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A clinico-microbiological profile, antimicrobial sensitivity and outcome of neonatal sepsis in NICU, Ajmer

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Abstract
Background: Neonatal septicaemia is a clinical entity that is characterized by systemic signs and symptoms of infection and accompanied by bacteraemia in first 4 weeks of life and is one of the four leading causes of neonatal mortality and morbidity in India.
Aim: To determine the bacterial spectrum and antimicrobial susceptibility pattern of neonatal septicaemia in a tertiary care hospital of Jaipur, Rajasthan.
Materials and Methods: In this prospective observational study, 346 blood samples were collected over period of 6 months and processed from clinically suspected neonates according to standard laboratory protocol. Antimicrobial susceptibility of the isolates was done by Kirby Bauer disc diffusion method according to Clinical and laboratory standard institution (CLSI) recommendations.
Results: Blood culture reports were positive in 53 (15.31%) cases. Commonest clinical presentation of neonates with septicemia was respiratory distress and Commonest maternal risk factor was PROM >18 hours. Gram negative septicaemia (55.10%) was encountered more than Gram positive (44.90%). Coagulase negative Staphylococci (38.78%) was the predominant isolate followed by, Klebsiella spp in 34.69% cases. Best overall sensitivity among Gram-negative isolates was to polymyxin B, colistin and meropenem (100%). Gram-positive isolates had highest sensitivity to Linezolid (100 %) and Vancomycin (100%).
Conclusion: Gram negative organisms are the leading cause of neonatal septicaemia with Klebsiella spp being commonest. Coagulase negative Staphylococci is the predominant isolate among Gram positive organisms. Most of the isolates are resistant to common antibiotics.

Keywords: neonatal sepsis, antimicrobial sensitivity, clinical profile, microbiological profile, NICU

Introduction

Neonatal septicemia is a clinical entity that is characterized by systemic signs and symptoms of infection and accompanied by bacteriaemia in first 4 weeks of life and is one of the four leading causes of neonatal mortality and morbidity in India [1]. Incidence of neonatal septicemia in developed countries varies from 1-10/1000 live birth, whereas it is 3 times more common in India [2]. The incidence of neonatal sepsis according to the data from National Neonatal Perinatal Database (NNPD, 2002-03) is 30 per 1000 live births in India [3]. Incidence differs among hospitals depending on various factors such as obstetric and nursery practices, sex, gestational age, birth weight, out born or inborn status of babies, perinatal care, and health and nutrition of mother [4].

Early onset sepsis (EOS) presents within the first 72 hours of life and the source of infection is generally the maternal genital tract. Knowledge about these potential risk factors would help in early diagnosis of sepsis [5].

Late onset sepsis (LOS) usually presents after 72 hours of age. The source of infection in LOS is either nosocomial (hospital-acquired) or community-acquired [6, 7].

Neonatal sepsis is caused by a variety of Gram-positive as well as Gram-negative bacteria, and sometimes yeasts. According to data from National Neonatal Perinatal Database (NNPD, 2002-03) in India, among intramural births, Klebsiella pneumoniae is the most frequently isolated pathogen (32.5%), followed by Staphylococcus aureus (13.6%). Among extramural neonates (referred from community/other hospitals), Klebsiella pneumoniae is again the commonest organism (27%), followed by Staphylococcus aureus (15%) and Pseudomonas (13%) [3].

Uncontrolled use of various potent and broad-spectrum antibiotics has led to emergence of resistant strains which has become a major problem in various Intensive care units [8]. Early diagnosis and to treat neonatal infections by empirical use of antimicrobial drugs as soon as possible is must to reduce the mortality. Various diagnostic tests (hematological, biochemical and radiological) can be performed easily and results may be available in an hour or so. However, blood culture remains the gold standard for the diagnosis of neonatal septicemia [9].

The uncertainty surrounding the clinical approach to treatment of neonatal septicemia can be minimized by periodic surveys of etiological agents and their antibiotic susceptibility patterns leading to recognition of the most frequently encountered pathogens in a particular neonatal setting. The rational and correct use of antibiotics requires

understanding of common pathogens and their drug sensitivity pattern in the regions. Due to constantly evolving antimicrobial resistant patterns there is the need for constant antimicrobial sensitivity surveillance. This will help clinicians provide safe and effective empirical therapies, develop rational prescription programs and make policy decisions and finally assess the effectiveness of all [10].

Present study is conducted to determine the clinical profile, risk factors and organisms associated with bacteraemia and to find out susceptibility pattern of pathogens causing neonatal sepsis so as to provide antibiogram to NICU of Neoclinic for better patient management.

Method and material

The present prospective observational study was carried out on 346 blood samples from neonates with clinical suspicion of septicaemia, admitted in NICU of JLN Medical College, Ajmer from March 2018 to September 2018.

Inclusion Criteria

All neonates who require admission to neonatal intensive care unit (NICU) for any indication during the study period

Exclusion Criteria

The caretaker unwilling to provide written informed consent.

The neonatal history including sex, gestational age, birth weight, term or preterm were taken. The data regarding maternal risk factor for neonatal sepsis including duration of labour, mode of delivery, maternal fever, chorioamnionitis (foul smelling liquor), maternal urinary tract infection, and duration of rupture of membrane were collected. Data were collected in a structured proforma and were classified, analysed & evaluated by using SPSS version 21 for Windows as per aims & objectives. About 1-2 ml of venous blood was drawn by a percutaneous venous puncture following strict aseptic precautions (3 swab technique) and aseptically inoculated into blood culture bottles containing 5 -10 ml of brain heart infusion broth. Blood culture bottles were incubated at 37°C overnight aerobically. Primary subcultures were done after 24 hours of incubation on to Blood agar & Mac- Conkey agar. If no growth occurred on plates after overnight incubation, bottles were incubated further & followed up by examining the broth daily and doing a final subculture at the end of day 7 or at appearance of signs of growth, whichever was earlier. The positive growth was identified by conventional methods according to the standard laboratory protocol, including colony morphology, Gram"s staining & biochemical reactions. After the identification of bacteria, antimicrobial sensitivity testing was done by Kirby- Bauer disc diffusion method on Muller Hinton agar as per Clinical and Laboratory Standards Institute (CLSI) guidelines [11]. The antibiotics which were used in our study were based on the standard protocol of the hospital and departmental policies (as per CLSI).

The clinical signs suggestive of infection include [5]

1. Refusal to feed, poor cry, lethargy
2. Temperature instability [Fever (>37.5°C), hypothermia (< 36.5 °C)]
3. Off color appearance, dusky peripheries
4. Prolonged CFT (>3sec)
5. Apnea, worsening respiratory distress
6. Feed intolerance, abdominal distension
7. Blood in stool and other bleeding manifestation

The perinatal risk factors include [5]

- Low birth weight (<2500 grams) or prematurity
- Febrile illness in mother with evidence of bacterial infection within in 2 weeks prior of delivery
- Rupture of membrane >18 hours
- Prolonged labor (sum of 1st and 2nd stage of labor ≥24 hours)
- Single unclean or >3 sterile vaginal examinations during labor
- Foul smelling liquor
- Perinatal asphyxia (Apgar score <4 at 1 min)

Presence of foul-smelling liquor or three of the above-mentioned risk factors warrant initiation of antibiotic treatment. Infants with two risk factors were investigated and then treated accordingly.

Various predisposing factors to increase risk of nosocomial sepsis include

- Low birth weight
- Prematurity
- Admission in intensive care unit
- Mechanical ventilation
- Invasive procedures
- Administration of Parenteral fluids, and
- Use of stock solutions

Results

During the study period, a total of 346 neonates with clinical sepsis were studied. Blood culture positivity was found in 53 cases (15.32%) while 293 (84.68%) were blood culture negative. Bacterial species were found in 49 (92.45%) and Candida species in 4 (7.55%) cases.

Incidence of septicaemia was higher in preterm neonates 26 (53.0%) as compared to term 23 (46.9%).

Of the various maternal risk factors affecting neonatal septicaemia, rupture of membranes for more than 18 hours was the commonest factor with 63.64% cases followed by foul smelling liquor in 27.27%, febrile illness in mother 18.18% and maternal urinary tract infection (UTI) in 9.09%.

According to clinical presentation, respiratory distress (65.30%) was commonest presentation among culture positive cases followed by encephalopathy (22.44%) and seizures (14.28%).

Etiology of the 49 bacterial culture positive isolates included Gram-negative bacilli (27/49, 55.10%) and Gram-positive cocci (22/49, 44.90%). Coagulase Negative Staphylococci (38.78%) was the commonest bacterial isolate followed by Klebsiella spp (34.69%), Acinetobacter (14.29%), Enterobacter (4.08%), Enterococcus spp (4.08%), Coagulase positive Staphylococci (2.04%) and Escherichia coli (2.04%).

Gram positive organisms showed highest sensitivity to Linezolid (100 %) and Vancomycin (100 %), followed by Doxycycline (86.36%), Meropenam (86.36 %) and Gentamycin (81.82 %) and least sensitivity to Cefuroxime (4.54 %).

Gram negative organisms showed good sensitivity to polymyxin B, colistin and meropenem i.e 100%, 96.27% and 88.88% respectively. Ceftazidime showed poor sensitivity amongst Gram negative organisms.

Out of 49 cases, 83.67 % baby survived and discharged while 10.20% expired and 6.13% baby was LAMA.

Table 1: Incidence of Neonatal septicemia

Cases	Number Of Cases (n= 346)	Percentage (%)
No Sepsis	180	52.02 %
Suspected Sepsis	113	32.66%
Culture proven sepsis	53	15.32%

Table 2: Distribution of incidence of gestational age in bacterial culture positive cases

Gestational age	Number of culture positive cases (n=49)	Percentage (%)
Full term (≥37 weeks)	23	46.93%
Pre term (<37 weeks)	26	53.06%

Table 3: Distribution of maternal risk factors (Early Onset Sepsis n=11) in bacterial culture positive cases

Maternal Parameters	Cases (n=11)	Percentage (%)
Prolonged rupture of membrane (PROM)> 18 Hrs	7	63.64 %
Maternal Urinary tract infection	1	9.09 %
Febrile illness in mother	2	18.18 %
Foul Smelling Liquor/ features of chorioamnionitis	3	27.27 %

Table 4: Spectrum of bacterial isolates

Isolates	Number of Cases (n=49)	Percentage (%)
CONS	19	38.78%
Klebsiella	17	34.69%
Acinetobacter	7	14.29%
Enterobacter	2	4.08%
Enterococcus	2	4.08%
COPS	1	2.04%
E coli	1	2.04%

Table 5: Antibiotic sensitivity pattern of Gram-positive bacteria (n=22)

Antibiotic	Number of cases	Percentage (%)
Amikacin	15	68.18%
Amoxycillin/ Clavulanic acid	2	9.09%
Ampicillin	2	9.09%
Ampicillin / Sulbactum	4	18.18%
Cefoxitin	12	54.54%
Gentamycin	18	81.82%
Levofloxacin	7	31.82%
Linezolid	22	100%
Meropenam	19	86.36%
Teicoplanin	17	77.27%
Vancomycin	22	100%

Table 6: Antibiotic sensitivity pattern of Gram-negative bacteria (N=27)

Antibiotic	Number of cases(n)	Percentage (n? N%)
Amikacin	14	51.85%
Colistin	26	96.27%
Ceftazidime + clavulamic acid	2	7.41%
Ceftriaxone	5	18.52%
Imipenam	22	81.48%
Meropenam	24	88.88%
Ciprofloxacin	13	48.15%
Polymyxin B	27	100%
Gentamycin	7	25.92%
Levofloxacin	14	51.85%
Piperacillin / Tazobactum	11	40.74%

Discussion

The present study was carried out in the NICU, Ajmer. Total 346 babies admitted during study period were enrolled and out of which 180 (52.02%) cases had no sepsis, 113 (32.65%) had suspected sepsis, 22 (6.35 %) had Gram positive sepsis, 27 (7.80%) had gram negative sepsis and 4 (1.11 %) cases had fungal sepsis. Out of 346 neonates, 53 were found to be blood culture positive, giving a culture positivity rate of 15.31%.

Culture positivity

According to previous studies blood culture positivity in neonatal septicaemia varies from 18.8% [48] to 64.87% [13]. Our results are comparable with studies conducted by P.Jyothi *et al* [14], Sanjay Rathod *et al*. [15], and Ramesh bhat *et al*. [16]. Low positivity might be due to administration of antibiotic before blood collection, possibility of infection with anaerobes or presence of fastidious organisms and quality controlled care in our NICU.

However, positivity rate in our study is low as compared to the results reported by Roy *et al*. [17], Hirah shah *et al*. [18] and Bheemasamudra *et al*. [19], which, might be attributed to the better infection control practices in our Neonatal ICUs.

Preterm Vs Term

Prematurity is an important neonatal factor predisposing to infection. Preterm neonates are more prone to septicaemia because of the immaturity of immune system as comparedto full term babies. In our study, blood culture positivity was found more in preterm neonates (53.0%) than full term (46.9%). Our results are similar to other studies like Bheema Samudra *et al*. [19] and Arpita Jigar Shah *et al*. [22]. However, surprisingly in a study by Dechen C Tsering et positivity was higher in full term as compared to preterm.

Clinical Presentation

Of the various clinical presentations of neonates with septicaemia, our study revealed that respiratory distress was the commonest presentation followed by dullness. Study by

Kavita nimboor [4] and Deepandra garg *et al*. [21] showed refusal to feed being the commonest symptom followed by respiratory distress. Mamta jagoo *et al*. [31] reported refusal to feed as leading symptom followed by respiratory distress. Khatua *et al*. [24] reported refusal to feed, hypothermia and respiratory distress as common clinical presentation.

Spectrum of organisms

Gram-negative organisms are more common pathogens and are mainly represented by Klebsiella, Escherichia coli, Pseudomonas, Enterobacter spp and Acinetobacter spp. Among the Gram-positive organisms, Staphylococcus aureus, CoNS, Streptococcus pneumoniae, and Streptococcus pyogenes are common isolates [14].

Gram negative septicaemia (55.10 %) was encountered more than Gram positive (44.90 %) in the present study which is comparable to studies conducted by Tsering DC *et al*. [23], Arpita Jigar *et al*. [22] and P. Jyothi *et al*. [14]. The increased susceptibility of neonates to the Gram negative bacteria may be explained by the fact that the antibodies against these organisms are primarily IgM type, which do not transfer passively through placenta and are at very low level in blood (about 5% of adult value) at birth, and reaches the adult level by 2 years of age. This is in contrast with IgG type, which are passively transferred to placenta and are almost at adult level at birth and falls gradually reaching lowest level around 3 to 4 months of age after which they start to rise again gradually. Adequate IgG (except IgG 2-subtype) levels at term, afford protection against several Gram-positive bacteria [32].

In the present study Coagulase negative Staphylococci (38.78%) was the predominant isolate followed by Klebsiella spp in 34.69 % cases. CoNS is normally considered as a skin contaminant when isolated from blood. The presence of this bacteria in blood in critically ill babies should be considered as significant and should be treated. In our study, we considered CoNS as a true pathogen because the antibiotic sensitivity pattern of our CoPS and CoNS isolates was almost similar and they correlated clinically. Moreover, the samples were collected with proper sterile precautions, so the chances of contamination with skin flora were minimal.

Among Gram negative bacteria, we found Klebsiella spp (62.96%) as commonest followed by Acinetobacter (25.93%), similar to study by K. Chug *et al*. [33], Anuradha de *et al*[12], and Anitha sharma *et al*[20]. This was in concordance with National Neonatal Perinatal Database (NNPD- 2003)[3] with Klebsiella spp as a predominant Gram-negative isolate associated with neonatal sepsis. However, in some studies by S.G Joshi *et al*. [34], Tsering DC *et al*. [23], and Ramesh bhat *et al*. [16], Pseudomonas spp was the commonest isolate among Gram negative bacteria.

In our study Coagulase negative Staphylococci was the commonest (86.36%) isolate among Gram positive cocci followed by Enterococcus spp (9.09%) and Coagulase positive Staphylococci (4.55%). This is in accordance to study by Edwin dias *et al*. [35], Daynia E *et al*. [36], G.P Mondal *et al*. [37] and Isaacs D *et al*. [38].

Antimicrobial susceptibility

The antimicrobial susceptibility (AST) pattern differs in different studies as well as at different times in the same hospital in Indian and overseas studies because of the different hospital based antibiotic policies.

In our study AST revealed that majority of Gram-negative bacteria were sensitive to polymycin B (100%), colistin (96.27%), meropenem (88.88%) and imipenam (81.48%). P Jyothi *et al*. [14] also found best overall sensitivity among Gram negative isolates to imipenem (93%). Among aminoglycosides maximum sensitivity was seen to amikacin (57.78%) which is in line with Madavi *et al*. [39], who reported 60.60% sensitivity to amikacin. Least sensitivity was seen to extended spectrum cephalosporins in our study. Among Gram negative bacteria, the predominant Klebsiella spp showed good sensitivity to polymyxin B (100%), colistin (100%), meropenem (94.12%) and imipenam (88.23%), which is similar to results reported by Kaushal seth *et al*. [29] and Maimoona mustafa *et al*. [40] with 100% sensitivity to imipenem. Sensitivity to amikacin (52.94%) was better than gentamycin (35.29%) among amino-glycosides in our study which was comparable to results of studies by Bheemasamudra *et al*. [19], Ramesh bhat *et al*. [41] and Maimoonamustafa *et al*. [40]. In our study Gram positive bacteria showed good sensitivity to Linezolid (100%), vancomycin (100%), meropenem (86.36%), doxycycline (86.36%) and Gentamycin (81.82%) which is comparable to study by Mamtajagoo *et al*. [31], Arpita shah *et al*. [22], and Kaushal v *et al*. [29]. Sensitivity to ampicillin (9.09%), amoxicillin and clavulanic acid (9.09%) and cefuroxime (4.54%) was lowest among Gram positive bacteria in our study.

Carbapenems (imipenem and meropenem), colistin and polymyxin B were found to be the most potent antimicrobial agents against Gram negative organisms. Majority of Gram-positive isolates were sensitive to linezolid and vancomycin.

Outcome of neonatal septicemia

Out of 49 babies, 23 (46.94%) babies discharged, 18 (36.73%) went Discharge on request, 3 (6.13%) left against medical advice and 5 (10.20%) babies expired as a consequence of the underlying disease. Iyer*et al*. [42] also showed similar outcome in his study.

Conclusion

Gram negative organisms are the leading cause of neonatal septicaemia with Klebsiella spp being commonest. Coagulase negative Staphylococci is the predominant isolate among Gram positive organisms. Most of the isolates are resistant to common antibiotics.

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