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BACTERIOLOGICAL PROFILE OF NEONATAL SEPTICEMIA, ASSOCIATED RISK FACTORS AND ANTIBIOTIC SUSCEPTIBILITY PATTERN OF THE ISOLATES

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ABSTRACT

Introduction: Neonatal sepsis or sepsis neonatorum refers to systemic infection of the newborn and is broadly divided into two types according to age of onset: Early onset sepsis (<72 hours of birth) – is acquired during fetal life, delivery or at the nursery and Late onset sepsis (>72 hours of birth) – is generally caused by microorganisms acquired from the environment rather than from the mother. **Materials and methods:** blood culture samples of clinically suspected cases of neonatal septicemia from December 2015 to May 2017 were studied and Antibiotic sensitivity pattern of the isolates was analysed. **Results:** Out of 155 cases, Blood culture positivity was seen in 48 (30.97%) samples. Of these 48, 30 were EOS and 18 were LOS. In EOS cases, Pseudomonas (23.33%) was the most commonly found organism and in LOS, Klebsiella (27.78%) and Candida (27.78%) were the most commonly found organisms. Maternal risk factors PROM and Perinatal fever were significant indicators of neonatal septicaemia with P-values of 0.0001 and 0.016 respectively. The neonatal risk factors i.e. prematurity and low birth weight were found to be statistically significant with P-values of 0.020 and 0.0001 respectively. Pseudomonas showed 70% sensitivity to Amikacin, Gentamycin, Imipenem and Tobramycin followed by 60% sensitivity to Levofloxacin and Piperacillin-tazobactam and 40% to Cefotaxime and Ceftazidime. Klebsiellashowed 66.67% sensitivity toAmikacin, Meropenem and Piperacillin-tazobactam followed by 50% sensitivity to Ceftriaxone and Ceft-sulbactam each, 33.33% sensitivity to Ceftazidime, Levofloxacin and Netillimycin each.

KEYWORDS: Neonatal septicemia, early onset septicemia, Late Onset Septicemia, Maternal risk factors, Neonatal risk factors.

INTRODUCTION

Septicemia is a life threatening condition in which bacteria multiply at a rate that outdoes their removal by phagocytes. The symptoms produced are due to microbial toxins and cytokines produced by inflammatory cells.[1]

Neonatal sepsis or sepsis neonatorum refers to systemic infection of the newborn. It is characterized by a constellation of a nonspecific symptomatology in association with bacteremia. The term "neonatal sepsis" used broadly in clinical context encompasses diagnosis of septicemia, meningitis, pneumonia, arthritis, osteomyelitis and urinary tract infection in the newborn.[2] Neonatal sepsis is broadly divided into two types according to age of onset: Early onset sepsis (<72 hours of birth) – is acquired during fetal life, delivery or at the nursery and Late onset sepsis (>72 hours of birth) – is generally caused by microorganisms acquired from the environment rather than from the mother.[3] Neonates are particularly vulnerable to infections because of weak immune barrier. Moreover, several risk factors have been identified in both neonates and the mother which make them susceptible to infections. The incidence of neonatal sepsis varies from 11 to 24.5 per 1000 live births in India.[2] Neonatal sepsis is an important cause of morbidity and mortality among neonates and is responsible for 30-40% of the total neonatal deaths in developing countries.[4]

An awareness of many risk factors associated with neonatal sepsis prepares the clinician for early detection and effective treatment, thereby reducing morbidity and mortality.

With this background the current study was undertaken to determine bacteriological profile and antibiotic sensitivity pattern of bacterial isolates from blood samples in the neonates admitted to the intensive care units in a tertiary care center as the timely detection of infection and the identification of the infecting pathogens

and their antibiotic susceptibility patterns can have a great prognostic significance.

MATERIALS AND METHODS

The present study was conducted in a Tertiary Care Hospital, in the department of Microbiology from December 2015 to May 2017and all cases of clinically suspected septicemia in neonates admitted to the NICU of tertiary care hospital were included in the study.

This is a hospital based cross sectional study. A detailed maternal history regarding risk factors was taken. The neonatal risk factors if any were also documented. Neonates suspected to have sepsis went through a septic screening.

The components of the Septic Screen are listed below.

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

Blood culture samples were collected from a peripheral vein under aseptic conditions. Blood was collected in 3 bottles: EDTA for CBC, and ESR, plain bottle for CRP, 1 ml blood in blood culture bottle containing 10 ml brain heart infusion broth.

The culture bottle was then incubated at 37ºC. Subcultures were done on 5% blood agar and Mac Conkey's agar after 24 hours, 48 hours, 72 hours, 5th and then finally on the 7th day as per standard protocol.

The various organisms were identified on the basis of colony morphology and standard biochemical tests.[5] The antibiotic sensitivity pattern was tested by **Kirby Bauer Disc diffusion method**[6] as recommended by the **CLSI guidelines (2011).**[7] All blood cultures were observed for at least 7 days before they were reported as sterile.

Gram negative isolates were subjected to testing for ESBL production.[8]

RESULTS

Out of 155 neonates, 56.13% of the neonates were males while 43.87% were females, mean age was 36.54 ± 3.00 weeks. The minimum gestational age was 29 weeks while the maximum was 42 weeks. 74.19% (115) had low birth weight, while 25.81% (40) had normal birth weight. Out of 155 cases, those with Early Onset Septicemia (EOS) and Late Onset Septicemia (LOS) were 92 (59.35%) and 63 (40.65%) respectively. Positive blood culture was seen in 48 (30.97%) samples, while remaining were culture negative. Out of 92 cases of EOS, positive culture was seen in 30 (32.61%) cases, while out of 63 cases of LOS, positive culture was seen in 18 (28.57%) cases.

Table 1: provides the distribution for blood culture outcome. Positive blood culture was seen in 48 (30.97%) samples, while remaining were culture negative.

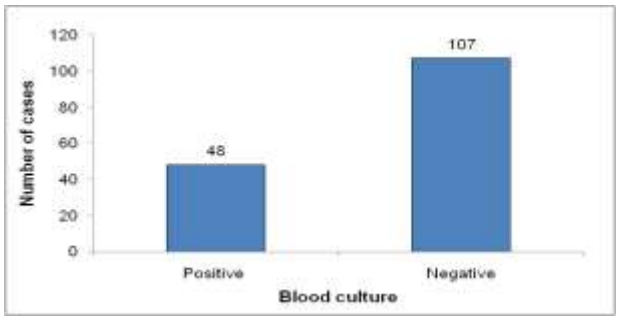

Table 2: Number of cases with positive blood culture according to onset.

Onset	Blood culture positive [Number (%)] (n=48)
EOS (n=92)	30 (32.61)
LOS (n=63)	18 (28.57)

Table 3: Bacteriological profile for cases with positive cultures in EOS (n= 30).

Bacteriological Profile	Number (%)
Pseudomonas	7 (23.33)
Candida	6 (20.00)
Acinetobacter	3 (10.00)
MSCONS	3 (10.00)
MSSA	3 (10.00)
MRCONS	2 (6.67)
E. coli	2 (6.67)
Non fermenter	1 (3.33)
Citrobacter	1 (3.33)
Coagulase positive (MRSA)	1 (3.33)
Klebsiella	1 (3.33)

Table 3: provides bacteriological profile in cases with positive culture and having EOS. Of the 30cases with EOS, Pseudomonas (23.33%) was the most commonly found organism, followed by Candida (20.00%), Acinobacter (10.00%), MSCONS (10.00%) and MSSA (10.00%). MRCONS (6.67%) and E.coli (6.67%) were the lesser observed organisms; and non-fermenter, MRSA, Klebsiella and Citrobacter were the least.

Table 4: Bacteriological profile for cases with positive culture in LOS (n=18).

Bacteriological Profile	Number (%)
Klebsiella	5 (27.78)
Candida	5 (27.78)
E. coli	3 (16.67)
Non fermenter	2 (11.11)
Enterobacter sp.	1 (5.56)
MRCONS	1 (5.56)
MSSA	1 (5.56)

Table 4: Provides bacteriological profile for cases with culture positivity and having LOS. Of the 18 cases with LOS, Klebsiella (27.78%) and Candida (27.78%) were the most commonly found organisms, followed by E. coli (16.67%) and non-fermenter (11.11%). Enterobacter sp. (5.56%), MRCONS (5.56%) and MSSA (5.56%) were the least common isolates found in LOS.

Table 5: Odds ratio associated with maternal risk factors.

Maternal risk factors	*Levels*	Blood Culture Positive/ Total	Unadjusted OR [95% CI]; P-value
Duration of pregnancy	*Term*	(22/93); 23.66%	1.00
	Preterm	(26/62); 41.94%	2.331 [1.163 - 4.671]; **0.016**
Perinatal fever	*No*	(44/150); 29.33%	1.00
	Yes	(4/5); 80.00%	9.636 [1.047 - 88.665]; **0.016**
PROM	*No*	(33/133); 24.81%	1
	Yes	(15/22); 68.18%	6.494 [2.438 - 17.295]; < **0.0001**
Premature labour	*No*	(42/143); 29.37%	1.00
	Yes	(6/12); 50.00%	2.405 [0.733 - 7.884]; 0.138
C section	*No*	(21/61); 34.43%	1.00
	Yes	(27/94); 28.72%	0.768 [0.384 - 1.533]; 0.453
Maternal illness	*No*	(32/110); 29.09%	1.00
	Yes	(16/45); 35.56%	1.345 [0.644 - 2.808]; 0.429

Table 5: gives the number of cases with positive blood culture according to categories/levels of various risk factors. The effect of change in the level of each factor on the likelihood of blood culture positivity was studied using unadjusted odds ratio (OR).

For duration of delivery, the OR corresponding to preterm delivery was 2.331 [95% CI: 1.163 - 4.671] with a *P*-value of 0.016. This indicated that the odds in favour of blood culture positivity increases 2.331 times for preterm neonates as compared to term babies; and the effect was statistically significant. For cases with perinatal fever, the odds in favour of positivity increase 9.636 [95% CI: 1.047 - 88.665] times as compared to those without fever; and the effect was statistically significant with *P*-value of 0.016. For cases with PROM, the odds in favour of positivity was 6.494 [95% CI: 2.438 - 17.295] times higher as compare to those without PROM; and the effect was statistically highly significant with *P*-value < 0.0001.For cases with premature labour, the odds in favour of positivity was 2.405 [95% CI: 0.733 - 7.884] times higher than those without such condition; but the effect was statistically insignificant with *P*-value of 0.138 (*P*>0.05). Also, for mothers with illness, the odds in favour of positivity was 1.345 [95% CI: 0.644 - 2.808] times higher as compared to those without illness, but the effect was statistically insignificant with *P*-value of 0.429 (*P*>0.05).

Table 6: Odds ratio associated with neonatal risk factors.

Neonatal risk factors	*Levels*	Blood Culture Positive/ Total	Unadjusted OR [95% CI]; P-value
Birth weight	Normal	(3/40); 7.5%	1
	LBW	(45/115); 39.13%	7.929 [2.307 - 27.254]; **<0.0001**
Asphyxia	*No*	(38/141); 26.95%	1
	Yes	(10/14); 71.43%	6.776 [2.005 - 22.901]; **0.001**
Premature	*No*	(28/110); 25.45%	1
	Yes	(20/45); 44.44%	2.343 [1.131 - 4.851]; **0.020**
RDS	*No*	(33/116); 28.45%	1
	Yes	(15/39); 38.46%	1.572 [0.735 - 3.364]; 0.242
Neonatal resuscitation	*No*	(41/134); 30.60%	1
	Yes	(7/21); 33.33%	1.134 [0.423 - 3.018]; 0.801
IUGR	*No*	(41/136); 30.15%	1
	Yes	(7/19); 36.84%	1.352 [0.496 - 3.680]; 0.554

Table 6: gives the number of neonates with positive blood culture according to categories/levels of various risk factors. The effect of change in the level of each factor on the likelihood of blood culture positivity was studied using unadjusted odds ratio (OR).

For birth weight, the OR associated with low birth weight was 7.929 [95% CI: 2.307 - 27.254] and was statistically highly significant with *P*-value < 0.0001. In other words, the risk of positivity increases 7.929 times higher in low birth weight neonates as compared to normal neonates. For neonates with asphyxia, the odds in favour of positivity increases 6.776 [95% CI: 2.005 - 22.901] times higher than those without asphyxia; and the effect was statistically significant with *P*-value of 0.001. For premature neonates, the odds in favour of positivity increases 2.343 [95% CI: 1.131 - 4.851] times as compared to mature neonates; and the effect was statistically significant with *P*-value of 0.020.For babies having RDS, the odds in favour of positivity increases 1.572 [95% CI: 0.735 - 3.364] times, but the effect was statistically insignificant with *P*-value of 0.242 (*P*>0.05). For neonates requiring neonatal resuscitation, the odds of positivity were1.134 [95% CI: 0.423 - 3.018] times higher as compared to those without such need; however, the effect was statistically insignificant with *P*-value of 0.801 (*P*>0.05). Also, for IUGR babies, the odds in favour of positivity increases1.352 [95% CI: 0.496 - 3.680] times as compared to those without IUGR; but the effect was statistically insignificant with *P*-value of 0.554 (*P*>0.05).

Of the 30 cases with EOS, Pseudomonas (23.33%) was the most commonly found organism, followed by Candida (20.00%). Of the 18 cases with LOS, Klebsiella (27.78%) and Candida (27.78%) were the most commonly found organisms, followed by E. coli (16.67%) and non-fermenter (11.11%).

Pseudomonas showed 85.71% sensitivity to Amikacin, Gentamycin, Imipenem and Tobramycin followed by 60% sensitivity to Piperacillin-tazobactam and Levofloxacin, 57.14% sensitivity to Ceftazidime and 42.86% sensitivity to Cefotaxime.

Klebsiellashowed 66.67% sensitivity to Amikacin, Meropenem and Piperacillin-tazobactam followed by 50% sensitivity to Ceftriaxone and Ceft-sulbactam each, 33.33% sensitivity to Ceftazidime, Levofloxacin and Netillimycin each.

For the reserved (higher) drugs Colistin and Polymixin – B, both Pseudomonas and Klebsiella showed 100% sensitivity to both Polymyxin – B and Colistin.

Out of the 16 Gram negative bacilli, ESBL production was seen in 3 (100%) of non-fermenter isolates followed by 2 (33.33%) of Klebsiella.

DISCUSSION

In the present study of 155 cases of neonatal septicemia, blood culture positivity was seen in 48(30.97%) whereas in 107(69.03%) there was no growth. The results of our study are consistent with Mondol GP et al 1991,[9] Gupta P. et al (1993)[10] who reported 40% culture proven sepsis.Out of 92 cases of EOS, positive culture was seen in 30 (32.61%) cases, while out of 63 cases of LOS, positive culture was seen in 18 (28.57%) cases.

Mane AKet al (2010)[11] studied 260 blood samples of clinically suspected cases of neonatal septicemia. Positive blood cultures were seen in 70 (26.9%) samples, out of which 48 were EOS and 22 were LOS.

Jyothi P et al (2013)[12] collected 683 blood samples of neonates, out of which blood culture was positive for 19.2% cases. EOS was found to be three times higher than LOS. Out of 131 cases 98(74.8%) and LOS was present in 33(25.2%) cases.

In our study, out of 48 blood culture positive cases, 15 had Premature Rupture of Membranes (PROM), while 33 did not; and of the 107 blood culture negative cases, 7 had PROM and 100 did not have PROM. Similarly, out of 48 culture positive cases, 4 had perinatal fever, while 44 had no fever. Both these maternal risk factors were significant indicators of neonatal septicemia with P-values of 0.0001 and 0.016 respectively.

Khatua SP et al[13] showed a strong association of PROM and neonatal septicemia, similar to our study.

In our study the neonatal risk factors i.e. prematurity and low birth weight were found to be statistically significant with P-values of 0.020 and 0.0001 respectively.

Low birth weight is an accepted risk factor for neonatal septicemia and has been reported and stated in the studies done by: Sinha N et al (1986)[14] mentioned that male babies with low birth weight dominated the cases i.e. 64.9%.

In our study out of the 155 cases, 69.03% had no growth out of the 30 cases with EOS, Pseudomonas (23.33%) was the most commonly found organism, followed by Candida (20.00%), Acinetobacter (10.00%), MSCONS (10.00%) and MSSA (10.00%). MRCONS (6.67%) and E.coli (6.67%) were the lesser observed organisms; and non-fermenter, MRSA, Klebsiella and Citrobacter were the least. Sinha N et al (1986)[14] stated Pseudomonas as the commonest organism isolated in his study on neonatal septicemia.

Of the 18 cases with LOS, Candida (27.78%) and Klebsiella (27.78%) were the most commonly found organisms, followed by E. coli (16.67%) and non-fermenter (11.11%). Enterobacter sp. (5.56%), MRCONS (5.56%) and MSSA (5.56%) were the least common isolates in women with LOS. [Table no. 7(b)]. Rani R et al (2002)[15] reported that out of 144 culture positive samples, 34.7% were of Candida isolates in his study on neonatal septicemia.

GPC showed 100% sensitivity to Linezolid and Vancomycin. **MRCONS** showed 100% sensitivity to Amikacin, Linezolid, Piperacillin-tazobactam and Vancomycin, followed by 66.67% sensitivity to Co-trimaxozole, Ciprofloxacin. It showed 33.33% sensitivity to Ceftazidime. **MRSA** showed 100% sensitivity to Amikacin, Ceftazidime, Linezolid and Vancomycin. **MSCONS** showed 100% sensitivity to Ciprofloxacin, Linezolid and Vancomycin followed by 66.67% sensitivity to Co-trimaxozole and Piperacillin-tazobactam and 33% sensitivity to Amikacin and Ceftazidime. **MSSA** showed 100% sensitivity to Vancomycin, Piperacillin-tazobactam, and Linezolid Cefoxitin followed by 80% sensitivity to Co-trimaxozole and Ceftazidime, 60% to Ciprofloxacin and 20% sensitivity to Amikacin.

Klebsiella showed 66.67% sensitivity to Amikacin, Meropenem and Piperacillin-tazobactam followed by 50% sensitivity to Ceftriaxone and Ceft-sulbactam each, 33.33% sensitivity to Ceftazidime, Levofloxacin and Netillimycin each. Enterobacter sp. showed 100% sensitivity to all the antibiotics except Levofloxacin to which it showed resistance. E. coli showed 100% sensitivity to Amikacin, followed by 80% sensitivity to Ceftriaxone, Levofloxacin and Piperacillin-tazobactam and 60% sensitivity to Ceftriaxone-sulbactam, Meropenem and Netillimycin. Citrobacter showed 100% sensitivity to Ceft-sulbactam, Levofloxacin, Netillimycin and Piperacillin-tazobactam. Non- fermenters showed resistance to the above mentioned antibiotics and thus reserved drugs were tested for them.

Gram negative organisms showed low sensitivity to all Cephalosporins which was similar to the sensitivity pattern reported by Thakur S et al (2016).[16]

Acinetobacter and Pseudomonas showed 70% sensitivity to Amikacin, Gentamycin, Imipenem and Tobramycin followed by 60% sensitivity to Levofloxacin and Piperacillin-tazobactam and 40% to Cefotaxime and Ceftazidime.

The sensitivity pattern of GNR types which were resistant to 1st line antibiotics were tested for **reserved antibiotics**. Klebsiella showed 100% sensitivity to both Polymyxin – B and Colistin, while Non fermenter showed 66.67% sensitivity to both Polymyxin – B and Colistin.

Acinetobacter and Pseudomonas which were resistant to 1st line antibiotics were tested for **reserved antibiotics** and showed 100% sensitivity to both Polymyxin– B and Colistin.

In our study, out of the 16 Gram Negative isolates, 5 (31.25%) were ESBL producers. Out of these 5, 3 isolates were Non-Fermenter isolates and 2 were Klebsiella spp. isolates.

Jain A et al[17] reported a high ESBL production by the Klebsiella isolates (86.6%), Enterobacter isolates (73.4%) and E.coli strains. This could be attributed to the selective pressure imposed by extensive use of antibiotics.

In our study out of the 48 blood culture positive cases, 28 had elevated CRP values. The rise in the CRP values was significantly associated with neonatal septicemia. A significant association is thus observed between rise in CRP in response to neonatal septicemia. Ahmed Z et al (2005),[18] who reported similar findings.

In our study we found out that Leucopenia (P-value of 0.0012), neutropenia (P-value of 0.0336) and high Band Cell count (P-value of 0.0011) were reliable indicators of neonatal septicemia and had a significant correlation with neonatal septicemia.

Gupta P in **1993.**[10] also reported granulocytopenia to be indicating severity of infection in neonates.

However **Sinha N et al (1986).**[14] stated that the peripheral cell count showed variation and failed to help as a diagnostic parameter as normal blood counts were seen in 69.5% cases of neonatal sepsis in their study.

CONCLUSION

Blood culture was performed on all 155 samples. Growth was obtained in 48 (30.97%) samples. Maternal risk factors for neonatal septicemia that were found to be significantly associated with neonatal septicemia were maternal fever and prolonged rupture of membranes. Neonatal risk factors that were found to be significantly associated with neonatal septicemia were prematurity and low birth weight. Out of 155 cases, those with Early Onset Septicemia (EOS) and Late Onset Septicemia (LOS) were 92 (59.35%) and 63 (40.65%) respectively. In cases of Early Onset Septicemia (EOS) which were clearly in excess of Late Onset Septicemia (LOS), *Pseudomonas spp.* were the most common and *Klebsiella spp. and Candida* were predominant isolates in LOS. *Pseudomonas spp.* showed 70% sensitivity to Amikacin, Gentamycin, Imipenem and Tobramycin followed by 60% sensitivity to Levofloxacin and Piperacillin-tazobactam and 40% to Cefotaxime and Ceftazidime. Klebsiellashowed 66.67% sensitivity toAmikacin, Meropenem and Piperacillin-tazobactam followed by 50% sensitivity to Ceftriaxone and Ceft-sulbactam each, 33.33% sensitivity to Ceftazidime, Levofloxacin and Netillimycin each. Out of the 16 GNR isolates 5 (31.25%) were found to be ESBL producers. Out of these 2 isolates were *Klebsiella spp.* and 3 were Non-Fermenters.

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