates helps prevent morbidity, mortality and the development of antibiotic resistance.

**Keywords**: neonatal sepsis, antibiotic sensitivity, Klebsiella, low birth weight

## Introduction

Sepsis in neonates continues to be one of the leading causes of morbidity and mortality despite the advances in the field of neonatology. Sepsis is a clinical syndrome characterized by the presence of bacteremia along with signs and symptoms of infection and inflammation [1]. Inherent factors like a poorly developed innate immune system, immature skin barrier, mucosal defence mechanisms and blood-brain barrier contribute to the increased susceptibility of neonates to infection. Early recognition and aggressive treatment play a pivotal role in saving the lives of those neonates.

Based on the time of onset, neonatal sepsis is classified as early-onset sepsis and late-onset sepsis. Early-onset sepsis is defined as the occurrence of features of septicemia within the first 72 hours of life and is largely attributed to the perinatal transmission of infection from the mother to the neonate. Therefore, the pattern of microorganisms causing early-onset sepsis are those present in the maternal genital tract, labour room or operating theatre. On the other hand, late-onset sepsis occurs when features of sepsis develop in a neonate older than 72 hours and is predominantly community or hospital-acquired. The pattern of microorganisms causing it are those present in the environment where the neonate is cared for and nursed [2,3]. Recent data published by the World Health Organization (WHO) estimates that 5 million neonates die each year and around a quarter of those deaths are sepsis-related [3]. Data from the National Neonatal Perinatal Database (NNPD, 2002-03) attributes 19% of all neonatal deaths to sepsis [4].

The usual presentation of neonatal sepsis is septicemia, meningitis, pneumonia, rarely septic arthritis and osteomyelitis, and in very few cases a urinary tract infection. Neonatal sepsis is caused by Gram-positive as well as Gram-negative bacteria and rarely by fungus and yeast [5]. Making a clinical diagnosis of neonatal sepsis is very difficult as the symptoms and signs are non–specific and often missed in the early stages. It is therefore required to have a high index of suspicion to identify sepsis and intervene at an early stage.

Antimicrobial agents form the backbone of neonatal sepsis treatment. Supportive management includes maintenance of euthermia, euglycemia and fluid and inotropic support. GM-CSF, G-CSF, blood products and exchange transfusion are other adjuvants that play a key role in affecting the overall outcome of the neonate.

The patterns of microorganisms causing neonatal sepsis vary according to place and time even within the same department [5,6]. Therefore, regular testing of the microbe agents and their sensitivity patterns must be done by the infection control team of the hospital to aid in choosing appropriate antibiotics.

### Objective

This study was conducted to determine the microbial pattern and the clinical presentation of neonates admitted with suspicion of sepsis to the Government Kilpauk Medical College and Hospital, a tertiary medical care centre.

### Methods

After the approval of institutional ethics committee and the signing of full informed consent by every patient who participated in the study, we performed a descriptive 2-years study in Government Kilpauk Medical College and Hospital, India.

**Inclusion criteria:** Neonates who satisfied any one of the following criteria:

**Neonatal criteria:** Neonates showing the under-mentioned signs and symptoms: respiratory distress, apnea or gasping respiration; temperature instability – hypothermia or fever; lethargy; weak cry; the refusal of feeds; vomiting; ileus; abdominal distension; poor peripheral perfusion, bradycardia or tachycardia; more than 10 pustules on the body or purulent umbilical discharge along with periumbilical erythema; neonatal convulsions; irritability; hypotonia; altered sensorium.

**Maternal criteria:** maternal fever with evidence of bacterial infection within 2 weeks before delivery; rupture of membranes longer than 18 hours; foul smelling discharge; evidence of chorioamnionitis; more than 3 vaginal examinations or one unclean vaginal examination during labour; prolonged labour (sum of the first and second stage of labour lasting more than 24 hours).

Both term and preterm babies irrespective of gestational age and birth weight were included in the study. Newborns belonging to both sexes were included in the study.

**Exclusion criteria:** Extramural admissions with features of sepsis and those neonates who had priorly received antibiotics.

Blood culture was performed for all neonates suspected to have septicemia. The blood culture sample included a single sample collected from a peripheral vein under aseptic conditions. C-reactive protein estimation and the septic screen were also done as per department policy before administering an empirical antibiotic.

Neonates were classified as clinical sepsis, probable sepsis and proven sepsis based on the case definition described below.

### Case definitions

**Clinical sepsis:** Neonates in whom only clinical features were consistent with sepsis, without laboratory abnormalities or microorganism growth in body fluid cultures.

**Probable sepsis:** Neonates in whom clinical and laboratory findings are consistent with sepsis but the blood culture is negative. They can be either CRP-positive neonates or neonates who were positive for two haematological parameters.

**Proven sepsis:** Neonates with positive blood culture or positive cerebrospinal fluid culture or positive culture of other body fluids.

### Statistical analysis

All the statistical analysis in this study was performed by using the SPSS software version 17.0 package. Statistical tools such as the chi-square test, independent t-test and one-way analysis of variance (ANOVA) were used in the analysis. A P-value of $<0.05$ is considered statistically significant.

### Results

This study included 207 neonates with suspected sepsis admitted to the newborn department of the hospital. Sepsis workup was done for all the neonates, including blood culture, CSF culture (wherever indicated), tests for indirect evidence of infection like C-reactive protein (CRP), and haematological indicators such as peripheral blood smear studies for abnormal WBC counts, immature to mature leukocytes ratio (IT ratio) and the presence of toxic granules in neutrophils. Based on the sepsis screen results, the diagnosis was categorized into 3 categories.

**Table 1. Categories of neonatal sepsis**

| Classification | No. of neonates | % |
|---|---|---|
| Clinical | 67 | 32.4 |
| Probable | 52 | 25.1 |
| Proven | 88 | 42.5 |

Of the 207 neonates admitted with suspected sepsis, 112 were male and 97 female. Male to female ratio was 54.1% : 45.9 % or 1.2 : 1. On categorizing the newborns based on birth weight, 11 babies were of very low birth weight, 107 were of low birth weight, 88 babies were of normal birth weight and one baby weighed more than 4000 grams. (**Table 2**)

Blood culture was positive in 88 out of the 207 cases (42.51%). Based on their age at the time of clinical presentation, neonates were classified as **early-onset sepsis** (EOS) when the age was less than or equal to 3 days old and as **late-onset sepsis** (LOS) when the neonate was older than 3 days. According to that classification, 34 neonates had EOS and 54 had LOS.

**Table 2. Demographic Characteristics**

| Parameter | No. of neonates (%) |
|---|---|
| **Sex** | |
| Male | 112 (54.1%) |
| Female | 97 (45.9%) |
| **Birth weight** | |
| <1500 gm | 11 (5.31%) |
| 1500gm to 2500 gm | 107 (51.69%) |
| 2500 gm to 4000 gm | 88 (42.51%) |
| >4000 gm | 1 (0.48%) |
| **Blood culture** | |
| Positive | 88 (42.51%) |
| Negative | 119 (57.49%) |
| **Onset of sepsis** | |
| Early-onset | 34 (16.42%) |
| Late-onset | 54 (26.08%) |
| **CRP** | |
| Positive | 92 (44.44%) |
| Negative | 115 (55.55%) |
| **Platelet count** | |
| <150000 | 74 (35.75%) |
| >150000 | 113 (54.58%) |

**Clinical presentation of sepsis**

Most of the neonates presented with non-specific symptoms which included lethargy, poor feeding, excessive crying, apnea and temperature abnormalities. Only 12 of them presented with respiratory symptoms, which were diagnosed as pneumonitis. Another 16 neonates presented with seizures, some of which had hypoglycemia and hypocalcemia. The rest of the neonates had other presentations such as ecthyma or gastrointestinal symptoms (abdominal distention, excessive vomiting, blood-stained stools) (**Figure 1**).

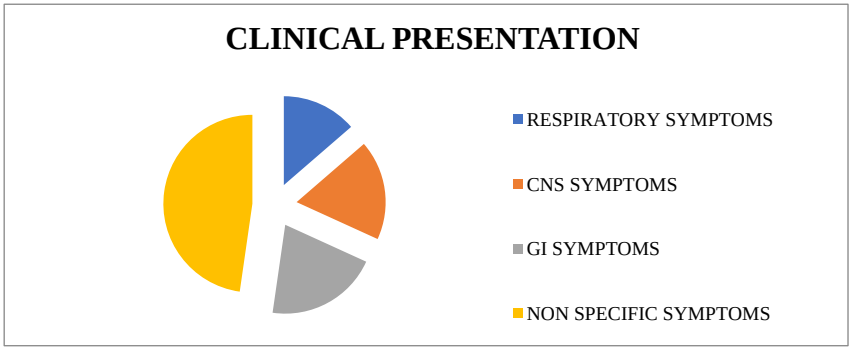


**Figure 1. Clinical presentation**

**Microorganisms causing sepsis and antimicrobial sensitivity patterns**

Klebsiella is the commonest microorganism causing sepsis (45%) in our Neonatal Intensive Care Unit. Other Gram-negative isolates included Escherichia Coli (31%), Pseudomonas (6%), Enterobacter (1%) and Acinetobacter (2%) (**Figure 2**).

The best overall sensitivity among Gram-negative isolates was to Imipenem (92%) followed by Amikacin (82.66%) and the best sensitivity among Gram-positive isolates was to Vancomycin (84.61%), followed by Cloxacillin and Ampicillin (61.53%).

Out of 88 positive cultures, 6 were multi-drug resistant (6.8%) (**Figure 3**).

The Gram-positive organisms grown were coagulase-positive and coagulase-negative Staphylococci (8%), group B beta-hemolytic Streptococcus (5%) and Enterococcus (2%) (**Figure 4**). Late-onset sepsis cases were found to be 1.5 times more common than early-onset sepsis.

Out of 88 cases, 34 (38.64%) had early-onset sepsis and 54 (61.36%) had late-onset sepsis (**Figure 5**).

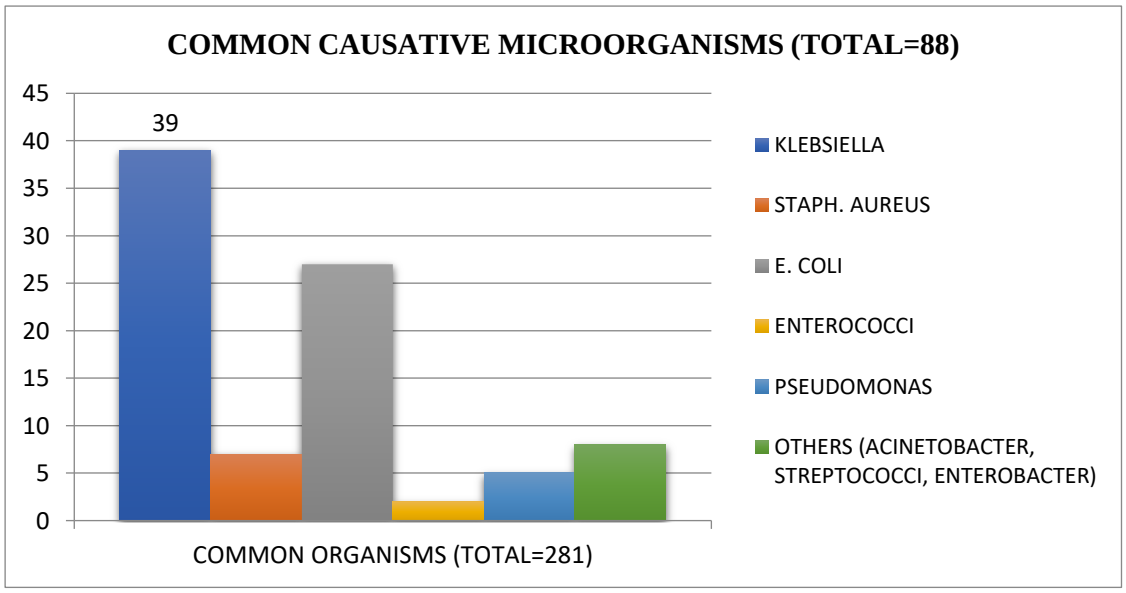


**Figure 2. Microorganisms causing neonatal sepsis**

ANTIBIOTIC SENSITIVITY PATTERN OF GRAM-NEGATIVE MICROORGANISMS

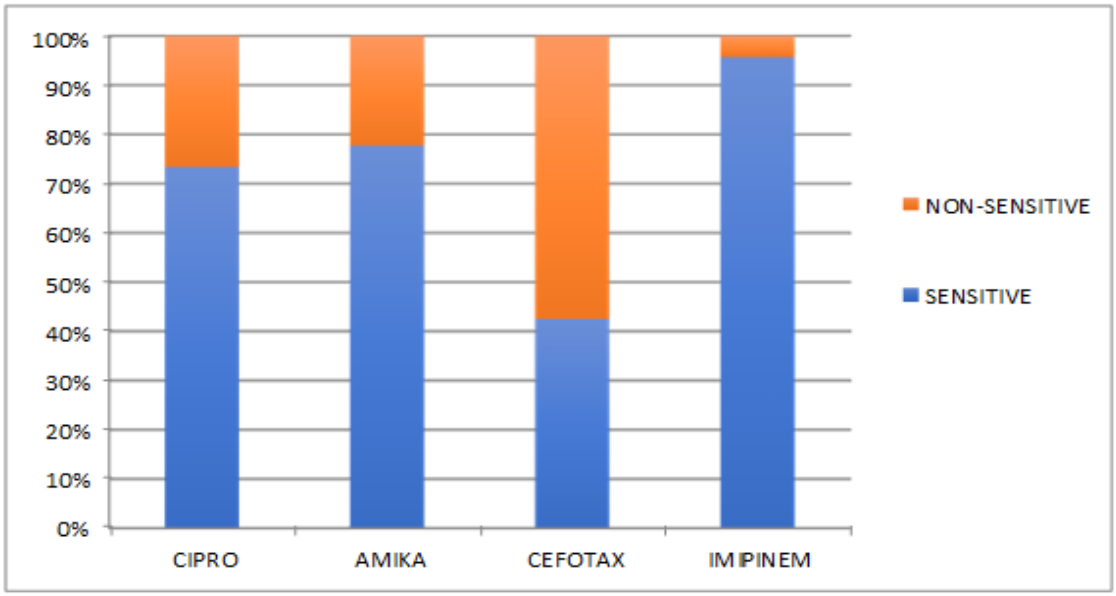


**Figure 4. Antibiotic sensitivity pattern among Gram-negative microorganisms**

ANTIBIOTIC SENSITIVITY PATTERN OF GRAM-POSITIVE ORGANISMS

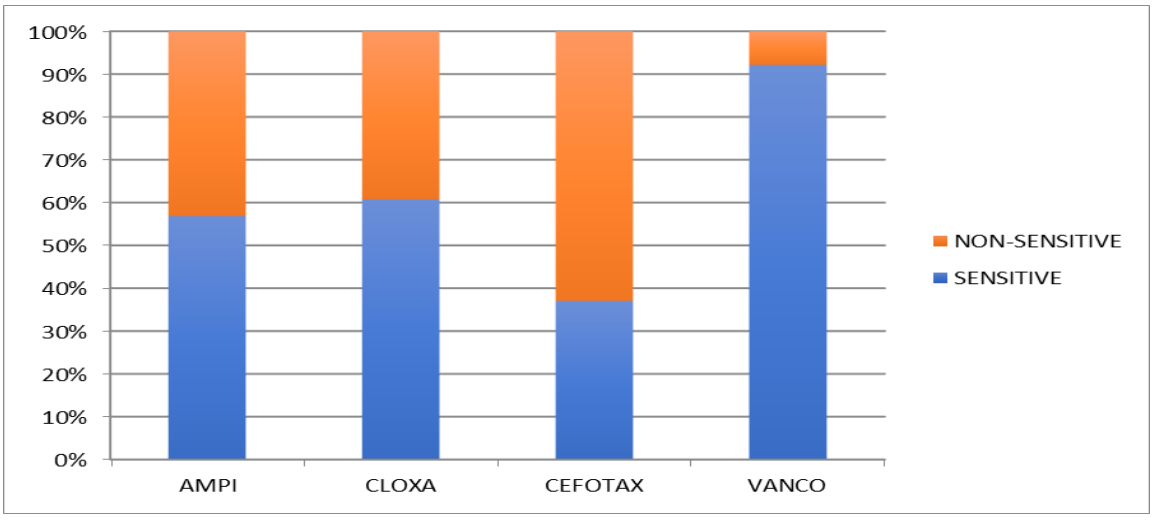


**Figure 5.Antibiotic sensitivity pattern among Gram-positive microorganisms**

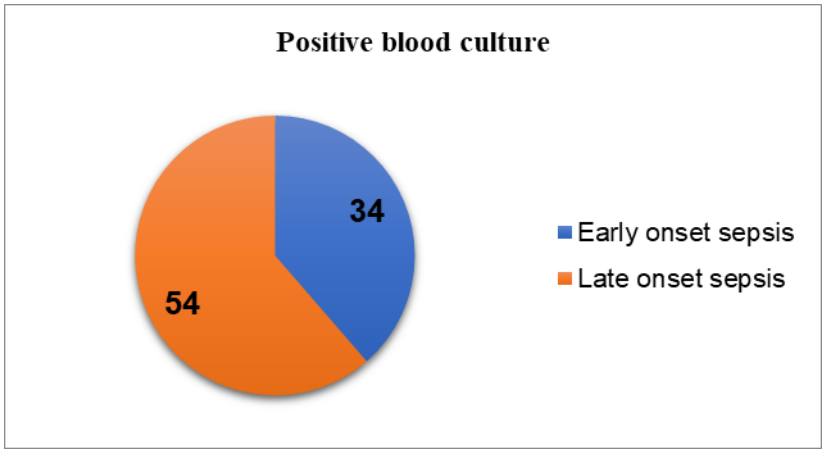


**Figure 2. Blood culture**

## Discussion

Sepsis in neonates continues to be a major cause of morbidity and mortality in both developed and developing countries. It accounts for more than a third of all neonatal deaths in neonatal departments in most countries. There has been a slight reduction in the sepsis rate in developed countries mainly due to effective prenatal checkups, preterm labour prevention, tocolytic use, prenatal steroids and good, clean intrapartum care and postnatal management of the neonate including hand hygiene and aseptic procedures by all those who care for the neonates during the postnatal hospital stay.

The clinical presentation of neonatal sepsis in our study was noticed to be similar to previously published reports. We reported nonspecific findings in most of the cases followed by gastrointestinal symptoms in 18 cases, meningitis in 16 cases and pneumonia in 12 cases. These presentations are similar to previously published clinical presentations [3-6].

The yield of the blood culture in our study was around 42.51% which is similar to the findings by Zuhair M. Al-Musawi et al [7], whose culture demonstrated a 45% growth. This is also similar to reports by K.V. Shyamala et al. [8] who reported a positive culture rate of 51.3% and Rekha Sriram et al. [9] who reported a positive culture rate of 50.4% in her study. The blood culture yield is affected by several factors which include the way the blood sample was collected, the volume of collected blood, and the amount of time passed between the collection and the inoculation into the culture plate.

The microorganisms implicated in neonatal sepsis in developing countries differ from those seen in developed countries [3]. In our study, out of 88 positive cultures, the majority of causative microorganisms were Gram-negative (85.22%), specifically Klebsiella (45%) and E. coli (31%). Among the Gram-positive microorganisms Staphylococcus aureus (8%) predominated. This is consistent with data from NNPD 2000, which states that the most common microorganism responsible for neonatal sepsis in India is Klebsiella [1].

These findings are similar to previous reports which have demonstrated a predominance of Gram-negative microorganisms as the cause of neonatal sepsis [6-10]. However, the recently concluded DeNIS study [11] has shown that Acinetobacter spp were the most common isolate followed by the Klebsiella spp. This differs slightly from our results.

The Gram-negative and Gram-positive septicemias were encountered in respectively 85.22% and 14.78% of the culture-positive cases in our study, which is in contradiction to the results of studies by Gudia et al. [10] and Agnihotri et al. [12], where Gram-negative microorganisms were predominant, but Gram-positive isolates contributed to nearly 40% to 50% of septic cases. This could be explained by the fact that most of our cases were late-onset sepsis. However, the early-onset cases of sepsis in our study were also predominantly caused by Gram-negative microorganisms.

The analysis of the drug resistance patterns showed that among Gram-negative isolates nearly 60% were resistant to cefotaxime and 66% were resistant to ciprofloxacin. Both of those drugs are commonly used as first-line drugs. Six out of 88 isolates were multidrug-resistant and this was even more common among the predominant pathogens (Klebsiella and E.Coli). These findings are also similar to the recently published DeNIS study reports [11].

The prevalence rate of group B beta-hemolytic Streptococcus in our study is comparable to the results of the study by Milton et al. [13].

## Conclusion

Neonatal sepsis is a common problem in neonatal units and is one of the leading causes of neonatal death. The causative microorganisms vary depending on place and time. The most common causative microorganisms in our country are Gram-negative bacteria as opposed to the western world where Group B beta-hemolytic Streptococcus is the most common. With regards to antimicrobial therapy, there is no universal recommendation which can be applied.

There is recent evidence of an increase in drug-resistant microorganisms. A careful analysis of prevailing microbial patterns and their sensitivity to antimicrobial agents must be done in all neonatal units to overcome the development of antimicrobial resistance. The hospital infection control team should work in liaison with treating physicians to create a protocol, which in turn needs to be revisited from time to time, to effectively control sepsis among neonates.

**Conflict of interest**: none declared.

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ORIGINALNI RAD

# NEONATALNA SEPSA – KLINIČKO-ETIOLOŠKI PROFIL U ZDRAVSTVENOJ USTANOVI TERCIJARNOG NIVOA U JUŽNOJ INDIJI

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**SAŽETAK**

**Uvod/Cilj** Neonatalna sepsa je vodeći uzrok mortaliteta i morbiditeta novorođenčadi. Neonatusi su zbog svojstvene nezrelosti, podložni razvijanju sepse. Sepsa se po vremenu nastanka deli na sepsu sa ranim i kasnim ispoljavanjem, pri čemu je patogeneza kod ta dva oblika različita. Cilj studije je da se definišu mikrobiološki izazivači sepse i klinička prezentacija neonatusa, koji su pod dijagnozom sumnje na sepsu primljeni u GovtKilpauk Medical College Hospital, zdravstvenu ustanovu tercijarnog nivoa.

**Metodologija** Sprovedena je deskriptivna studija poprečnog preseka u Govt Kilpauk Medical College Hospital, Južna Indija.

**Rezultati**: Od 207 neonatusa koji su primljeni zbog sumnje na sepsu, 112 je bilo muškog pola i 97 ženskog pola. Odnos muškog i ženskog pola je bio 54.1% : 45.9% (muški pol : ženski pol = 1.2:1). Po kategorizaciji novorođenčadi na osnovu telesne težine na rođenju, 11 novorođenčadi je imalo izuzetno malu telesnu težinu na rođenju, 107 je imalo nižu telesnu težinu, 88 je imalo normalnu telesnu težinu i jedno novorođenče je imalo više od 4000g. Hemokultura je bila pozitivna u 88 od 207 slučajeva (42.51%). Klebsiella je bila najčešći izazivač sepse (45%) na našem odeljenju intenzivne nege za novorođenčad. Drugi Gram negativni izazivači koji su izolovani iz uzoraka su bili Escherichia Coli (31%), Pseudomonas (6%), Enterobacter (1%) i Acinetobacter (2%). Gram pozitivni organizmi koji su porasli na podlogama su bili koagulaza pozitivni i koagulaza negativni Stafilococcus (8%), Streptococcus Beta Haemolyticus grupe B (5%) i Enterococcus (2%). Sepsa sa kasnim ispoljavanjem je bila 1.5 put češća od sepse sa ranim ispoljavanjem. Pokazalo se da su Gram negativni mikroorganizmi bili najosetljiviji na Imipenem (92%), zatim na Amikacin (82.66%), dok su Gram pozitivni mikroorganizmi bili najosetljiviji na Vankomicin (84.61%), a zatim na Cloxacillin i Ampicillin (61.53%). Od 88 pozitivnih hemokultura, 6 je bilo rezistentno na više antibiotika (6.8%).

**Zaključak** Poznavanje prirode mikroorganizama koji izazivaju sepsu kod novorođenčadi pomaže u sprečavanju morbiditeta, mortaliteta i razvoja rezistencije na antibiotike.

**Ključne reči**: neonatalna sepsa, osetljivost na antibiotike, Klebsiella, niska težina na rođenju