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CLINICAL PROFILE OF NEONATES ADMITTED WITH SEPSIS – A TERTIARY CARE EXPERIENCE

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ABSTRACT:- ***Background:*** *Sepsis is the commonest diagnosis of most neonatal units and is responsible for increasing morbidity, mortality and cost of treatment. A triad of high index of clinical suspicion, early lab diagnosis, with judicious use of antibiotics will lead to favorable outcome.*
Aims and objectives of the study: *To study the clinical presentation, investigative profile and outcome of neonates admitted with sepsis.*
Study design: *Prospective observational study.*
Materials and methods: *This study included prospective data of 109 newborns over a period of four months from June 2013 to September 2013 with clinical diagnosis of septicemia. Clinical suspicion was made on the basis of maternal risk factors like leaking per vaginum > 24 hours, foul smelling liquor, maternal fever or features in the neonates like refusal to feed, lethargy, respiratory distress, jaundice, abdominal distension, vomiting, cyanosis etc. Total WBC, platelet count, CRP, blood cultures were sent and all babies were followed up to final outcome either discharge or death.*
Results: *Amongst the study population, male to female ratio was 68:41. Majority of neonates were delivered by vaginal route. 51(46.7%) neonates had early onset sepsis whereas rest 58(53.3%) had late onset sepsis. The major clinical features of sepsis were refusal to feed, lethargy, respiratory distress, jaundice, convulsions, abdominal distension, vomiting, hepatomegaly and splenomegaly. CRP was positive in 42 babies. Blood culture was positive in 24(22%) neonates. Klebsiella was the most common organism isolated, followed by CONS and Enterococci, which were sensitive to Vancomycin and Cefoperazone. Leucopenia was observed in 14(12.8%) neonates and leucocytosis in 19(17.4%) neonates. Thrombocytopenia was seen in 61(55.9%) neonates. Total deaths were 16(14.6%), of which 9(56.3%) neonates had early onset and 7(43.7%) neonates had late onset sepsis.*
Conclusions: *Septicemia is a major cause of mortality and morbidity in neonates. Outcome to a great extent depends upon early identification and prompt intensive treatment.*
KEY WORDS: *Blood culture, early onset sepsis (EOS), late onset sepsis (LOS), neonatal sepsis, septic screen.*

I. Introduction

Neonatal sepsis is defined as a clinical syndrome of bacteremia with systemic signs and symptoms of infection in the first 4 weeks of life. It encompasses various systemic infections of the newborn such as septicaemia, meningitis, pneumonia, arthritis, osteomyelitis and urinary tract infections. Sepsis is the commonest cause of neonatal mortality. It is responsible for about 30-50% of the total neonatal deaths in developing countries[1, 2]. It is estimated that up to 20% of neonates develop sepsis and approximately 1% die of sepsis related causes[2]. Sepsis related mortality is largely preventable with rational antimicrobial therapy and aggressive supportive care.

The incidence of neonatal sepsis according to the data from National Neonatal Perinatal Database (NNPD, 2002-03) is 30 per 1000 live births. The database comprising 18 tertiary neonatal units across India found sepsis to be one of the commonest causes of neonatal mortality contributing to 19% of all neonatal deaths[3]. Septicemia was the commonest clinical category with an incidence of 23 per 1000 live births while the incidence of meningitis was reported to be 3 per 1000 live births.

CLASSIFICATION OF NEONATAL SEPSIS: Neonatal sepsis can be classified into two major categories depending up on the onset of symptoms[4].
EARLY ONSET SEPSIS (EOS): It presents within first 72 hours of life. In severe cases, the neonate may be symptomatic at birth. Infants with EOS usually present with respiratory distress and pneumonia[5]. The source of infection is generally the maternal genital tract.
LATE ONSET SEPSIS (LOS): It usually presents after 72 hours of age. The source of infection in LOS is either nosocomial (hospital acquired) or community acquired and neonates usually present with septicemia, pneumonia or meningitis[6, 7].

CAUSATIVE ORGANISMS: The main offenders for early onset sepsis are E.coli, Klebsiella and group B streptococcus. The main organisms causing late onset sepsis are Klebsiella pneumoniae, Enterobacteria, Pseudomonas and Staphylococcus aureus.

CLINICAL FEATURES: The earliest signs of sepsis are often subtle and nonspecific; indeed, a high index of suspicion is needed for early diagnosis. Neonates with sepsis may present with one or more of the following symptoms and signs

1. Hypothermia or fever (former is more common in preterm low birth weight infants), lethargy, poor cry, refusal to suck
2. Poor perfusion, prolonged capillary refill time
3. Hypotonia, absent neonatal reflexes
4. Brady/tachycardia
5. Respiratory distress, apnea and gasping respiration
6. Hypo/hyperglycemia
7. Metabolic acidosis

Specific features relating to various systems include bulging anterior fontanelle, seizures, abdominal distension, vomiting, diarrhea, necrotizing enterocolitis (NEC), direct hyperbilirubinemia, hepatomegaly, bleeding, sclerema, umbilical redness and discharge.

INVESTIGATIONS: Since treatment should be initiated in a neonate suspected to have sepsis without any delay, only minimal and rapid investigations should be undertaken[8].

BLOOD CULTURE: It is the gold standard for diagnosis of septicemia and should be performed in all cases of suspected sepsis prior to starting antibiotics. A positive blood culture with sensitivity of the isolated organism is the best guide to antimicrobial therapy. All blood cultures should be observed for at least 72 hours before they are reported as sterile. Bacterial growth can be detected within 12-24 hours by using improved bacteriological techniques such as BACTEC and BACT/ALERT blood culture systems. These advanced techniques can detect bacteria at a concentration of 1-2 colony-forming units (cfu) per mL.

SEPTIC SCREEN: All neonates suspected to have sepsis should have a septic screen to corroborate the diagnosis[9,10]. The various components of the septic screen include total leukocyte count, absolute neutrophil count, immature to total neutrophil ratio, micro-erythrocyte sedimentation rate and C reactive protein as shown in Table no 1.

TABLE NO 1: A PRACTICAL SEPSIS SCREEN

COMPONENTS	ABNORMAL VALUES
Total leukocyte count	<5000/mm^3
Absolute neutrophil count	Low counts as per Manroe chart[11] for term and Mouzinho's chart[12] for VLBW infants
Immature/total neutrophil	>0.2
Micro-ESR	>15 mm in 1st hour
C reactive protein (CRP)	>1 mg/dl

II. Aims & Objectives

1. To study the clinical presentation and evaluate profile of neonates admitted with sepsis.
2. To study the outcome of neonates admitted with sepsis.

III. Materials And Methods

This is a prospective observational study which was conducted at Niloufer Hospital, Institute of Child Health, Hyderabad over a period of 4 months from June-2013 to September-2013. This is a teaching institution with a tertiary level NICU care. The study population included 109 neonates under the age of 28 days, admitted in NICU with features of sepsis between June-2013 to September-2013.

Detailed antenatal, natal and post-natal history was recorded. Thorough physical examination was done. 1- 2 ml venous blood samples were collected for blood culture, serum C - reactive protein, total leucocyte count, absolute neutrophil count and platelet count. The results were analyzed using Chi-square test.

INCLUSION CRITERIA: Neonates under the age of 28 days admitted in NICU with a suspicion of neonatal sepsis. Clinical suspicion was made on the basis of maternal risk factors like leaking per vaginum > 24 hours, foul smelling liquor, maternal fever or features in the neonates like refusal to feed, lethargy, respiratory distress, jaundice, abdominal distension, vomiting, cyanosis etc.

EXCLUSION CRITERIA: Neonates who were admitted to the NICU for other clinical conditions like respiratory distress syndrome, meconium aspiration syndrome, transient tachypnoea of newborn, birth asphyxia, congenital anomalies etc. were excluded from this study.

IV. Results

During the study period, a total of 109 neonates who were clinically suspected to have neonatal sepsis were included for the study and the hematological parameters were evaluated in them.

AGE DISTRIBUTION: Based on the age of the baby, the clinically suspected neonatal sepsis group was further categorized into early onset neonatal sepsis for neonates who were 3 days of age or less and late onset neonatal sepsis for those who were >3 days of age but less than 28 days.

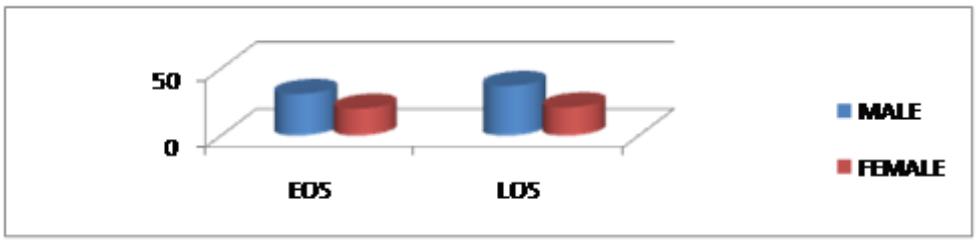
There were 51(46.7%) neonates in the early onset sepsis group and 58(53.3%) in the late onset group.

SEX DISTRIBUTION: Of the 109 neonates, 68(62.38%) were male babies and 41(37.61%) were female babies. In the early onset sepsis group 31(60.7%) were male and 20(39.3%) were female neonates. In the late onset sepsis group 37(63.7%) were male and 21(36.3%) were female neonates.

TABLE NO 2: AGE & SEX DISTRIBUTION

	Male	Female	Total	
EOS	31 (60.7%)	20 (39.3%)	51	P = 0.74
LOS	37 (63.7%)	21 (36.3%)	58	

CHART NO 1: AGE & SEX DISTRIBUTION

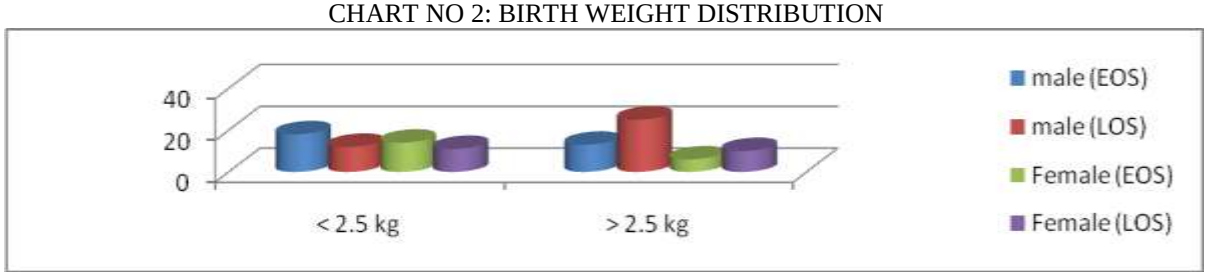


BIRTH WEIGHT DISTRIBUTION: Based on the birth weight, the distribution of these babies into EOS and LOS groups is as follows.

TABLE NO 3: BIRTH WEIGHT DISTRIBUTION

	EOS			LOS		
	Male	Female	Total	Male	Female	Total
< 2.5 kg	18	14	32	12	11	23
> 2.5 kg	13	6	19	25	10	35

CHART NO 2: BIRTH WEIGHT DISTRIBUTION

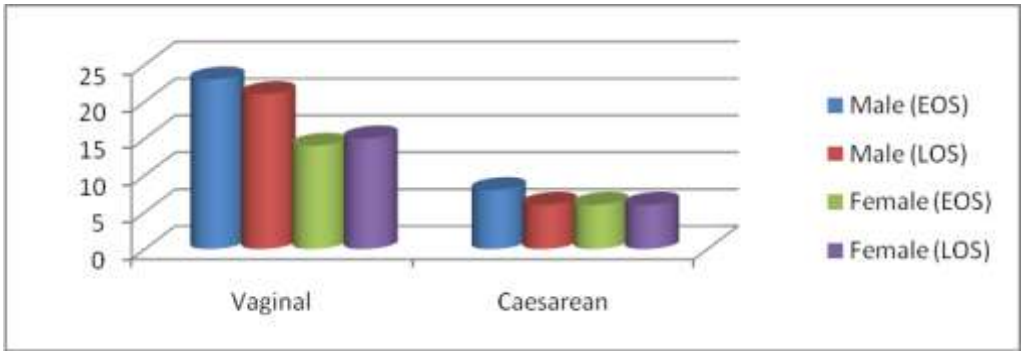


MODE OF DELIVERY: Of the studied 109 neonates, more number of neonates were delivered by vaginal route.

TABLE NO 4: MODE OF DELIVERY

	EOS			LOS		
	Male	Female	Total	Male	Female	Total
Vaginal	23	14	37	21	15	36
Caesarean	8	6	14	16	6	22

CHART NO 3: MODE OF DELIVERY EOS AND LOS



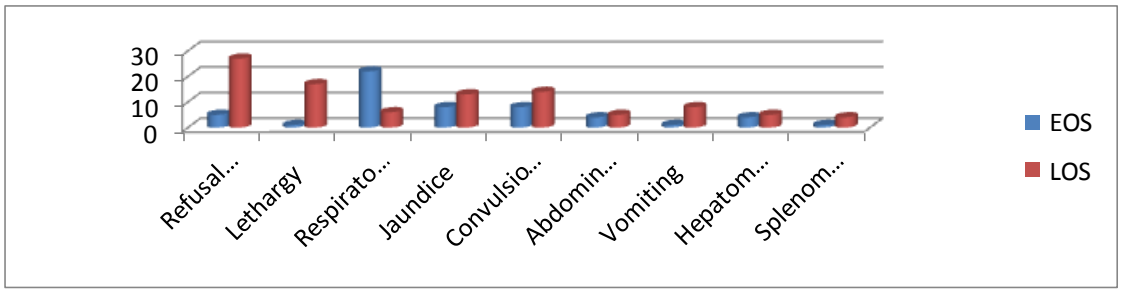
CLINICAL PRESENTATION: Of the 109 cases evaluated, the babies presented with refusal to feed, lethargy, respiratory distress, jaundice, convulsions, abdominal distension, vomiting, hepatomegaly and splenomegaly.

TABLE NO 5: CLINICAL PRESENTATION

CLINICAL PRESENTATION	EOS	LOS	Total
Refusal to feed	5	27	32(29%)
Lethargy	1	17	18(17%)
Respiratory Distress	22	6	28(26%)
Jaundice	8	13	21(19%)
Convulsions	8	14	22(20%)
Abdominal distension	4	5	9(8%)
Vomiting	1	8	9(8%)
Hepatomegaly	4	5	9(8%)
Splenomegaly	1	4	5(5%)

P = 0.000005

CHART NO 4: CLINICAL PRESENTATION



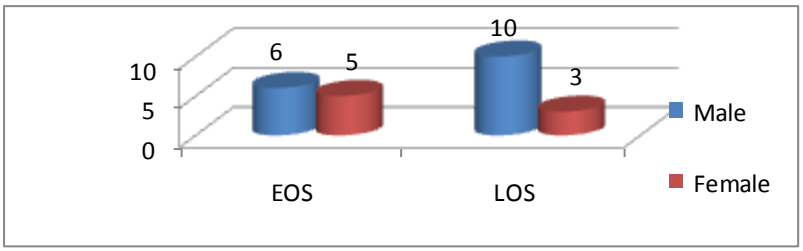
BLOOD CULTURE: Of the 109 cases evaluated for sepsis, blood culture was positive in 24(22%) cases.

TABLE NO 6: POSITIVE BLOOD CULTURE

Group	Male	Female	Total
EOS	6(55%)	5(45%)	11
LOS	10(76.9%)	3(33.1%)	13

P = 0.46

CHART NO 5: POSITIVE BLOOD CULTURE



ORGANISMS ISOLATED: The following was the distribution of the organisms isolated in 24 cases on the blood culture. The organisms were sensitive to Vancomycin and Cefoperazone.

TABLE NO 7: MICRO-ORGANISMS ISOLATED

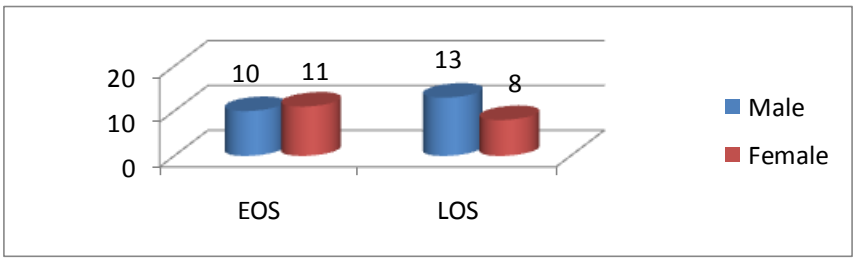
Sl. No	Microorganism	Number
1	Klebsiella	12(50%)
2	CONS	8(33.3%)
3	Enterococci	4(26.7%)

C-REACTIVE PROTEIN: Of the 109 cases evaluated for sepsis CRP was positive in 42 cases. Of these 21(50%) cases were early onset and 21(50%) cases were late onset sepsis.

TABLE NO 8: POSITIVE CRP

Group	Male	Female	Total	P = 0.35
EOS	10(47.6%)	11(52.4%)	21	
LOS	13(61.9%)	8(39.2%)	21	

CHART NO 6: POSITIVE CRP

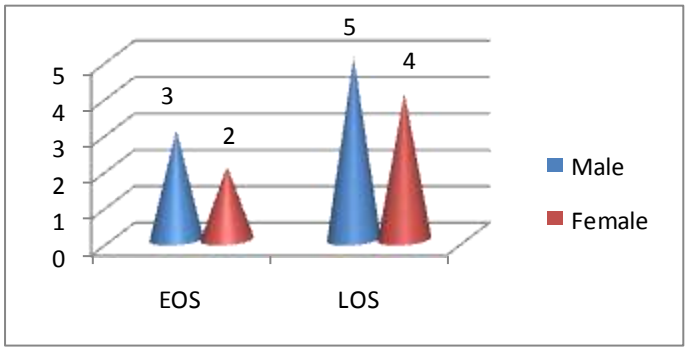


TOTAL LEUCOCYTE COUNT: Leucopenia i.e. TLC < 5000/mm3 was observed in 14(12.8%) neonates. Of these 5(35.7%) cases were early onset and 9(64.3%) cases were late onset sepsis.

TABLE NO 9: LEUCOPENIA

Group	Male	Female	Total	P = 0.68
EOS	3(60%)	2(40%)	5	
LOS	5(55.5%)	4(44.5%)	9	

CHART NO 7: LEUCOPENIA

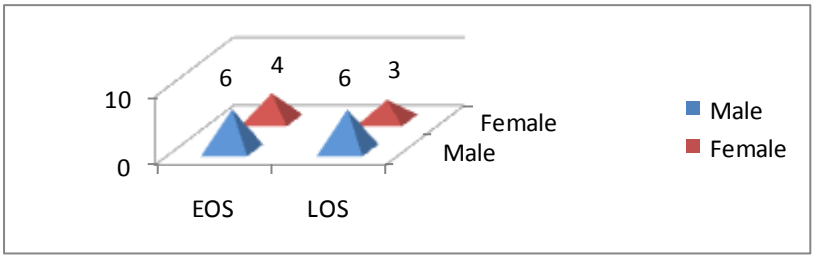


Leucocytosis i.e. TLC > 20000/mm^3 was observed in 19(17.4%) neonates. Of these 10(52.6%) cases were early onset and 9(47.6%) cases were late onset sepsis.

TABLE NO 10: LEUCOCYTOSIS

Group	Male	Female	Total	P = 0.86
EOS	6(60%)	4(40%)	10	
LOS	6(66.6%)	3(33.4%)	9	

CHART NO 8: LEUCOCYTOSIS

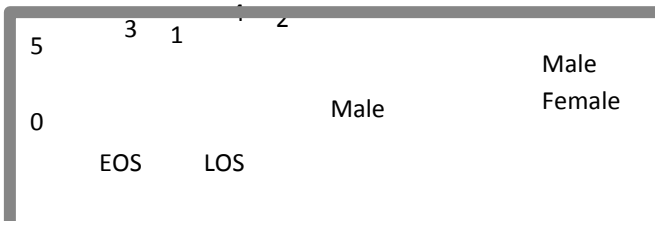


ABSOLUTE NEUTROPHIL COUNT**:** ANC < 1800/mm^3 was observed in 10 neonates. Of these 4(40%) cases were early onset and 6(60%) cases were late onset sepsis.

TABLE NO 11: ANC

Group	Male	Female	Total
EOS	3(75%)	1(25%)	4
LOS	4(66.6%)	2(33.4%)	6

CHART NO 9: ANC

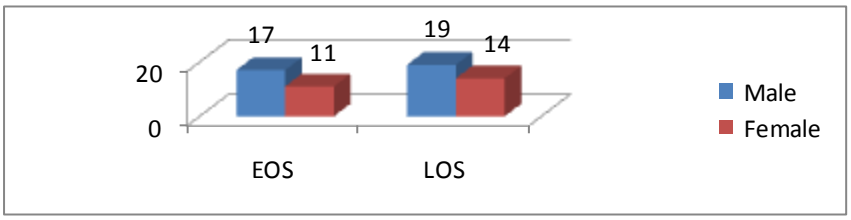


PLATELET COUNT: Thrombocytopenia i.e platelet count < 1.5 lakhs was observed in 61(55.9%) neonates. Of these 28(45.9%) cases were early onset and 33(54.1%) cases were late onset sepsis.

TABLE NO 12: PLATELET COUNT

Group	Male	Female	Total	
EOS	17(60.7%)	11(39.3%)	28	P = 0.8
LOS	19(57.5%)	14(42.5%)	33	

CHART NO 10: PLATELET COUNT

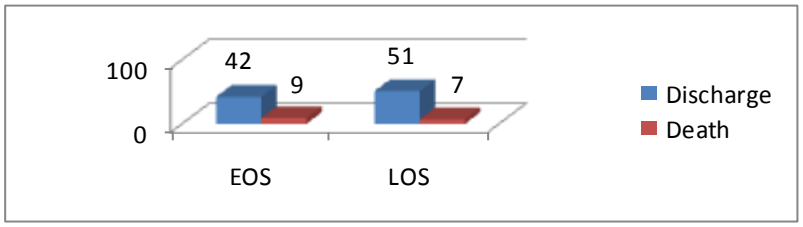


OUTCOME: Mortality was slightly more in EOS in comparison to LOS.

TABLE NO 13: OUTCOME

Group	Discharge	Death	Total	
EOS	42(82.3%)	9(17.7%)	51	P = 0.41
LOS	51(87.9%)	7(12.1%)	58	

CHART NO 11: OUTCOME



DURATION OF HOSPITAL STAY: Late onset sepsis neonates had longer duration of hospital stay compared to early onset sepsis neonates.

TABLE NO 14: DURATION OF HOSPITAL STAY

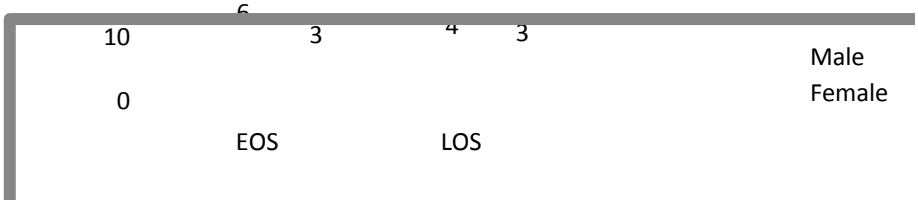
Group	Total	Mean(days)
EOS	42	6.4
LOS	51	7.6

DEATHS: Of the 109 cases studied, total deaths were 16(14.6%). Of these 9(56.3%) cases were early onset and 7(43.7%) cases were late onset sepsis.

TABLE NO 15: NEONATAL DEATHS

Group	Male	Female	Total	
EOS	6(66.7%)	3(33.3%)	9	P = 0.89
LOS	4(57.1%)	3(42.9%)	7	

CHART NO 12: NEONATAL DEATHS



V. Discussion

Neonatal septicemia is one of the major factors contributing to the high perinatal and neonatal mortality and morbidity. The major problem in neonatal infections is the identification of the sick infant. It is desirable to administer appropriate therapy as early as possible to the infected infant.

The incidence of septicemia has been reported by several workers to be higher in males than females[13, 14, 15, 16]. In the present study, it was found that the incidence of septicemia was higher in males compared to females. Varsha et al[13] reported in their study that 74.6% of neonates evaluated for sepsis were less than 3 days of age and 25.3% were in the late onset sepsis group of greater than 3 days of age. In the present study, 51 neonates (46.7%) were aged less than or equal to 3 days of age and the rest 58 neonates (53.3%) belonged to the late onset sepsis group of greater than 3 days of age. In studies done by Khatua et al[18], Klein Jo et al[19], refusal to feed, lethargy, diarrhea, hypothermia were the main clinical features in neonates with sepsis. In the present study, refusal to feed, lethargy, respiratory distress, jaundice and convulsions were the main clinical features.

Despite the increased availability of innovative molecular technologies for detecting and reporting microbial pathogens, most clinicians still regard the isolation of bacteria and antimicrobial susceptibility report as the most important test results generated by clinical microbiology laboratory[20]. However, blood culture may be sterile many a times in spite of presence of clinical and laboratory signs. This could be because the bacterial inoculum may be small, transitory or the blood culture may be unable to pick it up because of pre existing antibiotics. Knowing that up to a third of cultures can be sterile, then it is evident that actual number of infected neonates will be under reported and as a result the positive predictive value of a test used in sepsis screen will be lowered[21]. In the present study, blood culture positivity was observed in 24(22%) neonates. Of these 11(46%) were EOS and rest were LOS. Klebsiella was isolated in 50% of culture positive cases followed by CONS and Enterococci. They were sensitive to Vancomycin and Cefoperazone.

A comparative table on the reported blood culture positivity by various authors is depicted below.

TABLE NO 16: COMPARATIVE TABLE ON RESULTS OF BLOOD CULTURE.

Author	Year	Result
Sharma A.et al[14]	1993	5.5%
Franz A.R et al[22]	1999	5.5%
Varsha et al[13]	2003	14%
Zawar M.P et al[17]	2003	59%
Present study	2013	22%

CRP is synthesized within 6 to 8 hours of an inflammatory stimulus. As infection is the most likely cause of inflammation in the neonate, elevation of CRP has been a useful marker for sepsis in many studies, although sensitivity and negative predictive values are not high enough for CRP alone to be a definitive diagnostic test. A single CRP value done at the time of admission may not identify all neonates with sepsis;

serial levels done 24 hours apart increase the sensitivity of CRP determinations. In the present study CRP was positive in 42(38.5%) cases with equal distribution between EOS and LOS. TLC less than 5000/mm^3 was observed in 14 neonates. Number of LOS neonates, who had leucopenia, is more compared to EOS. TLC more than 20000/mm^3 was observed in 19 neonates. EOS and LOS were almost equal in distribution. ANC < 1800/mm3 was observed in 10 neonates. LOS neonates were more in number.

A reduction in the number of circulating platelets has been shown to be an insensitive, a non specific and a relatively late indicator of serious bacterial infection during the neonatal period[23]. Thrombocytopenia was observed in 61 neonates. It is observed more in LOS neonates. Mortality was observed in 16(14.6%) neonates. The rest were discharged with an average duration of hospital stay of 7 days.

VI. CONCLUSIONS

Neonatal septicemia constitutes an important cause of morbidity and mortality amongst neonates in India. Accurate and timely diagnosis of neonatal sepsis is a challenge both to the clinician and the laboratory. A positive blood culture and the antibiotic susceptibility testing of the isolates are the best guide in choosing the appropriate antimicrobial therapy in treating neonatal septicemia.

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