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Original Article

Neonatal infections: Incidence and Outcome in a Tertiary Level Hospital in North India

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Abstract
Background: *Neonatal sepsis remains one of the biggest clinical challenges in the Indian intensive care nurseries despite continuing advances in diagnosis and management it is a leading cause of morbidity and mortality in neonatal period.*
Objectives: *This study was undertaken to determine the demographic profile, haematological parameters, outcome and pattern of bacterial isolates responsible for early and late onset neonatal sepsis based on the presence of one or more clinical signs.*
Methods: *This was a tertiary hospital based; observational & prospective study conducted over a period of one year (May 2012 to April 2013) at the Neonatal Intensive Care Unit of Kamla Nehru hospital, Shimla. Total 156 newborns (0-28 days) of >30 weeks gestation and >1000grams weight with features suggestive of sepsis were included in the study.*
Results: *In our study out of 156 newborns, 95(60.8%) presented with Early onset sepsis (EOS) and 61(39.2%) with late onset sepsis (LOS). Overall blood culture positivity in septicemia came out to be 44.8%. Significantly high incidence of sepsis was seen in preterms, males, LBW and newborns delivered vaginally but these parameters were not statistically significant (p value > .05). TLC, IT Ratio, Toxic granules, platelet count and Micro – ESR were statistically significant (p value of <.05) in both EOS as well as LOS. Gram negative organisms accounted for septicaemia in 67.1%, Gram positive organisms in 27.1% and Candida in 5.7% of neonates. In the present study overall mortality was 30.1% with 80.8% mortality in EOS and 19.2% in suspected LOS.*
Conclusion: *The spectrum of organisms that cause neonatal sepsis changes overtime. Therefore, it is necessary to conduct periodic surveillance to assess the changing pattern of organisms causing neonatal sepsis. In our study there was significant correlation between mortality rate and type of causative pathogen, gestational age, birth weight and onset of sepsis.*
Keywords: *Early onset sepsis, late onset sepsis, septicaemia, blood culture, neonatal mortality.*

Introduction

Neonatal sepsis refers to systemic infection of the newborn. It is characterized by a constellation of a nonspecific symptomatology in association with bacteremia. Prompt recognition, appropriate antimicrobial therapy and judicious supportive care are the key determinants of positive outcome in this serious pediatric emergency. In developing countries, sepsis including meningitis, respiratory infections, diarrhea, and neonatal tetanus are the commonest cause of mortality responsible for 30-50 per cent of 5 million total neonatal deaths each year. It is estimated that almost 20 per cent of all neonates develop infection and approximately 1% die of the serious systemic infections.[1]

Depending on the onset of symptoms neonatal sepsis is categorized as early (EOS) or late onset sepsis (LOS). Majority (85%) of newborns with EOS present within 24 hours, 5% present at 24-48 hours, and a smaller percentage of patients present between 48 hours and 6 days of life.[2]

Early onset sepsis usually presents as respiratory distress and pneumonia within the first 72 hours of life and is associated with acquisition of microorganisms from the mother either transplacentaly or during delivery. The main organisms responsible are GBS, *Escherichia Coli, K. pneumoniae*, *S.aureus, Enterococcus, and Chlamydia*.[3]

Late onset sepsis usually presents as pneumonia or meningitis after 72 hours of life. The source of infection is nursery, community or NICU. Common organisms responsible for LOS include Coagulase Negative *staph. aureus, Group B Streptococcous*, *Enterococcus, Escherichia Coli, Klebsiella, Pseudomonas*.[4]

Prominent respiratory signs are the presenting features of EOS while LOS has more varied presentations. Signs of sepsis in newborn are non –specific and early diagnosis of neonatal sepsis is still a great challenge as there is no laboratory test with 100% sensitivity and specificity.[5,6] Blood culture is a gold standard for diagnosis of septicemia with a yield of 8-73% as shown in various studies[7]. The detection of microorganisms in a patient's blood has a great diagnostic and prognostic significance. Many infections in the neonatal age group can only be established on the basis of etiological agent recovered from blood.[8]

Methods

The study was conducted at the Neonatal Intensive Care Unit of Kamla Nehru hospital, Shimla from May 2012 to April 2013. Newborns (0-28 days) of >30 weeks gestation and >1000grams weight with features suggestive of sepsis constituted the study cohort. Neonates who had received antibacterial therapy within the last 48 hours and those with Respiratory Distress Syndrome (RDS) due to HMD, major congenital anomalies, haemolytic jaundice and inborn error of metabolism were excluded from the study.

Each neonate was examined thoroughly and signs and symptoms of the neonate were recorded in the proforma. The gestational age was assessed by period of gestation (POG) and if not known by New Ballard Scoring System. A detailed history including adverse perinatal factors; intra-partum fever (>37.50C), chorioamnionitis, prolonged rupture of membrane (>18 hours) and unclean vaginal examination were recorded in each case.[9]

Blood samples of the neonates were collected at the time of admission and before initiation of antibiotic therapy. Blood sampling was done under all aseptic precautions in the NICU. Soon after admission two ml blood sample was taken in EDTA vacutainer and processed for TLC and platelet count by MS -9 (3-part) Coulter hematology autoanalyser. TLC < 5000 or >20,000 /mm3 were considered abnormal.[10]

Peripheral blood smears were drawn on clean slides and stained by Giemsa stain. A differential leukocyte count (DLC) was done to obtain the total neutrophil count (TNC), immature neutrophil count (IM), including bands and stabs; and mature neutrophil count.[11]

Neutrophils were classified as band forms when there were no nuclear segmentation or when the width of the nucleus at any constriction was not

less than one third the width of its widest portion. Band forms together with less mature cell forms were classified as immature polymorphonuclear (PMN) leukocytes. Using these values, I/M and I/T ratios were computed. Neutrophils were further examined for degenerative changes such as toxic granulation, Dohle bodies, and vacuolization on PBS by Giemsa stain. Immature to total neutrophil ratio (IT Ratio) of >0.2 was taken significant. Micro - ESR was done by capillary method. (μ - ESR) $\geq$15 mm at the end of 1 hour was taken significant.[10,11] In addition blood for CRP was also tested.

Another 1 ml blood sample was inoculated into 5 ml of culture media - brain heart infusion (BHI) broth in all the cases of suspected EOS prior to starting antibiotics and were observed for at least 72 hours before they were reported as sterile.[12,13]

After detailed investigation and culture reports neonates were further categorised into culture positive sepsis or culture negative sepsis. The clinical manifestations and hematological parameters were compared, individually and in combination, with the blood culture result.

Statistical analysis

Sensitivity, specificity, positive and negative predictive values were calculated for each parameter. P values were also calculated for different parameters. Data was statistically analyzed using SPSS software.

Observations and Results

During the study period (1st May, 2012 to 30th April, 2013) there were 6964 live births in KNH of which 1258 (18.1%) were admitted to newborn nursery. Out of 156 newborns with suspected sepsis 61 newborns presented with LOS and 95 newborns that had maternal history of one or more risk factors presented with EOS. The overall incidence of neonatal sepsis was 22.4/1000 live births.

Overall blood culture positivity in septicemia came out to be 44.8% while it was 48.4% in EOS and 39.3% in LOS. In our study a significantly high incidence of EOS as well as LOS was seen in preterms, males, LBW and newborns delivered vaginally but these parameters were not statistically significant (p value > .05) as shown in table 1.

Table 1: Distribution of Demographic Profile in Newborns with EOS (n=95) and LOS. (n=61)

NEONATAL PROFILE	EOS (n=95).				LOS (n=61)			
	BLOOD C/S(+) (n = 46)	BLOOD C/S(-) (n= 49)	TOTAL (n = 95)	p value	BLOOD C/S(+) (n = 24)	BLOOD C/S(-) (n= 37)	TOTAL (n = 61)	p value
Gestational age (wks)		Blood CS (-) (n=49)	TOTAL (n=95)	.212.2.12				
≤37	27(58.6%)	26(49.1%)	53(55.7%)	.212	15(62.5%)	17(45.9%)	32(52.5%)	.553
≥37	19(41.4%)	23(54.7%)	42(44.3%)		9(37.5%)	20(54.1%)	29(47.5%)	
Sex								
Male	30(65.3%)	26(46.5%)	56(58.9%)	.5	16(66.7%)	26(70.3%)	42(68.9%)	.5
Female	16(34.7%)	23(58.9%)	39(41.1%)		8(33.3%)	11(29.7%)	19(31.1%)	
Birth weight (gms)								
≥2500	7(15.3%)	11(22.5%)	18(27.3%)	.661	4(16.6%)	5(13.5%)	9(14.8%)	.663
2499-1500	24(52.1%)	20(40.8%)	44(42.1%)		7(29.2%)	17(45.9%)	24(39.3%)	
<1500	15(32.6%)	18(36.7%)	33(30.6%)		13(54.2%)	15(40.6%)	28(45.9%)	
Mode of delivery								
Vaginal	37(80.4%)	27(55.2%)	64(67.4%)	.053	18(75%)	27(72.9%)	45(73.7%)	.056
Cesarean Section	9(19.6%)	22(44.8%)	31(32.6%)		6(35%)	10(27.1%)	16(26.3%)	

Majority of the clinical manifestations of the newborns with suspected sepsis included fever ,refusal to feed, lethargy, followed by pneumonia, disseminated intravascular coagulation (DIC), feed intolerance, birth asphyxia, shock, respiratory failure, neonatal hyperbillrubinemia, necrotising enterocolitis, hypoglycemia and apnea (Figure 1.)
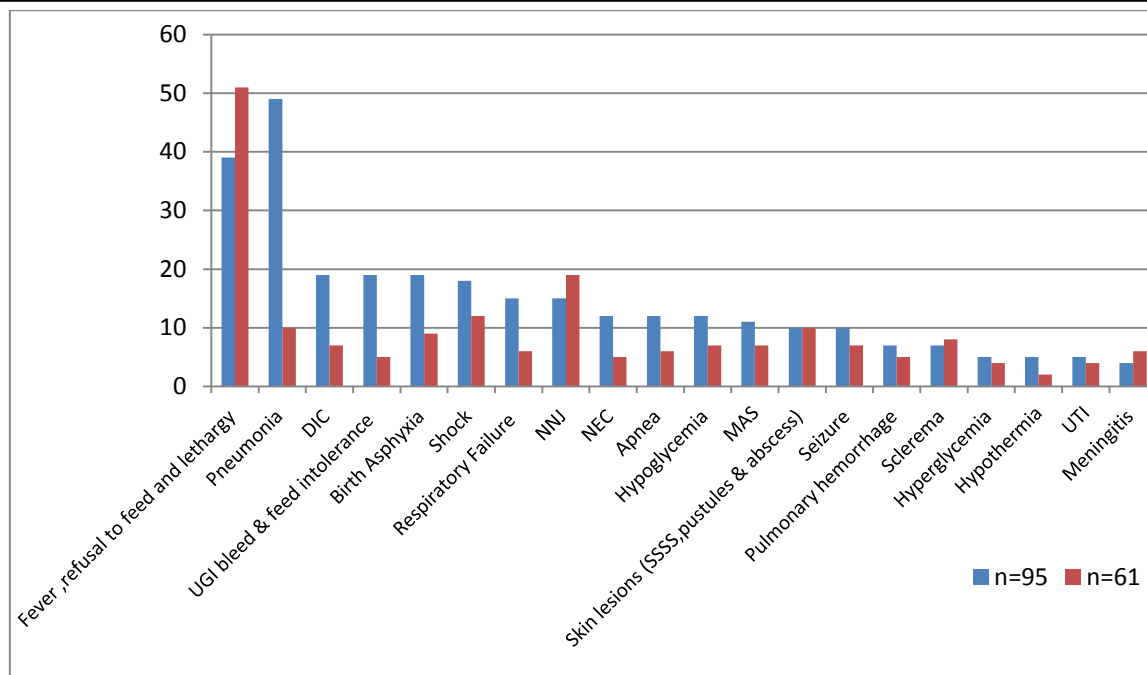
Figure 1: Distribution of Clinical Manifestations in newborns with EOS (n=95) and LOS (n=61).

Among the haematological parameters in EOS, toxic granules had a highest sensitivity and Negative Predictive Value (NPV) of 100%, specificity of 61.2% and Positive Predictive Value (PPV) of 32.6% whereas, raised Micro–ESR had a sensitivity of 92.1%, specificity of 80.7%, PPV of 76% and NPV of 93.8% (Table 3). In LOS toxic granules had a highest sensitivity and NPV of 100%, specificity of 72.5% and PPV of 41%

whereas raised Micro –ESR had a sensitivity of 88.2%, specificity of 79.5%, PPV of 62.5% and NPV of 94.5% (Table 4). In our study among the neonatal haematological parameters in both EOS as well as LOS ,TLC, IT Ratio, Toxic granules , platelet count and Micro – ESR were statistically significant (p value <.05) as compared to rest of the parameters which had low sensitivity, specificity, PPV and NPV.

Table 3: Distribution of various Hematological Parameters in Newborns with EOS (n=95) and LOS (n=61).

NEONATAL HEMATOLOGICAL PARAMETERS	EOS (n=95)			LOS (n=61)		
	BLOOD C/S (+) (n =46)	BLOOD C/S (-) (n =49)	p value	BLOOD C/S (+) (n =24)	BLOOD C/S (-) (n =37)	p Value
TLC (<5,000/mm3 or >20,000/mm3)	Leukopenia -7(15.2%) Normal TLC- 25(54.3%) Leukocytosis –14(30.5%)	Leukopenia -4(8.1%) Normal TLC- 35(71.5%) Leukocytosis –10(20.4%)	.006	leukopenia -3(12.5%) Normal TLC- 10(41.7%) Leukocytosis – 11(45.8%)	leukopenia -4(10.8%) Normal TLC- 29(78.4%) Leukocytosis –4(10.8%)	.0006
Total PMNs	Neutropenia-7(15.2%) Neutrophilia -14(30.4%)	Neutropenia -2(4.08%) Neutrophilia -7(14.2%)	.085	Neutropenia- 2(8.3%) Neutrophilia -5(20.8%)	Neutropenia -4(10.8%) Neutrophilia -2(5.4%)	
I/T Ratio >.2	22(47.8%)	2(4.08%)	.000	12(50%)	2(5.4%)	.000
Immature PMNs	21(45.6%)	5(10.2%)	.072	10(41.7%)	3(8.1%)	.341
Thrombocytopenia	28(60.8%)	3(6.1%)	.000	17(70.8%)	3(8.1%)	.000
Toxic Granules	15(32.6%)	0	.000	10(41.7%)	0	.000
Raised µ-ESR	35(76%)	3(6.1%)	.000	15(62.5%)	2(5.4%)	.000
CRP	34(73.9%)	14(28.5%)	.067	18(75%)	3(8.1%)	.121

In our study E. coli (34.7%) was the commonest micro-organism in neonates with EOS while in LOS *Klebsiella* (29.1%) was the commonest

followed by *S. aureus*, CONS, *Streptococcus*, *Pseudomonas*, *Proteus* sp., *Enterococcus*, *Enterobacter*, NLF and *Candida*.(Figure 2.)
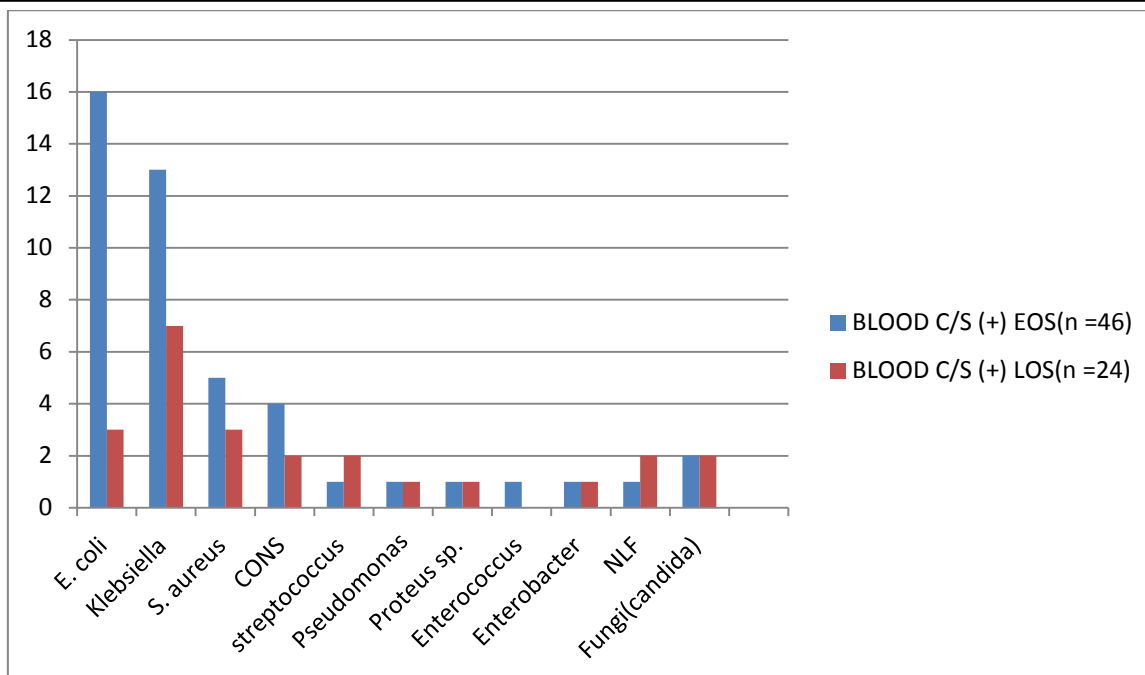
Figure 2: Distribution of Micro-organisms in Newborns with BLOOD C/S (+) EOS (n =46) and LOS (n=24).

Outcome

In our study out of 156 neonates with suspected sepsis 99(63.5%) were discharged after treatment and 47(30.1%) died whereas 10(6.4%) left or were discharged against medical advice.

Out of 47 deaths, mortality was high in neonates (40%) with EOS as compared to neonates with LOS (14.7%). Major cause of death in EOS was DIC and shock while in LOS it was respiratory failure .As shown in Table no.3 neonatal deaths in

EOS as well as LOS were more common in preterms, males and those with Low Birth Weight. Neonates born by caesarean deliveries in EOS group had a high mortality rate of 18.8% as compared those born by vaginal deliveries in LOS because of high incidence of prolonged labour, meconium stained liquor, intrapartum fetal distress and prolonged hospital stay contributing to late onset septicaemia.

Table 3: Representation of mortality in relation to demographic profile in EOS (n=95) and LOS (n=61).

NEONATAL PROFILE	EOS (n=95)				LOS (n=61)			
	Total No. of patients (n=95)	BLOOD C/S(+) (n = 46)	No. Of Deaths (n=38)	Incidence	Total No. of patients (n=61)	BLOOD C/S(+) (n = 24)	No. Of Deaths (n=9)	Incidence
Gestational age (wks)								
≤37	53	27	29	54.7%	32	15	7	21.8%
≥37	42	19	9	21.4%	29	9	2	6.8%
Sex								
Male	56	30	26	46.4%	42	16	7	16.7%
Female	39	16	12	30.7%	19	8	2	10.5%
Birth weight (gm)								
≥2500	18	7	3	16.7%	9	4	0	0
2499-1500	44	24	15	34.1%	24	7	4	16.6%
<1500	33	15	20	60.6%	28	13	5	17.8%
Delivery type								
Vaginal	64	37	28	43.7%	45	18	6	13.3%
C. Section	31	9	10	32.2%	16	6	3	18.8%

Mortality in relation to bacterial isolates

In our study maximum mortality rate of 55.5% was seen in Gram negative sepsis, 33.3% in Gram

positive sepsis and 11.1% in fungal sepsis (Figure 3 and 4).

In blood culture positive EOS group, mortality rate of 76.9% was seen in *Klebsiella* sepsis which was very high when compared with LOS. Majority (97.6%) of the patients with *Klebsiella* sepsis had a typical clinical presentation in the form of petechiae over skin, altered nasogastric aspirate, feed intolerance and abdominal distension. Most common cause of death in all these patients was DIC followed by pulmonary haemorrhage and eventually leading to refractory shock. Most specific hematological features in these patients were thrombocytopenia, presence of toxic granules and raised IT ratio.

Among the blood culture positive LOS group, *E. coli* and *Staphylococcal* sepsis were predominant with a mortality rate of 66.6% each when compared to EOS. *E. coli* and *Staphylococcal* sepsis presented with shock and respiratory failure in 85.8% newborns while late onset *Klebsiella* sepsis had presentation similar to EOS. Most specific hematological features in LOS were leukocytosis (65.4%), toxic granules and raised IT ratio (45.1% each). In our study there were 10(26.3%) neonatal deaths in EOS group with blood culture negative sepsis but had clinical and hematological features suggestive of severe sepsis. There were 4(40%) newborns with clinical presentation like *Klebsiella* sepsis and also had maternal risk factors for EOS but had a negative blood culture.
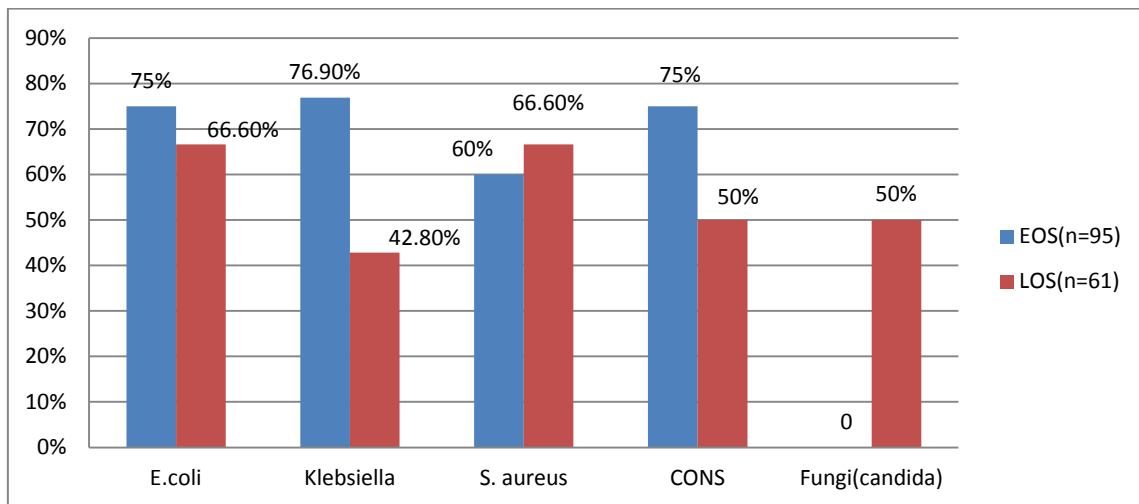

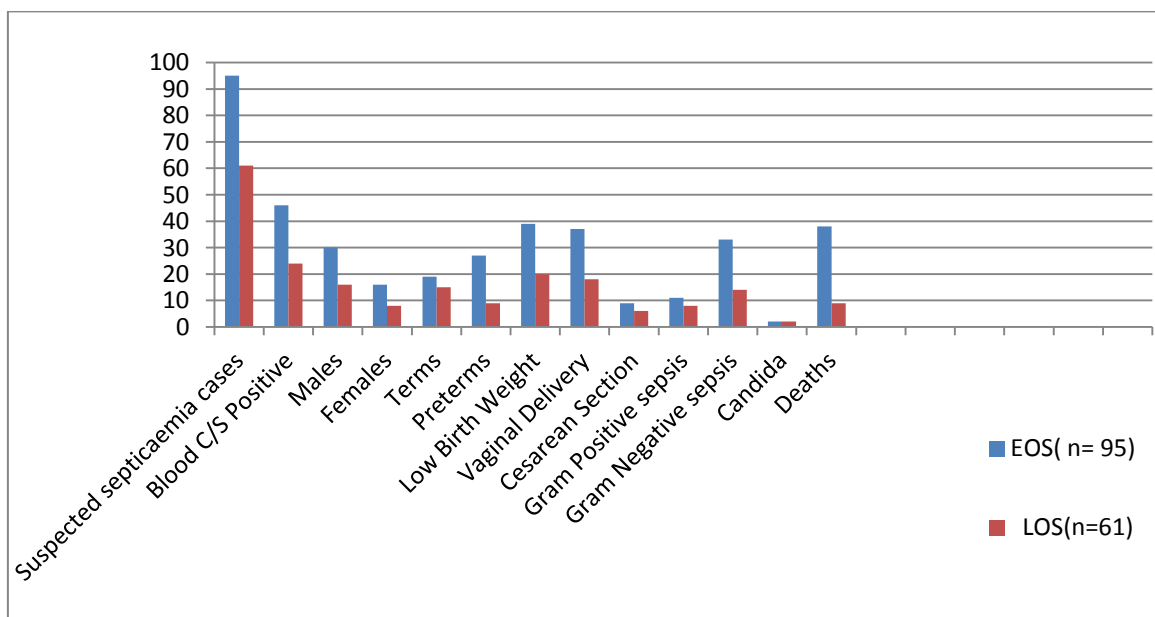**Figure 3:** Representation of mortality in relation to bacterial isolates in EOS (n=95) and LOS (n=61).

Figure 4: Comparison of demographic profile of EOS (n=95) and LOS (n=61) in newborns

Discussion

The present study aims to evaluate the clinico – bacteriological as well as hematological profile of neonates in a tertiary care hospital. This knowledge is a prerequisite in determining the management strategy of neonates with septicemia.

The overall incidence of septicemia among the neonates born at KNH during the study period from 1st April, 2012 -31st May 2013 came out to be 22.4/1000 live births. Early onset sepsis had an incidence of 6.6/1000 live births which is less than that reported by Chaudhary S et al[14] (17.3 /1000 live birth) from the same institution two decade ago and by Mondal GP et al[13] (15.5/1000 live births).

Overall blood culture positivity in suspected septicaemia in the present study was 44.8% .In EOS blood culture positivity was seen in 48.4% newborns while it was 39.3% in LOS group which is higher than that 17% reported by Willa Antoniette et al[15] (2003) , 12% by Khalada Binte Khair et al[16] (2010), 26.9% by Mane A K et al[17] (2005-2007) this difference in blood culture positivity in different studies may be due to number of factors like prior administration of antibiotics, difference in prevalence of septicaemia in different region, blood sampling technique and amount of blood taken.

Incidence of both EOS and LOS was more common in males and LBW neonates which is similar to that reported by A.C. Buch et al[18] (2011), Trotman H et al[19] (2000) and Gheibi S et al [20] (2006). Important adverse maternal factors associated with sepsis in the present study were similar to those studied by Willa Antoniette et al[15] (2003) and Khalada Binte Khair et al[15] (2010).

Majority of the neonates with sepsis presented with fever and refusal to feed (41%), pneumonia (31.4%), DIC, UGI bleed & feed intolerance , birth Asphyxia (12.1%) and shock (11.5%) which was in agreement to study done by Dawodu et al[21] (1997) and Fanaroff et al[22].

Among the most significant haematological parameters in both EOS and LOS, toxic granules, raised Micro–ESR, I/T Ratio>.2, thrombocytopenia and raised TLC were the most significant markers for early diagnosis of neonatal sepsis which was similar to that observed by Singhi Sunit et al[23]. Khalada Binte Khair et al[16] Rodwell et al[24]

In present study Gram positive organisms were the cause of septicaemia in 27.1%, Gram negative organisms in 67.1% and Candida in 5.7% of neonates. In early onset sepsis E. coli (34.7%) was the commonest micro-organism whereas, Klebsiella (29.1%) was predominant in LOS. This was similar to that reported by Kumhar GD et al[25] (1996) Chaudhary H et al[26] (2005) Kapoor L[27] (2001) Jain NK et al[28](2010) whereas a study by Gheibi S et al[20] (2006) documented CONS(54.6%) as the commonest organism to be isolated in the both EOS and LOS.

Overall mortality rate in our study was 30.1% and neonates with EOS(80.8%) had much higher mortality rate than those with LOS (19.2%). Khinchi Y R et al[29] (2009), Tiskumara R et al[30] 2009 reported a mortality of 10.2% and 10.4 % respectfully. In our study preterm, LBW and male neonates in both EOS and LOS had a high mortality rate which was in agreement with the study by Mathur NB et al[31] (1996).

In our study Gram negative sepsis was responsible for a high mortality rate as compared to Gram positive and fungal sepsis which was similar to that reported by Ahmed N U et al[32] 1998 .

Conclusion

Neonatal sepsis is a serious illness associated with high mortality so a high index of suspicion is important in the diagnosis and treatment of neonatal infection because it is hampered by vague & nonspecific clinical manifestation.

Study of neonatal clinical and haematological profile is important to predict the risk of septicaemia so that appropriate treatment can be started without any delay in diagnosis. Different neonatal intensive care unit (NICU) show different epidemiological data for neonatal sepsis.

So collection of up-to-date and site specific data is mandatory for appropriate use of antibiotics.

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