

CLINICAL AND BACTERIOLOGICAL PROFILE OF EARLY ONSET NEONATAL SEPSIS ADMITTED IN NICU OF TERTIARY HOSPITAL IN BIRATNAGAR

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ABSTRACT

Introduction

Neonatal sepsis is one of the major causes of neonatal morbidity and mortality especially in developing countries. The clinical signs and symptoms of neonatal sepsis are non specific and blood culture report is considered gold standard for confirmation of neonatal sepsis. Organisms and their sensitivity pattern vary from place to place. The confirmation of diagnosis and management of neonatal sepsis is challenging and time consuming.

Objective

The aim of this study was to find incidence of blood culture proven sepsis in suspected early onset neonatal sepsis, find out sensitivity pattern of isolated organism and to find association of risk factors and clinical signs and symptoms with blood culture proven sepsis.

Methodology

Prospective study was conducted in Nobel Medical College, Biratnagar from November 2016 to November 2017. Sample size was calculated to be 300 and blood culture was sent of each neonates admitted with suspected early onset neonatal sepsis before giving neonates with first dose of antibiotics and report of 72 hours was taken into consideration.

Results

Out of 300 cases of suspected early onset neonatal sepsis 70.3% presented with lethargy, followed by other symptoms like poor feeding, respiratory distress, fever, hypothermia, feeding intolerance, abnormal body movement and abdominal distension. Low birth weight neonates, preterm neonates, prolonged duration of per vaginal leaking and low platelets count were significantly associated with blood culture proven sepsis in this study. Incidence of blood culture positive sepsis in suspected early onset neonatal sepsis was 27%. *Coagulase negative Staphylococcus aureus* (21%) was predominant organism isolated followed by *Klebsiella Pneumonia*, *Pseudomonas*, *Escherichia coli*. All of the isolated *Klebsiella* and *Pseudomonas* and 86% of *Escherichia coli* were found to be resistant to ampicillin. All isolated *Coagulase negative Staphylococcus aureus* were sensitive to vancomycin.

Conclusion

Coagulase negative *Staphylococcus aureus* was predominant organism detected but majority of organisms were gram negative organisms. High resistance to ampicillin was found and cefotaxime was also less sensitive to isolated organism. Vancomycin was found to be sensitive to all isolated *Staphylococcus aureus* and coagulase negative *Staphylococcus aureus*. Amikacin was highly sensitive among causative organisms isolated.

KEY WORDS

Antibiotics sensitivity, blood culture, early onset neonatal sepsis



INTRODUCTION

Neonatal sepsis (NS) is a serious bacterial infection in bloodstream in neonate at the age equal to or less than 28 days of life which is manifested by systemic signs and symptom of infection.¹ Neonatal infection account for a significant cause of death in first week of life.² Case fatality rate associated with possible bacterial infection in neonates was 9.8%. It is estimated that 3.5 million neonates are of possible bacterial infection in South Asia.³

The clinical presentation of neonatal sepsis are non-specific and includes: fever, respiratory distress, lethargy, impaired or refusal of feeding, jaundice, absent Moro reflex, hypothermia, convulsions, bleeding disorder and bulging fontanel.⁴

Neonatal sepsis is of two types. Early onset neonatal sepsis- when features of sepsis appear within first 72 hours and late onset sepsis- when features of sepsis appear beyond 72 hours.⁵ Early onset neonatal sepsis is acquired from maternal genital tract microorganisms and late onset sepsis is hospital acquired.⁶

Globally neonatal sepsis is one of the most important causes of morbidity and mortality among neonates during the neonatal period (0-28 day). Out of 5.9 million child deaths in 2015, almost 1 million occur in the first day of life and close to 2 million occurs in the first week of life.³ The main causes of neonatal deaths were preterm birth complications (35%), intrapartum related complications (24 %), and sepsis (15 %) globally.⁷ According to 2011 UNICEF report , neonatal deaths accounted for 52% of all under five child mortality in South Asia, 53% in Latin America and Caribbean and 34% in sub-Saharan Africa.⁸ According to global health observatory data report of 2015 approximately 4.5 million(75%) of all under five mortality occurred within first year of life which was highest in Africa and accounted for 55/1000 live birth but was greater than five times higher than that of Europe (10/1000) live birth.⁹ In developing countries, neonatal mortality rate per 1000 live birth from all causes was about 34 of which most deaths occurred in the first week of life, mostly on first day of life.¹⁰

As per Nepal demographic health survey (NDHS), 2016 neonatal mortality rate in Nepal was 21 deaths per 1000 live birth.¹¹

Antibiotics are the mainstay of treatment of sepsis. Antibiotics resistance has become challenge to the management of both early onset and late onset neonatal sepsis.¹² 77% of isolated organism in neonatal sepsis were multidrug resistance, 60% of gram positive bacteria and 83.4% of gram negative bacteria) and nearly 80% of mortality was caused by multidrug-resistant organisms.¹³ Prolonged antibiotics therapy is associated with antimicrobial resistance and increased mortality in preterm infants.¹⁴

There is huge burden of neonatal sepsis and is one of the important causes of neonatal death. Antibiotics resistance

has become alarming problem as per World Health Organization. To prevent antibiotics resistance as well as treat neonatal sepsis it is important to know common organisms and susceptibility pattern of antibiotics. Current study aim is to find pathogens and their antibiotics resistance pattern so that we can choose empirical antibiotics without any delay.

METHODOLOGY

This is a prospective cross-sectional hospital based study conducted in Nobel Medical college Teaching Hospital and Research Centre located in Khanchanbari, Biratnagar, Nepal from November 2016 to November 2017. After ethical clearance from the institutional review committee, data was collected from 300 newborns admitted to the department of pediatrics by means of interview with the parents and obstetricians, clinical examination and laboratory report tracing and entered into a Performa. The sample size was calculated based on a similar research conducted in Nepal Medical College Teaching Hospital, Kathmandu, Nepal.¹⁵ Taking into account the prevalence of early onset sepsis in previous study, sample size was determined and first 300 neonates fulfilling the inclusion criteria were included in the study.¹⁵ Neonates with suspected early onset sepsis born in Nobel Medical College, Biratnagar and delivered outside arriving before 72 hours of life and who had not received prior antibiotics were included in the study and neonates with gross congenital anomalies, birth weight less than 1000 grams and those who had already received antibiotics before drawing blood samples were excluded from the study.

Diagnosis of early onset neonatal sepsis was made based on the presence of symptoms, septic screening and presence of risk factors. Clinical sepsis was considered if one or more of the following symptoms were present-respiratory distress, abdominal distension, and lethargy, feeding intolerance, convulsions and temperature instability.¹⁶ Septic screening included total leukocyte count (TLC), absolute neutrophil count (ANC), C-reactive protein and platelets count.¹⁷ Risk factors considered for early onset neonatal sepsis were low birth weight (<2500 grams) or prematurity, febrile illness in the mother with evidence of bacterial infection within 2 weeks prior to delivery, foul smelling liquor, meconium stained liquor, rupture of membranes >18 hours, more than 3 vaginal examination and prolonged labor (sum of 1st and 2nd stage labour >24 hours). Early onset neonatal sepsis was suspected in presence of three or more risk factors, and presence of foul smelling liquor, presence of two or more antenatal risk factors and a positive septic screen and in strong clinical suspicion of sepsis.¹⁸ The associations between the clinical and bacteriological profile were analyzed using chi-square test. Level of significance in this study was considered < 0.05.

The collected data was then coded and entered into Microsoft Excel and transferred to Statistical Package for Social Sciences (SPSS) version 20 for analysis.



RESULTS

A total of 300 neonates were studied and analyzed. There was a male preponderance in our study with 57% (n=171) males and 43% (n=129) females. Twelve (4%) neonates were of birth weight of 1000grams -1499 grams, 129(43%) were of birth weight 1500-2499grams and 159(53%) were of birth weight more than 2500 grams and 141 (47%) were preterm and 159(53%) were term neonates (all appropriate for gestational age).

Table 1: Association of birth weight and blood culture in neonatal sepsis (n = 300)

Birth weight	Blood Culture		P value	Remarks
	Negative	Positive		
<1500gm	5(41.7%)	7(58.3%)		
1500-2499gm	86(66.7%)	43(33.3%)	0.02	Significant
>=2500gm	127(79.9%)	32(20.1%)		

Table 2: Association of blood culture with gestational age (n = 300)

Gestational Age	Blood Culture		P value	Remarks
	Negative	Positive		
Preterm	91 (64.5%)	50 (35.5%)		
Term	127 (79.9%)	32 (20.1%)	0.03	Significant

Table 3: Association of duration of PV leaking with blood culture (n = 300)

Duration of PV Leaking	Blood Culture		P value	Remarks
	Negative	Positive		
< 18 hr	139 (77.2%)	41 (22.8%)		
≥ = 18hr	79 (65.8%)	41 (34.2%)	0.03	Significant

Out of 300 cases of suspected early onset neonatal sepsis 32(10.7%) had prolonged labour, 120 (40%) had history of per vaginal leaking more than 18 hours duration, 37 (12.3%) had history of more than 3 maternal per vaginal examinations, 70(23.3%) had history of maternal fever within 2 weeks of delivery, 33 (11%) had history of delivery through meconium stained liquor and 42 (14%) had history of foul smelling per vaginal discharge in mother.

Of total 300 cases of suspected early onset neonatal sepsis 82 cases (27.3%) were found to be culture positive and among the studied risk factors, duration of labour, frequency of PV examination, maternal history of fever within 2 weeks of delivery, foul smelling liquor and meconium stained liquor had no significant associations with positive blood cultures. However birth weight, gestational age and history of PV leaking > 18 hours were significantly associated with positive blood cultures.

Out of 300 cases of suspected early onset neonatal sepsis 211 (70.3%) presented with lethargy, 196 (65.3%) presented with poor feeding, 122(40.7%) with respiratory distress, 62 (20.7%) were febrile, 54(18%) neonates had hypothermia, 58 (19.3%) had feeding intolerance, 26(8.7%) neonates had abnormal body movement and 12(4%) had abdominal distension. Among all the presenting symptoms, presentation with respiratory distress was significantly associated with positive blood cultures.

Of total 300 cases of suspected early onset neonatal sepsis 82 cases (27.3%) were found to be culture positive of which, *Coagulase negative Staphylococcus aureus* was found in 17(21%), *Pseudomonas aerogenosa* 14 (17%), *Klebsiella pneumonia* 16(20%), *Escherichia coli* 14(17%), *Staphylococcus aureus* 10(12%), *Citrobacter freundii* 4(5%), *Acinetobacter anitratus* 2(2%) and *Enterococcus faecalis* 5(6%).

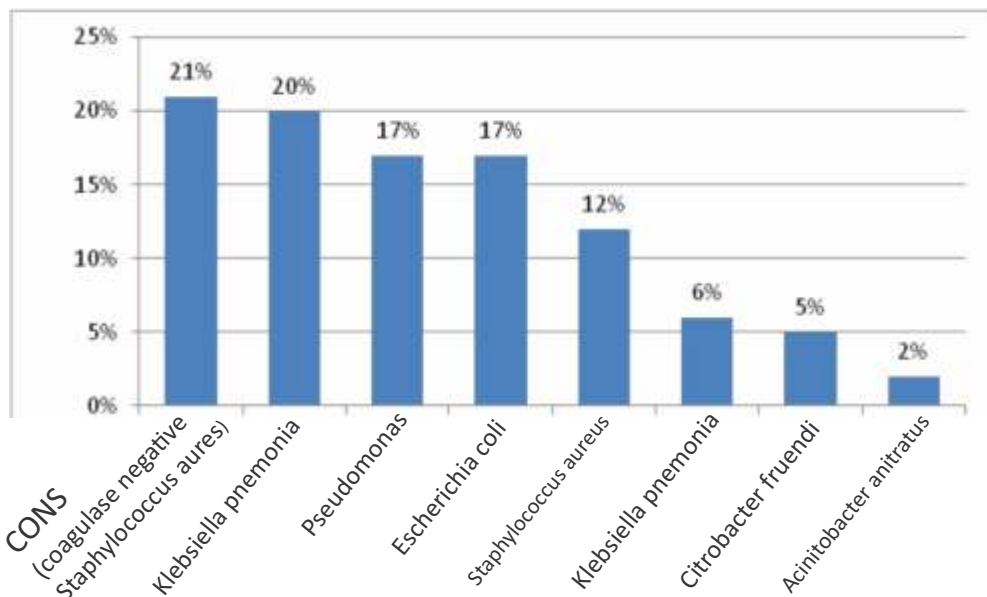


Figure 1: Distribution of detected organisms in blood culture reports (n = 82)

The results of antibiotic sensitivity patterns of various isolated organisms are listed in corresponding tabular forms

Table 4: Antibiotics sensitivity patterns of *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Escherichia coli*

S.N.	ANTIBIOTICS	<i>Pseudomonas aeruginosa</i>		<i>Klebsiella pneumoniae</i>		<i>Escherichia coli</i>	
		R	S	R	S	R	S
1.	Ampicillin	14 (100%)	0	16 (100%)	0	12 (86%)	2 (14%)
2.	Cefotaxime	6 (43%)	8 (57%)	12(75%)	4(25%)	9(64%)	5(36%)
3.	Ceftazidime	2 (14%)	12 (86%)	8(50%)	8(50%)	6(43%)	8(57%)
4.	Ciprofloxacin	0	14 (100%)	5(31%)	11(69%)	10(71%)	4(29%)
5.	Gentamicin	2 (14%)	12(86%)	6(37.5%)	10(62.5%)	3(21%)	11(79%)
6.	Amikacin	0	14 (100%)	6(37.5%)	10(62.5%)	5(36%)	9(64%)
7.	Tazobactum-Pipperacillin	0	14 (100%)	6(37.5%)	10(62.5%)	5(36%)	9(64%)
8.	Meropenem	4 (29%)	10(71%)	2(12.5%)	14(87.5%)	NA	NA
9.	Cefuroxime	NA	NA	NA	NA	10(71%)	4(29%)

S- Sensitive

R- Resistant

NA- not available

Table 5: Antibiotic sensitivity patterns of *Citrobacter freundii* and *Acinetobacter anitratus*

S.N.	ANTIBIOTICS	<i>Citrobacter Freundii</i>		<i>Acinetobacter Anitratus</i>	
		R	S	R	S
1.	Ampicillin	4(100%)	0	NA	NA
2.	Cefotaxim	2(50%)	2 (50%)	2(100%)	0
3.	Ceftazidime	1(25%)	3 (75%)	0	2 (100%)
4.	Ciprofloxacin	0	4 (100%)	0	2 (100%)
5.	Gentamicin	1(25%)	3 (75%)	0	2 (100%)
6.	Amikacin	1(25%)	3 (75%)	1 (50%)	1 (50%)
7.	Tazobactum-Pipperacillin	1(25%)	3 (75%)	1 (50%)	1 (50%)
8.	Meropenem	NA	NA	1 (50%)	1 (50%)

S- Sensitive

R- Resistant

NA- not available

Table 6: Antibiotics sensitivity patterns of *Staphylococcus aureus*, *CONS* and *Enterococcus fecalis*

S.N.	Antibiotics	<i>S. aureus</i>		CONS		<i>E. fecalis</i>	
		R	S	R	S	R	S
1.	Cloxacillin	5 (50%)	5 (50%)	12(71%)	5 (29%)	NA	NA
2.	Amikacin	1 (10%)	9 (90%)	0	17 (100%)	2 (40%)	3(60%)
3.	Linezolid	0	10 (100%)	0	17 (100%)	0	5(100%)
4.	Teicoplanin	0	10 (100%)	0	17 (100%)	1(20%)	4 (80%)
5.	Clindamycin	7 (70%)	3 (30%)	12 (71%)	5 (29%)	NA	NA
6.	Penicillin	9 (90%)	1 (10%)	17 (100%)	0	5 (100%)	0
7.	Vancomycin	0	10 (100%)	0	17 (100%)	0	5 (100%)
8.	Chloramphenicol	2 (20%)	8 (80%)	2 (12%)	15 (88%)	NA	NA
9.	Cotrimoxazole	NA	NA	11 (65%)	6 (35%)	NA	NA
10.	Gentamicin	NA	NA	NA	NA	3 (60%)	2 (40%)

S- Sensitive

R- Resistant

NA- not available

DISCUSSION

Neonatal sepsis remains a significant cause of mortality. Diagnosis and initiation of appropriate antibiotics will definitely save life of many newborns. The bacteriological profiles of early onset neonatal sepsis are different from hospital to hospital and antibiotics sensitivity pattern also varies.

Out of 300 cases of suspected early onset neonatal sepsis, 82(27.3%) cases were blood culture proven sepsis in this study whereas in study conducted in Kanti Children Hospital in 2005, 14% neonates with suspected early onset Neonatal sepsis had blood culture proven sepsis.¹⁹ In another study conducted blood culture positivity among suspected early onset neonatal sepsis was found to be 25% which is similar to result observed in this study.²⁰ In another study conducted at BPKIHS, Dharan, 20% was found to be blood culture proven early onset neonatal sepsis.²⁰ In a study conducted in Chitwan Medical College, Bharatpur 12.6% cases were blood culture proven early onset neonatal sepsis.²¹ Study conducted in Nepal Medical College Teaching Hospital, Kathmandu, 30.8% cases of suspected sepsis were blood culture proven sepsis.²² In study conducted in Dhulikhel, Kathmandu, 42.7% cases were found to be blood culture proven sepsis among suspected early onset neonatal sepsis. Hence incidence of blood culture proven sepsis is variable among various institutes.

Low birth weight, gestational age and prolonged duration of per vaginal leaking of more than 18 hours were significantly associated with blood culture positive cases. The possible reasons behind this may be babies with low birth weight or prematurity have immune dysfunction and often require prolonged intravenous access, endotracheal intubation and other invasive procedures and at 18 hours of membrane rupture, the incidence of early onset disease with group B streptococcus increases significantly.¹⁶

Regarding clinical manifestation poor feeding, lethargy, abdominal distension, feeding intolerance, temperature instability had no significant association with culture proven sepsis which was comparable to other studies with an exception of features of respiratory distress which was significantly associated with blood culture proven sepsis whereas study conducted in Dhulikhel hospital only seizure was significantly associated with blood culture proven sepsis.^{23,25,33,34}

Sex of neonate is not significantly associated with culture proven sepsis which is similar in study conducted in Makassar.²⁴ In our study low birth weight and prematurity was found to be significant risk factor of neonatal sepsis which is similar to study conducted by Dr. Wahidin Sudirohusodo hospital, Makassar.²⁴

Among organisms detected in blood culture after 72 hours, *Coagulase negative Staphylococcus aureus* (CONS) was seen as most common organism in 21% of neonates. In

study conducted in Chitwan Medical college in 2013 *Coagulase negative Staphylococcus aureus* (CONS) was most predominant organism isolated(46.6%).²¹ In similar study conducted in Egypt from March 2011 to August 2012 *coagulase negative Staphylococcus aureus* was predominant isolate in both early onset and late onset neonatal sepsis.²³ In another study conducted in tertiary care Hospital in North India *Coagulase negative Staphylococci* (17.4%) was predominant organism Followed by *klebsiella* (16.11%) which shows similar organism pattern found in this study.²⁴ Regarding antibiotics sensitivity pattern of CONS 29% of isolates in our study were found to be sensitive to cloxacillin whereas in study conducted in Dhulikhel, 57.1% were found to be sensitive to cloxacillin.²⁵ In this study 100 % of isolated CONS were found to be sensitive to vancomycin which is similar to result of study conducted in South India which shows sensitivity of CONS to vancomycin to be 100%.²⁶ Also sensitivity to amikacin was found to be 100 % in this study and in study at Dhulikhel sensitivity to amikacin was found to be 88.9%.²⁵ In this study all isolates of CONS were found to be resistant to ampicillin and in study conducted in Dhulikhel 40 % of isolates were found to be resistant to ampicillin.²⁵

Second common organism was *Klebsiella pneumonia* which accounted for 20% of isolates. In similar study conducted *Klebsiella* species accounted for 25% isolates.²⁷ In another study conducted in Nepal Medical College Teaching Hospital, Kathmandu, *Klebsiella pneumoniae* accounted for 20% of isolates.¹⁵ Regarding antibiotics sensitivity pattern 25% of isolates were found to be sensitive to cefotaxime whereas in study conducted in Dhulikhel only 5% of isolates were found to be sensitive to cefotaxime.²⁵ 62.5% of isolates were sensitive to amikacin in this study whereas, study conducted in Dhulikhel showed sensitivity of 88.9% to amikacin.²⁵ In this study 87.5% of isolates were sensitive to meropenem whereas study conducted in Dhulikhel, 100% of *Klebsiella pneumonia* were found to be sensitive to meropenem.²⁵

Pseudomonas species was isolated in 17% of neonates. In study conducted in Nepal Medical College Teaching Hospital *Pseudomonas* was isolated in 13.4% of blood culture proven sepsis.¹⁵ In study conducted in Peshawar, Pakistan *Pseudomonas* was isolated in 13 % of blood culture proven sepsis. In this study 100% cases were found to be sensitive to amikacin, tazobactam-piperacillin and ciprofloxacin and 57% were found to be sensitive to cefotaxime, and 71% were sensitive to meropenem. In similar study conducted in Rama Medical College 100% sensitivity was seen with Meropenem and amikacin and 66.67% were found to be sensitive to cefotaxime and tazobactam-piperacillin.²⁸ In our study study 86% of isolates of *Pseudomonas* were found to be sensitive to ceftazidime which was similar to study conducted in MR Medical College, Karnataka which showed sensitivity of 84.6%.²⁶



Escherichia coli was isolated in 17% of neonates. Regarding sensitivity pattern 14 % of isolates were found sensitive to ampicillin which is similar to results of study in Gujarat, India which shows 16.6 % of isolates were sensitive to ampicillin while in another study conducted in Paropakar Maternity and Women Hospital 42.85% of isolates were sensitive to ampicillin.^{30,31} In this study 64% of isolates were found to be sensitive to amikacin and 79% were found to be sensitive to gentamicin whereas in study conducted in Paropakar Maternity and Women Hospital 42.85% of isolates were found sensitive to both amikacin and gentamicin.³¹ 33.3 % and 16.6% of isolates were sensitive to amikacin and gentamicin respectively in study conducted in MP Shah Government College , Jamnagar, Gujarat, India.³⁰ twenty nine percent of isolates were found sensitive to ciprofloxacin which is similar to study conducted in Gujarat, India which accounted for 28.57% isolates being sensitive to ciprofloxacin.³⁰

Staphylococcus aureus was isolated in 12% of blood culture proven early onset neonatal sepsis. Similar study conducted showed *Staphylococcus aureus* accounted for 18% of blood culture proven sepsis.²⁷ In our study 50% cases were sensitive to Cloxacillin but studied conducted at Dhulikhel showed In our study of 91.7% to cloxacillin and study conducted in Baylesa state, Nigeria showed sensitivity of 40%.^{15,25} In this study 90% of isolates were found sensitive to amikacin and 100% were sensitive to vancomycin, similar pattern of sensitivity was seen in study conducted in Dhulikhel.²⁵

Enterococcus faecalis was isolated in 6% of neonates in blood culture proven sepsis. In similar Study conducted in Nigeria 8% of isolates were *Enterococcus* species among blood culture proven sepsis. All of them were sensitive to vancomycin, linezolid, similar sensitivity pattern to vancomycin were found in study conducted in Dhulikhel hospital, and Kanpur.^{25,32} In this study 60% were sensitive to Amikacin but 100% sensitivity was seen in study of Dhulikhel and Kanpur.

Acinetobacter anitratus was isolated in 2% of neonates in blood culture proven sepsis. In study Conducted in Chitwan Medical College, Bharatpur, *Acinetobacter* species accounted for 9.5% of blood culture proven sepsis.²¹ Regarding sensitivity pattern 100% of isolates were found to be sensitive to ciprofloxacin in this study but study conducted in Dhulikhel showed sensitivity to ciprofloxacin to be 25%. 50% isolates were sensitive to amikacin and

meropenem in this study but study conducted in Dhulikhel 20% of isolates were sensitive to amikacin and 100% were sensitive to meropenem.²⁵

CONCLUSION

The incidence of blood culture proven sepsis in suspected early onset neonatal sepsis was nearly one out of four. The most common organism isolated was coagulase negative *Staphylococcus aureus* followed by *Klebsiella pneumoniae*, *Pseudomonas*, *Escherichia coli*, *Staphylococcus aureus*, and *Enterococcus*. Overall incidence of gram negative organism was higher compared to gram positive organisms.

Low birth weight neonates, preterm neonates, prolonged duration of per vaginal leaking was found to be significantly associated with blood culture proven sepsis in this study.

Ampicillin was found to be resistant in most of isolated organisms and multidrug resistance was seen with isolated organisms. Cefotaxime was found to be resistant in gram negative organisms and cloxacillin was also found to be resistant to significant proportions of gram positive organisms.

RECOMMENDATIONS

With extensive use of antibiotics, emergence of resistance to various recommended antibiotics in early onset neonatal sepsis is seen in this study. Even resistance is seen with those antibiotics which were thought to be drugs of choice against those organisms. So antibiotics should be used judiciously and protocol for antibiotics use in different institute should be made on the basis of organisms and sensitivity pattern. Antibiotic stewardship should be used effectively.

LIMITATIONS

This study did not include anaerobic organism as culture media for anaerobic organism was found to be costly and incidence of anaerobic organism was found to be relatively very less compared to aerobic organism.

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CONFLICT OF INTEREST

We declare no conflict of interest.

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