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Burden, and Risk Factor Analysis of Neonatal Sepsis – are We the author of our Own Misfortune

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Abstract

Background: Neonatal infections still forms a significant burden to the health system of low and middle income countries (LMIC), as it increases hospital stay, number of interventions and poor Neuro-developmental outcome.The burden of neonatal sepsis in our country from a hospital based study is 30%. We try study the burden and contribution of various risk factors for neonatal sepsis in a tertiary care referral centre in south India. *Methodology:* We collected retrospective perinatal data of all neonates admitted in our unit from 01 Jul 2016 – 30 Jun 2017 who had a discharge or death diagnosis of sepsis. We classified our data based on predetermined case definitions for our study. *Statistics Analysis:* Descriptive and inferential statistical analysis has been 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 (%). Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale. *Results and Conclusion:* Our sepsis rates are 41.6 per 1000 live births.Our study had predominantly EONS of 30.8 per 1000 live births. Male Gender, Low Birth Weight, Preterm, babies born to mothers with risk factors are important risk factors for sepsis and related mortality. 38.3% babies from our study cohort were culture positive, contributing 48.5% of sepsis related mortality. Klebsiella species predominates both EONS & LONS. Ultra rapid horizontal spread might be the main cause of neonatal sepsis.Prevention is the key to combat Neonatal Sepsis.

Keywords: Neonatal Sepsis; Early Onset Neonatal Sepsis; Klebsiella Sepsis; Culture Positive.

Introduction

The global burden of neonatal infection as per WHO global health survey data 2013 states 15% of total neonatal deaths is due to neonatal sepsis. Millennium development goals (MDG), sustainable developmental goals (SDG) and every new born action plan (ENAP) are few of targets to reduce <12 neonatal deaths per 1000 live births by 2030 and <10 by 2035. Neonatal infections still forms a significant burden to the health system of low and middle income countries (LMIC), as it increases hospital stay, number of interventions and poor Neuro-developmental outcome. India is a major contributor to global burden of neonatal mortality (25%). Though Neonatal mortality rate (NMR) has declined from 52/1000 live births in 1999 to 28/1000 in 2013. The improvements come with caveat of regional difference and less average annual reduction rate in early neonatal deaths. Neonatal sepsis contributes to 21% of total NMR and its second only to prematurity related complications (43%).The burden of neonatal sepsis in our country ranges from 3 – 30%. Hospital based studies suggest a incidence of 30% and community based studies reporting 2.7% - 17% [1].

We present data on our unit burden of neonatal sepsis.

Methodology & Statistical Analysis

We collected retrospective data of all neonates admitted in our unit from 01 Jul 2016 – 30 Jun 2017 and had a discharge or death diagnosis of sepsis. We collected data from our unit, hospital records (Perinatal data) and Microbiology lab record for relevant reports of corresponding babies. We classified our data based on predetermined case definitions for our study [Table 1].

Descriptive and inferential statistical analysis has been 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 of significance. The following assumptions on data is made, Assumptions: 1.Dependent variables should be normally distributed, 2. Samples drawn from the population should be random, Cases of the samples should be independent

Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis. Fisher Exact test used when cell samples are very small.

The Statistical software namely SPSS 18.0, and R environment ver.3.2.2 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

Results and Discussion

15092 live babies were born during the study period out of which 5006 (33.1%) were admitted in NICU. 628 (12.5%) babies of those admitted were diagnosed to have sepsis at death or discharge. Neonatal sepsis forms a substantiate burden to the health system, global incidence of neonatal sepsis ranges from 7.1 – 38 per 1000 live births from Asian countries and 6-9 per 1000 live births from USA and Australia [2]. Our sepsis rates are 41.6 per 1000 live births, which is above the average reported incidence globally and hospital based data in India. The classification of neonatal sepsis based on time of onset was made to guide presumptive antibiotics therapy, as it implies a probable mode of transmission and hence group of organisms. Neonatal sepsis is classified by NICHD & International consensus statement on paediatric sepsis into early onset neonatal sepsis (EONS), if onset is within first 72 hours. The Centres for Disease Control and Prevention (CDC) defines early onset group B streptococcus (GBS) disease as blood or cerebral spinal fluid culture-proven infection occurring in the first 7 postnatal days. We attempt to classify a separate sub group of 3-7 days as early late onset of neonatal sepsis (ELONS) and late onset neonatal sepsis (LONS) occurring after 7 days. The incidence of EONS in western literature states 1.5 – 3.5 per 1000 live births, and our study had predominantly EONS of 30.8 per 1000 live births, with higher incidence between 3-7 days (ELONS) 19.1 per 1000 live births. The incidence of LONS in our study is 10.8 per 1000 live births, against the reported incidence of 6 per 1000 live births in developed countries [2].[Graph 1].

Gender (Male Vs Female)

Male gender is known risk factor for poor neonatal outcome. There is increased risk of neonatal sepsis for males (odds ratio (OR) = 1.75, p = 0.012). Gender differences in neonatal infections have been attributed to neuro-endocrinal, X- linked genes and its effects on the innate immune system. Animal studies have shown increased production of IL-2 and TNF- by the spleen cells of males and up-regulation of the Th1-type immune response in males compared to females [3]. Our study population had 333 (53%) male babies and 295 (47%) female babies with M:F ratio of 1.12:1. Male gender has a higher risk of sepsis and sepsis related mortality [Table 2,3].

Mode of Delivery (Vaginal Vs Cesarean)

Mode of delivery is one of the determinants of neonatal septicaemia. Indian study analysed 399 deliveries and found babies delivered by vaginal delivery have 2.29 [CI (1.22,4.3)] times more risk of neonatal sepsis than babies born through cesarean delivery. Obstetric practices that may promote ascending infection with vaginal flora, and/or disruption of amniotic membranes – increased frequency of intrapartum vaginal exams, invasive fetal monitoring, "membrane-stripping" to promote onset of labor, pharmacologic cervical ripening agents - have been variably associated with increased risk of EOS from observational studies [4]. 392 (62.5%) of our study cohort is delivered by cesarean section. In contrast to available literature, in our study vaginal delivery was not associated with increased risk of sepsis, this could be because of high referral cases after multiple handling, and Cesarean predominant study cohort [Table 2,3].

Birth Weight

Low birth weight babies suffer higher rates of morbidities and mortality. Low birth weight is an

important predictor of sepsis The incidence of EOS in VLBW babies ranges from 9.6 – 17per 1000 live births. A large multicentric study reported, VLBW infants are 1.45 times more prone for neonatal sepsis related mortality compared to normal weight babies [5]. Our study had 474 (74.3%) babies with low birth weight. [Table 2,3].

Gestation (Term Vs Preterm)

Gestational is one of the strongest predictor of neonatal sepsis, this is quantified to 10 – 11 fold increase in sepsis when compared to term babies, even a modest decrease in gestational age makes them susceptible for infection, like the risk of baby born at 32-34 weeks period of gestation is 3-5 times higher than babies born after 37 weeks of gestation. Our study cohort is preterm predominant, with 449 (71.5%) were born preterm & 179 (28.5%) babies born at term. The difference is attributed to immature innate immune system and denial of passive transfer of antibodies that occur in late gestation. Our study preterm neonates had higher odds developing and mortality sepsis [Table 2,3].

Table 1: Case Definitions & Unit Policy

S. No.	Terminology	Classification	Study Definition	Remarks
		Early onset Neonatal sepsis (EONS)	Clinical and/or laboratory and/or culture proven sepsis with onset less than 3 days	
		Early Late onset Neonatal sepsis (ELONS)	Clinical and/or laboratory and/or culture proven sepsis with onset between 4th – 7th days.	
		Late Late onset Neonatal sepsis (LONS)	Clinical and/or laboratory and/or culture proven sepsis with onset more than > 7days	
1	Sepsis	Culture positive sepsis	Blood culture growing an organism with clinical signs (Tachycardia or change in basal heart rate, requirement of ionotropic support not explained by other causes, sclerema, altered sensorium) and / or biochemical evidence of sepsis. [Abnormal ANC (gestational age specific nomogram), 2 Positive CRP after 6 hours of life or change from negative to positive CRP, Abnormal platelet count – any 2 of the above).	
		Culture negative sepsis	Blood culture not growing an organism with clinical signs (Tachycardia or change in basal heart rate, requirement of ionotropic support not explained by other causes, sclerema, altered sensorium) and / or biochemical evidence of sepsis. [Abnormal ANC (gestational age specific nomogram), 2 Positive CRP after 6 hours of life or change from negative to positive CRP, Abnormal platelet count – any 2 of the above).	
2	Maternal genital colonization	HVS Positive	Growth of pathogenic organism in High Vaginal swab	
		Unit Policy	HVS taken for (i) Mothers with prelabour rupture of membranes (ii) Mothers having documented >3 vaginal examinations (iii) Clinical evidence of chorioamnionitis	
3	CSF Analysis		(i) All LONS babies (ii) Culture Positive babies (iii) EONS with CNS Symptoms	
4	Urine Culture		(i) Neonatal chole stasis (ii) EUGR	

Table 2: Odds ratio for various risk factors for sepsis

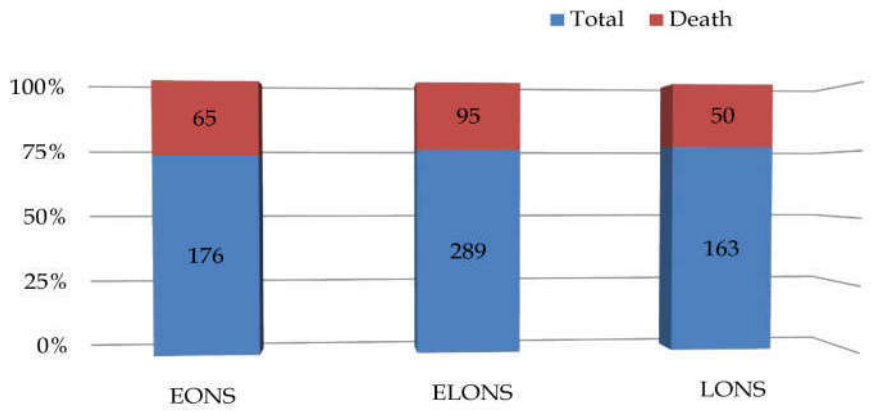
S. No	Variable (Risk for sepsis)	Odds ratio	95%CI	p value
1	Male sex	1.07	0.9118 - 1.2559	0.406
2	Vaginal delivery	0.754	0.6400 - 0.8900	0.0008
3	Preterm	9.18	7.6852 - 10.9659	<0.0001
4	Mothers with risk factors	2.0987	1.227 - 3.5889	0.0068
5	Low birth weight	10.294	8.548 – 12.397	<0.0001

Table 3: Odds ratio for risk of mortality for various risk factors

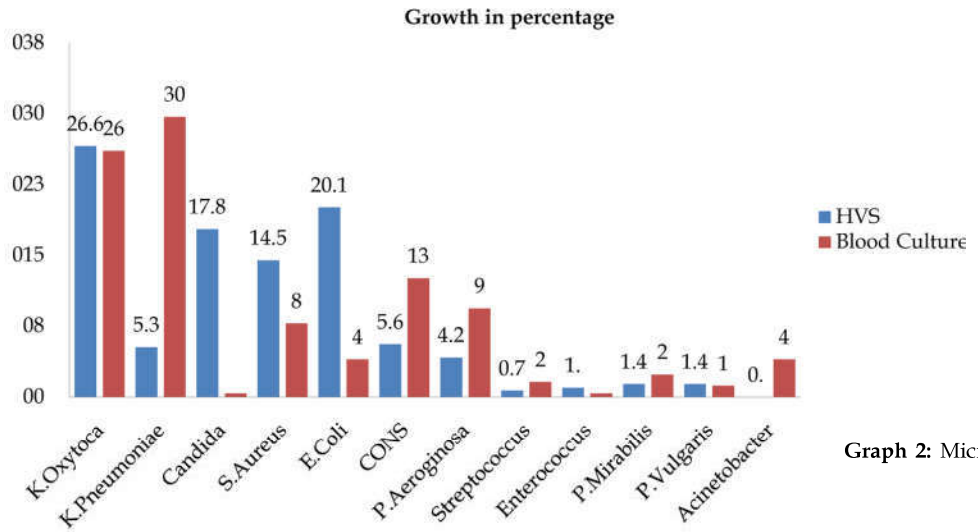
S. No	Risk of Mortality	Odds ratio	95%CI	p value
1	Culture positive sepsis	3.12	2.2166 - 4.4132	<0.0001
2	Male sex	1.05	0.7999 - 1.3785	0.725
3	Vaginal delivery	3.127	2.2166 - 4.4132	<0.0001
4	Preterm	9.16	6.7189 - 12.3973	<0.0001
5	Low birth weight	10.76	7.766 – 14.919	<0.0001

Table 4: Attack rate and Case fatality rates for organism in blood culture

S. No.	Organism	Attack rate (%)	Case fatality rate (%)
1	K.Pneumoniae	1.4	45.8
2	K.Oxytoca	1.2	62.5
3	P.aeruginosa	0.4	50
4	E.coli	0.1	60
5	Acinetobacter	0.1	60
6	CONS	0.6	38.7



Graph 1: Sepsis and mortality distribution



Graph 2: Microbiological Profile

Maternal Genital colonization

There is substantive evidence that maternal colonization increases the risk of neonatal infection, a recent meta-analysis concluded an odds of 13.7 (95% CI 4.2–45.1) for neonatal sepsis and odds off 11.0 (95% CI 2.3–54.0) for EONS. This increased to 37.0 (95% CI 9.7–140.9), in mothers not used antibiotic prophylaxis. This meta-analysis included studies for GBS colonization. The risk of maternal colonization of GBS for lab confirmed infection is 9.4 (95% CI 3.1–28.5; I2 = 76.3%, 95% CI 58%–87%), A sensitivity analysis excluding studies with high risk of bias increased the ORs to 13.7 (95% CI 4.2–45.1). Excluding studies without a specified early-onset period to measure neonatal infection increased the odds to 11.0 (95% CI 2.3–54.0) Maternal colonization and risk for clinical infection is 3 (1.42 – 6.32.I^2-64.1% CI (6%-86%) p = <0.025. Maternal colonization as risk factor, for any form of neonatal infection (Lab or clinical) is 3.25 (0.26 – 23.12). I^2 = 82.2% CI (45% - 94%), p =0.004) [6]. Our maternal genital colonization rates are 261 (41.5%). The flora of maternal genital tract is differs from data available from developed and LMIC. Various studies have quoted GBS, S.Aureus E.Coli as the predominant maternal genital tract flora and implicated in EONS. One Indian study showed E.Coli as the predominant organism of high vaginal swab done randomly in pregnant women attending antenatal OPD and the same was again the commonest organism in pPROM mothers. GBS constituted only 5% of the isolates.A study conducted in southern India tertiary care centre looking at vaginal flora, neonatal surface colonisation and neonatal infection concluded that, there was a significant correlation between surface colonisation of babies and maternal genital bacteria, so also was baby's surface culture and blood culture. However, correlation between maternal genital bacteria and baby's blood culture was not significant [7].

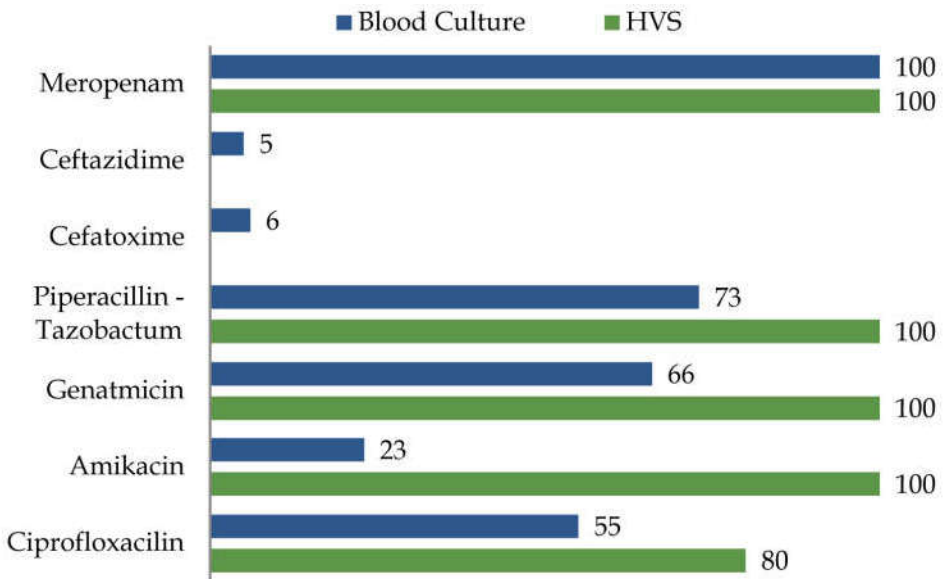
In our study K. Oxytoca (26.6%) is the predominant organism, followed by E.Coli (20.1%) & Candida (17.8%). [Graph 2]. We have similar flora profile reported from Germany, with predominance of E.Coli and Klebsiella species. Maternal genital colonization with Candida species ranges from 14.1% – 19.6%, in asymptomatic patients to 14 – 38% in symptomatic patients. Vulvo Vaginal Candidial colonization has been reported from India with prevalence as high as 35%, predominantly Candida albicans [8]. In our study we had 18% Candidial growth predominantly Candida non albicans (90%). In our study odds of a neonate to be diagnosed to have sepsis is higher if born to mother with genital colonisation [Table 2]. When we did correlation study phi co efficient was 0.132, for babies to be diagnosed with sepsis born to mothers with genital colonisation. The correlation between culture positive HVS & blood culture positivity was not significant.

Neonatal Infection

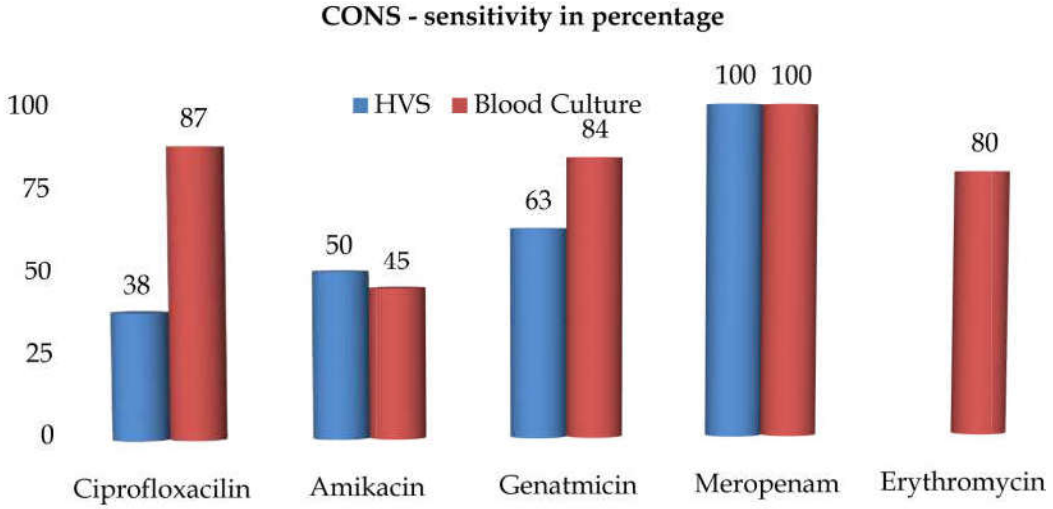
In our unit 628 of admitted babies (12.5%) were diagnosed to have sepsis. 176 (28%) diagnosed to have EONS, 289 (46%) were diagnosed to have ELONS, 163 (26%) diagnosed to have LONS. 241 (38.3%) babies from our study cohort were culture positive.A study from china reported 32% culture positivity with predominant isolate of Staphylococcus aureus, and Acinetobacter baumanni, 21.9%.

Microbiological profile of our study cohort had a Gram negative predominance, Klebsiella Pneumoniae (29.7%), Klebsiella Oxytoca (26.1%) and Pseudomonos aeruginosa (9.4%) being the three frequent gram negative organisms. CONS (12.6%), Staphylococcus Aureus (7.8%), & Streptococcus (1.6%) are the 3 commonest gram positive isolates [Graph 2]. Neonatal surveillance in developed countries generally identifies GBS and E coli as the dominant EOS pathogens and CONS the dominant LOS pathogen followed by GBS and S.aureus. Distribution of organisms in our study - EONS – K. Oxytoca (13%), K. Pneumoniae (8.5%), ELONS – K. Oxytoca (10.3%), K. Pneumoniae (13.8%), to gether if we consider 7 days as cut off for early onset sepsis Klebsiella species predominates K. Oxytoca (11.4%), K. Pneumoniae (11.8%) . LONS is predominated by CONS (12.8%) followed by Klebsiella species 17.7% (K. Pneumoinae (11%) & K. Oxytoca (6.7%). Acinetobacter baumanni which is the commonest isolate reported from largest reported data on neonatal sepsis from India (DeNIS) [8], constitutes only 4% of our isolates. Our study cohort had Klebsiella species (K.Pneumoniae (29.7%) & K.Oxytoca (26.1%)) as the predominant organism, which is similar to NNPD data. In our study cohort K.Pneumoniae has the highest attack rate 1.2%,[Table 4] the case fatality rate of K. Oxytoca is the highest with 62.5% [Table 4].

This species is a recognised nosocomial pathogen, cultured as the predominant organism in both High vaginal swab and neonatal infection is not reported to the best of our knowledge and the predominance of sepsis and mortality between 3-7 days of life, reinforces the fact and proposed theory of ultra rapid horizontal transmission of these pathogenic bacteria due to poor perinatal hygiene and practices. In our study cohort when early onset sepsis definition is extended to 7 days it forms 74% of the total neonatal sepsis.



Graph 3: Antibiotic sensitivity of Klebsiella Pneumoniae



Graph 4: Antibiotic sensitivity of CONS

Though the isolates of our study cohort is similar to the organisms in high vaginal swabs, sensitivity pattern differs considerably, this can be explained by the vaginal examinations done at referral centres at community level could be grown as high vaginal swab cultures, which is done at arrival, the poor perinatal practices might be implicated in introduction of hospital acquired resistant nosocomial species. [Graph 3,4].

Cerebrospinal fluid & Urine Culture

331 CSF examinations were done during study period out which 18 was culture positive, Urine culture was done for 26 babies out of which 2 babies were cultured positive. Low culture positivity may be due to sampling post antibiotic use.

Antibiotics

The greatest reduction in EONS is achieved by intrapartum intravenous antibiotic prophylaxis given >4hours prior to delivery, and Penicillin is the preferred agent. This strategy along with universal screening had shown 90% decrease in incidence of EONS. This reduction comes at a cost of false negative blood culture, emergence of E.Coli as predominant EONS organism and drug resistance. The western literature had shown still the benefits from the use of intrapartum antibiotic chemoprophylaxis offset the

risks of resistant bacterial infections [9]. Our institute follows universal antibiotic policy.

Treatment of neonate at risk of sepsis should be based on targeted approach, using the risk algorithms as recommended by CDC and AAP. Both recommendations aim at curtailing the use and reduce the duration of empiric antibiotics. The empiric and prolonged antibiotic usage in preterm neonates leads to increased incidence LONS, NEC and increase in mortality. This cannot be extrapolated to term babies. A study done in Sweeden found babies exposed to antibiotics in first 2 weeks of life have increased incidence of recurrent wheezing episodes at 12 months of age persisting to 4.5 years of age. Though the biological plausibility of this theory is questionable; there is still emerging evidence supporting change of micro biome in gut of babies exposed to antibiotics early in life [10]. With the evidence of negative effects of antibiotic usage both CDC and COFN had curtailed the usage of antibiotics in asymptomatic infants. The recent report of COFN still relies on clinical evidence of presence and persistence of symptoms as indication and continuation of treatment.

Mortality

Global burden of sepsis related mortality has been estimated by WHO global health observatory to be 0.421 million per annum, and the trend in India is, 20.8% of neonatal death occur due to neonatal sepsis. According to DeNIS study about one fifth of babies with neonatal sepsis die and this rise to 50% of the culture positive babies. In our study 211 (33.5%) of neonatal sepsis died which is higher than reported in literature, our mortality rate for culture positive sepsis was 119 (48.5%) which is comparable to that of DeNIS study. In our study odds of a neonate dying of culture positive sepsis is 3.1277 CI (2.2166 to 4.4132) $p<0.0001$.The odds of mortality due to sepsis with various risk factors are presented in [Table 3].

Conclusion

Neonatal sepsis continues to be one of the common and significant burden to our health care system and a major hindrance in achieving the set global health targets of various programmes. Prevention and targeted approach is the approved strategy combat EONS. These proven strategies in developed strategies can it be extrapolated to our settings, because our genital colonisation flora is predominantly gram negative organism unlike developed countries, will still penicillin group hold good for us.....for intrapartum antibiotic prophylaxis? Secondly, already we are in a epidemic of multi-drug resistant gram negative bugs as a cause of EONS as shown by DeNIS study, and our studies concurrence with fact, we should have further studies in our settings, forappropriate intrapartum antibiotic policy.....?.

The laboratory tests, which includes biomarkers with good diagnostic accuracy should be used for close monitoring and prolongation of empirical antibiotics, when the clinical evaluation is equivocal or complete resolution is delayed.

Prevention – improved Perinatal care, selective use of appropriate intrapartum antibiotic prophylaxis, and restricted use of empirical antibiotics in symptomatic, asymptomatic at risk preterm neonates. Early stoppage of empirical antibiotics based on clinical and laboratory evidence.

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