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Aetiological profile, risk factors, antibiotic sensitivity pattern and outcome of neonatal sepsis in tertiary care hospitals- a prospective observational study

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Abstract

Introduction:Neonatal sepsis is an important cause of morbidity and mortality in developing countries.According to the World Health Organization(WHO),around5 million newbornsdie yearly, 98% of deaths occurring in developing countries

Objectives: To identify prevalence of neonatal sepsis,aetiological profile,antibiotic sensitivity pattern and outcome in a tertiary care centre and to formulate a consensus recommendation for empirical antibiotic usage for neonatal sepsis in our hospital.

Method:A hospital based prospective observational study was done from March 2019 to August 2020 on babies diagnosed or suspected as cases of neonatal sepsis in our hospital.

Results:Atotal of 200 neonates were included in our study with clinical suspicion of sepsis during the study period. 127 (63.5%) neonates were identified as EOS (0-3 days) and 73 (36.5%) aslate onset sepsis (4-28 days).Prematurity was thecommonest predisposing factor(68.5%).Feeding intolerance was the commonest presentation (74%).Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of C-reactive protein (CRP) + absolute neutrophil count (ANC) were 93.8% ,90.8%, 34.9%,

99.6% and 90.9% respectively.(p <0.001).Klebsiella pneumonia + Klebsiellaoxytoca(16+1) was the most common isolate (35.4%),There were 6 (12.5%) isolates of Staphylococcus aureus out of which 2 were methicilin resistant aureus(MRSA).

Conclusions:Of the 200 neonates with suspected neonal sepsis,63.5% had EOS. Prematurity was the commonest predisposing factor(68.5%) and feeding intolerance was the commonest presentation (74%).Klebsiella (35.4%) was the most common isolate.

(Key words**:**Neonatal sepsis, blood culture, sepsis screen)

Introduction

Neonatal sepsis is an important cause of morbidity and mortality in developing countries[1]. Of the 130 million babies born yearly, around4 million die in the newborn period[2]. According to the World Health Organization(WHO),around5 million newbornsdie yearly, 98% deaths occurring in developing countries[3].According to national neonatal perinatal data (NNPD) 2002-2003, neonatal sepsis occur in around 30/1000 live births[4].Neonatal mortality of Odishawas 32 per 1000 live births, contributing to more than half the under 5-year mortality[5].

Neonatal sepsisencompasses systemic newborninfections like septicaemia,meningitis, pneumonia,osteomyelitis and urinary tract infection[6].Sepsis in the first 72hours of life is defined as early onset sepsis (EOS) and after 72hours to 28 days of life as late onset sepsis (LOS). Predisposing factors includeprolonged rupture of membrane(>18 hours.), multiple per vaginal examinations or single unclean vaginal examination, foul smelling liquor, low birth weight (LBW), maternal fever, prolonged labour andmeconiumaspiration[7].Group B *streptococcus* (GBS) is the commonestcausative agentand*Escherichia coli (E.coli)* the commonest cause of death[8].*E.coli* is often associated with severe infection and meningitis and is the chief cause of sepsis related deathsinvery low birth weight (VLBW) infants[9].GBS and E.coli together account for around 70% of EOS in neonates[10]**.**

Objectives

To identify prevalence of neonatal sepsis,aetiological profile,antibiotic sensitivity pattern and outcome in a tertiary care centre and to formulate a consensus recommendation for empirical antibiotic usage for neonatal sepsis in our hospital.

Method

A hospital based prospective observational study was conducted onneonatesdiagnosed or suspected to have neonatal sepsis in the neonatal intensive care unit (NICU) and special care baby unit (SNCU), IMS AND SUM Hospital, Bhubaneswar, India from March 2019 to August 2020.

Inclusion criteria: All babies 0-28 days of life admitted in NICU/ SNCU with either suspected or proven neonatal sepsis by blood and/or cerebrospinal fluid (CSF) culture.

Exclusion criteria:

1. Cases wherereporting wasincomplete.
2. Cases who left against medical advice.

3. Cases where parents did not given consent for study.

Criteria for diagnosis of neonatal sepsis were from theNational Neonatology Forum (NNF) Clinical Practice Guidelines.A panel of sepsis screen tests were performed from the blood samplesof all the neonates as per NNF guidelines of neonatal septicaemia.

Radiological tests and CSF study were done wherever indicated.

Data collection: Blood samples of newborn from 0-28 days of life having risk factor for sepsis or clinical sepsis admitted in IMS & SUM HOSPITAL NICU/SNCU were included.

Definitions

*Neonatal sepsis*wasdefined as the presence of generalized systemic features of sepsis associated with pure growth of organisms from one or more sites.

Probable sepsis: Clinical and laboratory findings consistent with sepsis without a positive culture.

Sample collection: Samples were collected aseptically.For blood culture, venepuncture site was cleansed with alcohol-providone iodine –alcohol after wearing sterile gloves. Cleansing was done from inside to outside in concentric circle and allowed to dry for 1 minute before sampling; 1-2 ml of blood was collected before starting empirical antibiotics and inoculated into a broth containing 10 ml of brain heart infusion agar and incubated aerobically at37^0c for 24hours by bact alert method. Subcultures were done on blood agar and Macconkey's agar and incubated overnight at 37^0c .The growth was identified by colony characteristics, gram's stain and standard biochemical tests.

*Antibiotic susceptibiloty testing:*This includes detection of methicillin resistance staphylococcus aureus (MRSA), D test (inducible clindamycin resistance) and screening tests for extended spectrum beta lactamase (ESBL),metalobetalactamase (MBL) among gram negative bacilli were carried out as per CLSI guidelines.For urine culture sample were collected by suprapubic aspiration or through catheterization. CSF samples were collected through lumbarpuncture.

*Ethical aspects:*This study was approved by the Ethical committee of IMS& SUM Hospital Medical College, Bhubaneswar, India.

*Statistical methods:*Descriptive statistical analysis were carried out in the present study. Results on continuous measurements are presented on Mean± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. 95% Confidence Interval has been computed to find the significant features. Confidence Interval with lower limit more than 50% is associated with statistical significance. Diagnostic statistics viz. Sensitivity, Specificity, PPV, NPV and Accuracy have been computed to find the correlation of blood investigations with culture report.

Results and analysis

A total of 200 neonates were included in our study with clinical suspicion of septicaemia. Of them,127 (63.5%) had EOS and 73 (36.5 %) hadLOS. Gender-wise, 125 (62.5%) were male and 75(37.5%) were female**.** In our study, 112 (56%) were delivered at the SUM hospital

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(inborn) and 88 (44%) were delivered outside (outborn).The mode of deliverywasvaginalin 104 (52%) cases and lower segment caesarean section (LSCS)in 96 (48%) cases. Figure 1 shows the distribution according to gestational age.

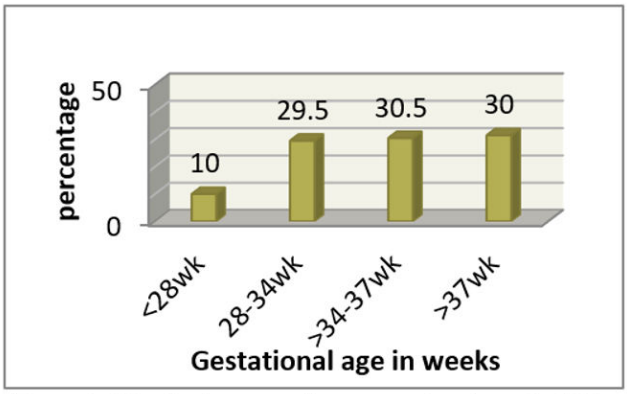

Figure 1: ***Distribution according to gestational age (n=200)***

Figure 2 shows the distribution according to birth weight.

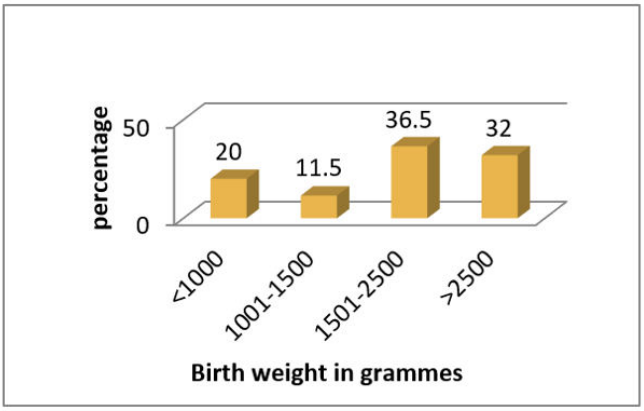

Figure 2: ***Distribution according to bith weight (n=200)***

Table 1 shows the predisposing factors of neonatal sepsis.

Table 1: ***Predisposing factors for neonatal sepsis (n=200)***

Predisposing factor	n (%)
Low birth-weight	136 (68.0)
Prematurity	137 (68.5)
Prolonged rupture of membranes >18 hrs.	60 (30.0)
Maternal complications	23(11.5)
Meconium stained liquor	21 (10.5)
Prolonged labour	28 (14.0)
No obvious factor detected	26 (13.0)

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Table 2 shows the clinical profile in neonates with sepsis.

Table 2: ***Clinical profile in neonates with sepsis (n=200)***

Clinical feature	n (%)
Respiratory distress	136 (68.0)
Feeding intolerance	148 (74.0)
Lethargy	98 (49.0)
Convulsions	55 (27.5)
Temperature instability	47 (23.5)
Refusal to feed	92 (46.0)
Hypoglycaemia	29 (14.5)
Hypocalcaemia	03 (01.5)
Bleeding	31 (15.5)
Meningitis	08 (04.0)
Fetal distress	27 (14.5)
Retinopathy of prematurity	10 (05.0)
Apnoea	07 (03.5)
Intraventricular haemorrhage	22 (11.0)
Necrotising enterocolitis	06 (03.0)
Heart disease	08 (04.0)
Pneumonia	07 (03.5)
Surgical abnormality	12 (06.0)
Haematological problem	23 (11.5)
Hypoxic ischaemic encephalopathy	12 (06.0)

The sepsis type and age of onset distribution among the 200 neonates with suspected sepsis are shown in Figure 3.

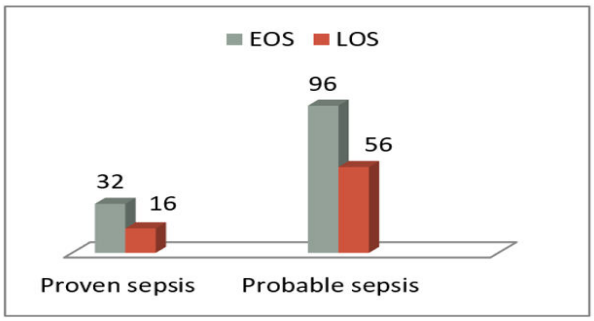

Figure 3: ***Sepsis type and age of onset distribution (n=200)***
EOS: Early onset sepsis; LOS: Late onset sepsis

Table 3 shows sepsis screening.

Table 3: ***Sepsis screening(n=200)***

Blood investigation	n (%)
Absolute neutrophil count	
<1750 /cu mm	53 (26.5)
	147 (73.5)

>1750 / cu mm	
Micro ESR Positive Negative	 52 (26.0) 148 (74.0)
Total leucocyte count < 5000 >5000	 29 (14.5) 171 (85.5)
C-reactive protein Positive Negative	 99 (49.5) 101 (50.5)

Table 4 shows the correlation of sepsis screen with culture findings.

Table 4: ***Correlation of sepsis screeningwith culture findings***

	Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
Absolute neutrophil count (ANC)<1750/cu mm	52.08 %	81.58 %	12.95 %	97.00 %	80.10 %
Total leucocyte count (TLC) <5000/cu mm	41.67 %	94.08 %	27.03 %	96.84 %	91.46 %
Micro erythrocyte sedimentation rate (ESR)	54.17%	82.89 %	14.29 %	97.17 %	81.46 %
C-reactive protein (CRP)	47.92 %	48.68 %	4.68 %	94.67 %	48.65 %
Combinations					
CRP +ANC	93.75 %	90.79 %	34.88 %	99.64 %	90.94 %
CRP+ESR	77.08 %	73.03 %	13.07 %	98.38 %	73.23 %
CRP + TLC	64.58%	44.08%	26.72 %	79.76 %	49.00%

Sensitivity, specificity, PPV, NPV and accuracy of CRP+ANC are 93.75 %, 90.79 %, 34.88%, 99.64%, 90.94 % respectively. This is strongly significant with p<0.001.

Blood culture showed no growth in 152 (76%) of neonates and growth in 48 (24%) of neonates. The growth was bacteria in 93.8% of cases and fungi in 6.2% of cases.

Table 5 shows the different aetiological agents in blood culture positive sepsis.

Table 6 shows the organisms isolated in culture positive cases of EOS and LOS.

Table 5

Different aetiological agents in blood culture positive sepsis

Organism	**n (%)**
Klebsiellapneumoniae (16) *Klebsiellaoxytica* (01)	17 (35.4)

Staphylococcus aureus (2 MRSA)	06 (12.5)
Escherichia coli	04 (08.3)
Enterobacteraerogenes	04 (08.3)
Staphylococcusepidermidis	03 (06.3)
Streptococcus haemolyticus	02 (04.2)
Enterococcus	01 (02.1)
Acinetobacter	02 (04.2)
Pseudomonasaeruginosa	03 (06.3)
Candida	03 (06.3)
Streptococcuspneumoniae	01 (02.1)
Streptococcusviridans	01 (02.1)
Citrobacterfreundi	01 (02.1)
Total	48 (100)

Table 6: ***Organisms isolated in culture positive cases of early onset sepsis (EOS) and late onset sepsis (LOS)***

Organisms isolated	EOS(Number of isolates)	LOS(Number of isolates)
Klebsiella species	9	8
Staphylococcus aureus	4	2
Enterobacteraerogenes	2	2
Escherichia coli	4	0
Staphylococcusepidermidis	3	0
Pseudomonas aeruginosa	3	0
Candida	1	2
Acinetobacter	1	1
Enterococcus faecalis	1	0
Streptococcus haemolyticus	1	1
Streptococcusviridans	1	0
Streptococcuspneumoniae	1	0
Citrobacterfreundi	1	0

In both types of sepsis Klebsiella species is the most common isolate i.e. 9 cases in EOS and in 8 cases in LOS.

Out of 48 culture isolates 31 were gram negative organisms and 14 were gram positive organisms. Table 7 shows the gram positive organisms and Table 8 shows the gram negative organisms.

Table 7: ***Gram positive organisms***

Organism	n (%)
Staphylococcus aureus	06(12.5)
Coagulase negative staphylococcus	06(12.5)

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Enterococcus faecalis	01(02.1)
Streptococcuspneumoniae	01(02.1)
Total	14 (29.2)

Table 8: ***Gram negative organisms***

Organism	n (%)
Klebsiella species	17 (35.4)
Escherichia coli	04(08.3)
Pseudomonas aeruginosa	03(06.3)
Acinetobacter	02(04.2)
Enterobacteraerogenes	04(08.3)
Citrobacterfreundi	01(02.1)
Total	31 (64.6)

Table 9 shows the correlation of gestational age with culture positivity. Preterm neonates constitute 93.8% of the total culture positive cases.

Table 9: Correlation of gestational age with culture positivity

Gestational age	Number of neonates	Culture report	
		Positive n (%)	Negative n (%)
Preterm	138 (69.0)	45 (93.8)	93 (61.2)
Term	62 (31.0)	03 (06.2)	59 (38.8)
Total	200 (100.0)	48 (100.0)	152 (100.0)

Table 10 shows the correlation of birth weight with culture positivity.

Table 10

Correlation of birth weight with culture positivity

Birth weight (g)	n (%)
<1000	12 (25.0)
1001-1500	15 (31.3)
1501-2500	15 (31.3)
>2500	06 (12.5)
Total	48 (100.0)

Out of the 48 culture positive cases 28 (58.3%) were male neonates and 20 (41.6%) were female neonates, 32 (66.6%) were EOS and 16 (33.3%) were LOS, 54% were outborn and 46% were inborn.

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Table 11 shows the sensitivity/resistance pattern of antibiotics according to bacterial growth.

Table 11:*Sensitivity/ resistance pattern of antibiotics according to bacterial growth(n=200)*

Antibiotic	Sensitivity/resistancepattern	
	Sensitivity n (%)	**Resistance n (%)**
Ampicillin	28 (58.3)	17 (35.4)
Amoxycillin	19 (39.5)	26 (54.0)
Amikacin	39 (81.3)	06 (12.5)
Cefotaxime	38 (79.0)	07 (14.5)
Ceftazidime	17 (35.4)	11 (22.9)
Cefuroxime axetil	12 (25.0)	07 (14.5)
Ciprofloxacin	25 (52.0)	11 (22.9)
Cotrimoxazole	14 (29.2)	11 (22.9)
Penicillin	02(04.1)	19 (39.5)
Gentamicin	23 (47.1)	13 (27.0)
Piperacillin/ Tazobactam	36 (75.0)	08 (16.6)
Vancomycin	16 (33.3)	02 (04.1)
Meropenem	34 (70.8)	04(08.3)
Linezolid	14 (29.1)	00
Netilmicin	15 (31.2)	00
Colistin	05 (10.4)	00

The above table showed that amikacinwas the most sensitive drug (81.3%) followed by cefotaxime (79%). Vancomycin resistance was found in 2 (4.1%) cases all gram negative bacteria. Majority of cases were found to be amoxicillin resistant.

Complications of neonatal sepsis are shown in Table 12.

Table 12:*Complications of neonatal sepsis(n=200)*

Complication	n (%)
Hypoglycaemia	29 (14.5)
Hypocalcaemia	03 (01.5)
Shock	55 (27.5)
Bleeding	31 (15.5)
Meningitis	08 (04.0)
Retinopathy of prematurity	10 (05.0)
Apnoea	07 (03.5)
Intraventricular haemorrhage	17 (08.5)
Necrotising enterocolitis	06 (03.0)
Pneumonia	07 (03.5)
Broncho-pulmonary dysplasia	10 (05.0)

Periventricular leucomalacia	05 (02.5)
Neonatal jaundice	98 (49.0)
Hypoxic ischaemic encephalopathy	12 (06.0)

Out of the 200 cases deathsoccurred in 8 cases giving a case fatality rate of 4%.The correlation of mortality with culture positivity is shown in Table 13.

Table 13:*Correlation of mortality with culture positivity*

Blood culture	Mortality n (%)	Survival n (%)	Total n (%)
Positive	06(03)	42 (21)	48 (24)
Negative	02(01)	150 (75)	152 (76)
Total	08 (04)	192 (96)	200 (100)

The correlation of mortality with the type of organism is shown in Table 14.

Table 14

Correlation of mortality with type of organism (n=8)

Organism	n (%)
Methicillin resistant staphylococcus aureus	1 (12.5)
Pseudomonas aeruginosa	2 (25.0)
Klebsiella pneumonia	2 (25.0)
E.coli	1 (12.5)
No organism	2 (25.0)
Total	8 (100.0)

Discussion

Neonatal mortality rate in India is currently 32.3 per thousand live births[12].In this study 200 neonates suspected of neonatal sepsis were investigated. Of them, 127 (63.5%) had EOS (0-3 days) and 73 (36.5%) had LOS (4-28 days).Similarly, Subudhi KT, *et al*[13] found EOS in 57% and LOS in 43% whilstTewabeT, *et al*[14] observed 72.9% EOS and 27.1% LOS.Culture positive cases were more in EOS(68.8%) than LOS (31.3%). Most studies reported higher culture positive rates in EOS except Ahmad AS, *et al*[15]who reported low culture positive rates in EOS (26%).In this study there were 125 (62.5%) males and 75 (37.5%) females. Gupta P, *et al*[16]found64.7% male neonates. Sharma A, *et al*[17] reported a 74%male predominance.

In the present study 52% were delivered vaginally and 48%by LSCS. In a study by Subudhi KT, *et al*[13] 62.8% were delivered vaginallyand 37.2% by LSCS. In a study by TewabeT, *et al*[14] 62.9% were delivered vaginallyand 27.1% by LSCS.In the present study 68.5% were preterm and 31.5% were term. Subudhi KT, *et al*[13] observed 39.5% preterm and 60.6% term

neonates which is not congruent to our study.In our study 68% were LBW and 32% had birth weights above 2500g. KhatuaSP, *et al*[18]reported a higher incidence of septicaemia in LBW infants. Higher incidence and mortality of LBW infants were also observed by other workers[19-21]. LBW infants, both preterm and term, have low IgGandplacental transport of IgG from maternal to fetal circulation increases with maturity[22].In our study, prematurity was the most common predisposing factor, being found in 68.5% neonates.

In our study,the major presenting features of neonates with suspected sepsis were feeding intolerance (74%), respiratory distress (68%) and hypoglycemia(14.5%).JaswalRS, *et al*[23] observed that 66% of neonates with sepsis presented with refusal of feeds, followed by lethargy and jaundice.Sharma A, *et al*[17]reported the common symptoms to be refusal of feeds (76%),lethargy (60%) and temperature changes (52%) which is similar to our study. SinhaN, *et al*[24] observed that in gram negative infection, diarrhoea, dehydration, abdominal distension, refusal to take feeds, shock/circulatory failure were important presenting features. KhatuaSP, *et al*[18]observed that refusal of feeds, lethargy, diarrhoea, hypothermia, abdominal distension, jaundice and vomiting were the common presenting features**.**

This study reveals 24% culture positive sepsis cases. The study byMathurM, *et al*[25] obtained a similar culture positive rate of 24.9%**.**However, a higher culture positivity rate of 42% was reported by Kumhar GD, *et al*[26].Sharma A, *et al*[17]reported aculture positivity rate of 20%.KhatuaSP, *et al*[18]reported a culture positivity rate of 59.8%. Negative culture does not exclude sepsis Possibility of infection with anaerobes cannot be ruled out. Chow AW,*et al*[27] reported that 26% of all neonatal septicaemia was caused by anaerobes.Inthis study, of 48 culture positive isolates, 45 (93.8%) were bacteria and 3 (6.2%)were candida(fungus).Subudhi KT, *et al*[13]found 2.7% fungal isolates. In our study, among bacteria 13 (27.1%) were gram positive and 31 (64.6%) were gram negative organisms.Ahmad AS, *et al*[15]observed 57.8% gram positive and 42.2% gram negative isolates.Various studies have shown that in last 2 decades, the isolation of Gram positive organisms has increased significantly[28]**.**

Out of 48 culture proven sepsis common isolates were*Klebsiellaspecies*(35.4%), *Staphylococcus aureus*(12.5%) and *Escherichia coli*(8.3%). Klebsiella was also the predominant pathogen in studies byKumhar GD, *et al*[26](33.8%),MathurM, *et al*[25](38.5%) andKaisthaN, *et al*[28](28.3%). However, studies by Ahmad AS, *et al*[15] and AgnihotriN, *et al*[29]found the predominant pathogen to be *Escherichia coli*(30%) and*Staphylococcus aureus*(35.3%) respectively**.**KarthikeyanG, *et al*[30] reported that *Staphylococcus aureus* was the predominant pathogen followed by *Klebsiella pneumonia*.MohantyR, *et al*[31] reported that *Staphylococcus aureus*was a major cause of neonatal septicaemia.Banerjee M, *et al*[32] reported an outbreak of neonatal septicaemia with multidrug resistant *Klebsiella pneumonia*.Klebsiellaspecieswere isolated both in EOS and LOS (9 in EOS and 8 in LOS). Candida was associated with both EOS and LOS (1 in EOS and 2 in LOS).

Present study showed amikacinto be the most sensitive drug (81.3%) followed by cefotaxime (79%). Vancomycin resistance was found in 2 (4.1%) cases bothin gram negative bacteria. Majority of cases were found to be amoxicillin resistant. MathurM, *et al*[25]reportedcefotaxime

to have maximum sensitivity. According to Banerjee M, *et al*[32] the isolates of *Klebsiellapneumoniae* were resistant to all drugs except third generation cephalosporins.

Sensitivity, specificity, PPV, NPV and accuracy of ANC were 52.1%, 81.6%, 12.95%, 97% and 80.1% respectively. Sensitivity, specificity, PPV, NPV and accuracy of CRP were 47.9%, 48.7%,4.7%, 94.7% and 48.7% respectively. Combined sensitivity, specificity, PPV, NPV and accuracy of CRP+ANC were 93.8%, 90.8%, 34.9%, 99.6%, 90.9% respectively. Most sensitive test among all was CRP plus ANC in our study. CRP hadlow sensitivity and specificity in present study. From our result it can be said that sepsis screen has low sensitivity but more specificity, so these tests are useful for excluding sepsis rather diagnosing it.According to Sharma A, *et al*[17]the sensitivity and specificity of CRP was 80% and 93.8% respectively. AnuradhaD, *et al*[33] reported a sensitivity of 100%, specificity of 87.3%, PPV of 88.3% and NPV of 100% which is different to our present study.The early evaluations of CRP provide indications of the response to treatment. A good response to antibiotics is indicated by a rapid return to normal of CRP, whereas persistent elevations of serum CRP suggest inadequate treatment[34].Out of the 8 deaths 6 had positive culture and 2 hadnegative culture i.e 75% deathsoccurredin culture positive sepsis and 25% deathsin culture negative neonatal sepsis. Mortality was 12.5% in culture positive cases and 1.3% in culture negative cases. Out of the 6 deaths in culture positive neonatal sepsis,5 (83%)were due to gram negative isolates and 1(17%) due to gram positive organisms.Mortality in out-born neonateswas more than in in-born neonates. Among 8 deaths 5 were out-born in our study.SinhaN, *et al*[35]similarly reported that the fatality rate was high in out-born neonates and with infection of gram negative bacilli about 83% which is similarto our study.

Conclusions

Of the 200 neonates with suspected neonal sepsis, 63.5% had EOS. Prematurity was the commonest predisposing factor(68.5%) and feeding intolerance was the commonest presentation (74%).Klebsiella (35.4%) was the most common isolate.

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