Original Article

Microbial Profile of Neonatal Septicemia and its Antibiogram Prevalent in a Tertiary Care Hospital of Western Odisha

Tanushree Ghosh[1], Swetalina Jena[2], Aruna Rani Behera[3], Sangeeta Panigrahy[4], Rajesh Kumar Sethi[5]

Introduction : A disseminated disease with positive Blood Culture during the first month of life and encompasses various systemic infections of the newborn such as septicemia, meningitis, pneumonia, arthritis, osteomyelitis and Urinary Tract Infection is defined as Neonatal Sepsis. It is one of the leading causes of morbidity and mortality amongst neonates of developing countries.

Aim : To determine the microbial profile of Blood Culture-positive Septicemia cases and study their antimicrobial susceptibility pattern.

Materials and Methods : Blood Culture and C-reactive Protein (CRP) estimation were done for all 220 clinically suspected neonates. All the pure Bacterial and Candida isolates were identified using standard biochemical tests. Antimicrobial susceptibility testing was done for all bacterial isolates using the Kirby-Bauer disk diffusion method as per Clinical and Laboratory Standards Institute (CLSI) guidelines.

Results : Out of 220 cases, 68.2% were culture positive. Early-onset Neonatal Septicemia (EONS) cases were 74% and Late-onset Neonatal Septicemia (LONS) 26%. The male to female ratio was 1.9:1. Bacterial cases were 66% and 34% were due to *Candida*. Gram-negative isolates predominated, with *Klebsiella pneumonia* being the most common one. In the case of Gram-positive isolates, *Staphylococcus aureus* was most common. The best overall sensitivity of Gram-negative isolates was to Amikacin (100%), Colistin (100%), and Imipenem (96%). Gram-positive isolates reported 100% sensitivity to Vancomycin, Teicoplanin and 97.4% to Linezolid.

Conclusion : Gram-negative isolates were the leading cause of Sepsis in our study. Strict antimicrobial stewardship should be implemented to prevent the emergence of multi-drug resistant strains.

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Key words **: Neonatal septicemia, Blood culture, CRP, Antimicrobial susceptibility.**

A disseminated disease with positive Blood Culture during the first month of life and encompasses various systemic infections of the new born such as Septicaemia, Meningitis, Pneumonia, Arthritis, Osteomyelitis and Urinary Tract Infection is defined as Neonatal Sepsis[1]. The first 28 days of life (neonatal period), represents the most vulnerable time for a child's survival. In 2013, roughly 45% of under-five deaths occurred during this period. The proportion of child deaths which occur in the neonatal period has increased in all WHO regions over the past 20 years[2]. According to National Neonatal Perinatal Database (2002-2003) the incidence of Neonatal Sepsis in India was 30 per 1000 live-births and total neonatal deaths in developing countries was 30-50%[3-5]. It is estimated that about 20% of neonates develop Sepsis and Sepsis related death are approximately 1%[6]. When onset of septicemia occurs within the first 72 hours of life, ie, Early Onset Septicemia (EOS) prenatal factors mainly predominate, when onset is after 72 hours of life, ie, Late Onset Septicemia (LOS) it mostly points towards postnatal infection or Nosocomial infection[7]. Maternal risk factors include fever, bacteriuria, Premature Rupture Of Membrane (PROM), amnionitis, prolonged labour, poor hygiene and genitourinary colonization

Editor's Comment :

- Neonatal Septicemia is one of the leading causes of neonatal mortality world wide, therefore our aim was to study in depth the various treatment and management options available. Strict antimicrobial stewardship should be implemented to prevent the emergence of multidrug resistant strains.

[1]MD (Microbiology), Demonostrator, Department of Microbiology, Murshidabad Medical College and Hospital, Berhampore 742101 Corresponding Author

[2]MD (Microbiology), Assistant Professor, Department of Microbiology, VSS Institute of Medical Science and Research, Burla, Odisha 768017

[3]MD (Microbiology), Assistant Professor, Department of Microbiology, Great Eastern Medical School and Hospital, Srikakulam, Andhra Pradesh 532484

[4]MD (Microbiology), Assistant Professor, Department of Microbiology, Great Eastern Medical School and Hospital, Srikakulam, Andhra Pradesh 532484

[5]MD (Paediatrics), Professor, Department of Paediatrics, Great Eastern Medical School and Hospital, Srikakulam, Andhra Pradesh 532484

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with micro organisms[8]. Neonatal risk factors include prematurity, low birth weight, congenital anomalies, male sex and birth asphyxia[9].

Bacterial causative agents vary from institution to institution but commonly found organisms are Gram negative rods like *Escherichia coli, Klebsiella pneumoniae*, *Enterobacter species, Pseudomonas*, *Proteus*, *Citrobacter* and *Serratia* comprising of two thirds of cases of Septicemia and one third cases by Gram positive organisms like *Staphylococcus*, *Streptococcus*, *Listeria monocytogenes*[10]. Clinical presentation may be silent in a very small baby who may suddenly die without exhibiting any signs. In others, there is change in behaviour and feeding pattern like refusal to suck, unresponsiveness, lethargy, pallor and vacant stare[11]. Early Onset Sepsis (EOS) is more likely associated with respiratory distress. Hypothermia is a common manifestation in preterm babies while term babies may manifest with Fever, Diarrhoea, Vomiting, Abdominal distension, Jaundice and episodes of apneic spells with cyanosis. Only about half of the babies of proven sepsis are febrile, about 15 percent have hypothermia, remaining may be normothermic. Signs of meningitis is seen in less than one-third of babies[12]. The most important and dependable diagnostic parameter for Neonatal Septicemia is positive blood culture[13]. However, it is time consuming, requiring at least 48 to 72 hours to generate final report. For emergency management of the case, empirical antimicrobial therapy is generally started immediately after inoculating blood sample for culture, but the treatment needs to be modified after receiving the final blood culture and sensitivity report[14]. The outcome depends on the weight and maturity of the infant, type of etiologic agent, its sensitivity pattern and adequacy of supportive and specific therapy[15]. Specific complications include shock, adrenal insufficiency, consumptive coagulopathy, congestive heart failure, hyponatremia, etc[16]. Keeping in view the above facts the present study was designed with the following aim: To determine the microbial profile of septicemic neonates admitted to Neonatal Intensive Care Unit (NICU) of VIMSAR, Burla, and to undertake antimicrobial sensitivity testing of the microorganisms isolated.

Materials and Methods

This was a hospital-based cross-sectional study conducted over a period of 2 years, from November, 2013 to October 2015, at the Department of Microbiology, VIMSAR, Burla, after getting approval from the institutional Ethics Committee with no. IEC/IRB- 50/13.

Study group : The study group comprised 220 neonates admitted to VIMSAR, Neonatal Intensive Care Unit with clinical signs of Septicemia.

Inclusion criteria : All the neonates who were admitted with clinical signs of Sepsis.

Exclusion criteria : Neonates born to mothers who had received Antenatal Antibiotic Therapy within 48 hours prior to delivery and symptomatic neonates who had been started on antibiotics.

The diagnosis of Neonatal Septicemia was based on clinical criteria like poor activity, lethargy, inability or poor sucking, hypothermia, abdominal distension, and diminished or absent Neonatal Reflexes.

Media preparation : Brain Heart Infusion Biphasic Media (BHIBPM) culture bottles were used for performing Blood Culture. Commercially available Brain Heart Infusion (BHI) dehydrated media obtained from Himedia, (India) was used as per instruction[17].

Specimen collection and Transport : Any peripheral vein was chosen as the venepuncture site. The site was cleaned and disinfected with povidone-iodine followed by 70% Isopropyl alcohol and allowed to dry. Two milliliters of blood was collected with the help of a sterile disposable scalp vein (24G) and syringe (2 ml.) and immediately transferred to BHIBPM. Then the bottles were shaken gently to mix the blood with the broth homogeneously and transferred to the Microbiology laboratory in an upright position for incubation and culture[18].

Culture : In the laboratory the, bottles were incubated at 37°C for a maximum period of 7 days. The bottles were observed daily for signs of growth like turbidity, air bubbles and colonies on the surface of the sedimented red cells or over the solid slant portion of the biphasic medium. As soon as growth was observed, subculture was done on Blood agar and CLED agar plates and incubated at 37°C[19]. The bottles that showed no growth for 7 days were discarded.

Identification : Isolates were identified by their characteristic appearance on the respective media, Gram staining, and confirmed using standard biochemical tests[19]. For Gram-positive bacteria catalase, coagulase bile aesculin and other tests were performed. Gram-negative isolates were identified by motility test, indole production, citrate utilization, oxidase, sugar fermentation, and other tests. In the case of Candida isolates first of all Germ tube test was done to differentiate Candida albicans from Non-albicans. Carbohydrate Assimilation and Carbohydrate Fermentation test was done for further speciation[20].

Antibiotic Sensitivity Testing: The antimicrobial sensitivity testing was done for all pure bacterial

isolates in Mueller- Hinton agar plate by using Kirby-Bauer disk diffusion technique. The antibiotic discs used were obtained from Himedia (India) Laboratories. The sensitivity pattern was studied depending on the zone of inhibition as per the standard CLSI guidelines[21]. The antibiotic discs used in the study were:

Ampicillin (10µg), Amikacin (30µg), Amoxycillin/ Clavulanic acid (20/10µg), Ciprofloxacin (5µg), Cefuroxime (30µg), Cefotaxime (30µg), Cefoxitin (30µg), Colistin (10µg), Gentamicin (10µg), Imipenem(10µg), Linezolid (30µg), Piperacillin/ Tazobactam (100/10µg), Teicoplanin (30µg), Vancomycin (30µg).

CRP (C-reactive protein) estimation: TURBILYTE-CRP, a turbidimetric immunoassay for the determination of C-reactive protein based on the principle of latex agglutination was performed for each suspected neonatal septicemic case at the same time when blood was sent for culture.

Statistical Analysis: Data were collected in a Microsoft Excel sheet. Results expressed in percentage and ratio.

Results

During the study period, 220 newborns with clinical sepsis were admitted. Blood cultures were positive in 150 cases.(68.2%). Out of 150 cases, 111(74%) were having EOS and 39 (26%) were having LOS. Among the culture-positive cases, 98 (65.3%) were male and 52 (34.6%) were female neonates (Table 1). The ratio of male to female babies was 1.9:1.

Table 1 — *Age at onset of Septicemia in neonates of both sexes*

Age at onset of sepsis	Total number of cases (%)	Number of male babies	Number of female babies
0-3 days(EOS)	111 (74%)	70	41
4-28 days(LOS)	39 (26%)	28	11
Total	150	98	52

In 92 (61%) of the culture-positive cases were low birth weight and 58 (39%) were of normal body weight (Table 2).

Table 2 — *Distribution of culture-positive neonates in relation to birth weight*

Birth weight	Number of cases (%)
<2500gm (LBW)	92 (61%)
>2500gm (Normal)	58 (39%)
Total	150

Out of the 150 culture-positive cases, 81(54%) were preterm and 69 (46%) were term babies (Table 3).

The detailed etiology of the 150 culture-positive isolates was as follows: bacteria were 99 (66%) and

Table 3 — *Distribution of culture-positive neonates in relation to Gestational age*

Gestational age in weeks	Number of cases (%)
<37 weeks (Preterm)	81 (54%)
>37 weeks (Term)	69 (46%)
Total	150

51 (34%) were various species of candida. Among the bacterial isolates, 60 (60.6%) were Gram-negative bacilli and 39(39.4%) were Gram-positive cocci. In the case of Gram-negative bacilli, *Klebsiella pneumoniae* 34 (34.3%) and among Gram-positive cocci *Staphylococcus aureus* 26 (26.3%) were most commonly isolated. The rest of the pathogenic bacteria isolated in descending order were *Escherichia coli* 19 (19.1%), *Coagulase-negative Staphylococcus* 11(11.1), *Acinetobacter species* 3 (3.03%), *Citrobacter species* 3(3.03%), *Enterococcus species* 2(2.02%), and *Serratia species* 1(1.01) (Table 4).

Table 4 — *Pathogenic bacteria isolated from Blood culture*

Bacteria	Number (%)
Klebsiella pneumoniae	34 (34.3%)
Staphylococcus aureus	26 (26.3%)
Escherichia coli	19 (19.1%)
Coagulase negative staphylococcus	11 (11.1%)
Enterococcus species	2 (2.02%)
Serratia species	1 (1.01%)
Acinetobacter species	3 (3.03%)
Citrobacter species	3 (3.03%)
Total	99

Out of the 51(34%) pathogenic Candida species isolated, 18 (35.3%) were *Candida tropicalis*, followed by *Candida kruzei* 11(21.6%), *Candida parapsilosis* 9(17.6%), *Candida albicans* 7(13.7%), and *Candida glabrata* 6(11.8%) (Table 5).

Table 5 — *Pathogenic Candida species isolated from blood culture*

Candida species	Number (%)
Candida tropicalis	18 (35.3%)
Candida albicans	7 (13.7%)
Candida kruzei	11 (21.6%)
Candida parapsilosis	9 (17.6%)
Candida glabrata	6 (11.8%)
Total	51

Antibiotic susceptibility pattern was studied for all bacterial isolates causing Neonatal Septicemia.

For the Gram-negative isolates (Total no. 60), the highest sensitivity was reported for Amikacin (100%), Colistin (100%), Imipenem (96.7%), followed by Gentamicin (86.7%), Ciprofloxacin (86.7%), Amoxycillin/Clavulanic acid (48.3%). Out of the total Gram-negative isolates, 40% were ESBL producers. The highest resistance was observed to Ampicillin (100%)(Table 6).

Table 6 — *Antimicrobial sensitivity pattern of Gram negative bacilli (N=60)*

Antibiotic	Number of organisms sensitive (%)
Amikacin	60 (100%)
Gentamicin	52 (86.7%)
Cefotaxime	5 (8.3%)
Cefuroxime	4 (6.7%)
Ciprofloxacin	52 (86.7%)
Piperacillin/Tazobactam	51 (85%)
Amoxycillin/Clavulanic Acid	29 (48.3%)
Imipenem	58 (96.7%)
Ampicillin	0 (0%)
Colistin	60 (100%)

For Gram-positive isolates, the highest sensitivity was reported for Vancomycin (100%), Teicoplanin (100%), Linezolid (97.4%) followed by gentamicin (95%), and Amoxicillin/clavulanic acid (79.4%).

Methicillin-resistant Staphylococcus aureus was reported in 33.3% of the cases (Table 7).

Table 7 — *Antimicrobial sensitivity pattern of Gram positive isolates (N=39)*

Antibiotic	Number of organisms sensitive (%)
Gentamicin	37 (95%)
Ciprofloxacin	29 (74.4%)
Amoxycillin/Clavulanic Acid	26 (66.7%)
Cefoxitin	26 (66.7%)
Vancomycin	39 (100%)
Linezolid	38 (97.4%)
Teicoplanin	39 (100%)

CRP estimation was done for 220 clinically suspected neonates and it was correlated with Blood culture positivity (Table 8).

Table 8 — *Correlation of Blood culture with CRP*

	Blood Culture positive	Blood Culture negative
CRP positive	142	40
CRP negative	8	30

Sensitivity, Specificity, Positive Predictive value (PPV) and Negative predictive value (NPV) for CRP were 94.66%, 42.85%, 78.02%, and 78.94% respectively.

Out of the 150 culture-positive cases, death occurred in 17 (11.3%) neonates.

Discussion

Early diagnosis and therapy are essential for the prevention of morbidity and mortality due to neonatal sepsis in the Neonatal Intensive Care Unit (NICU).

Out of 220 clinically suspected cases of neonatal Sepsis in our study, 150 were Culture positive with a Blood Culture positivity rate of 68.2%. This finding correlates well with the study of other workers like Premlatha DE *et al*,- 72.3%[22]. EOS culture-positive cases were 74% and 26% were LOS. A higher prevalence of EOS was also reported by another study like Galhotra S *et al*,[23]. The ratio of culture-positive Male to Female babies was 1.9:1. Similarly, Buch *et al* found a Male to Female ratio of 1.8:1[24]. Several explanations had been laid down for higher male susceptibility, it may be due to a gene located on the X Chromosome involved in the synthesis of immunoglobulins in the male infants thus conferring less immunological protection compared to females[25].

In this study it was observed that low birth weight babies were more prone to Sepsis, observed frequency in the present study was 61%, comparable to the study done by Tallur SS *et al*, -55%[26]. The immature cellular immunity and low level of immunoglobulin (IgG), excessive handling and contaminated incubators expose them to infecting organisms, thus increasing infections rate. Second, to low birth weight, prematurity is the most important predisposing factor for Septicemia. In the study, preterm neonates accounted for 54% of the cases. This coincides with, a study by Khinchi YR *et al*,- 54.6%[27]. It has been established that several phagocytic functions are impaired including chemotaxis, phagocytosis and bacterial killing in preterm neonates. Also, there is impaired opsonic activity of the serum in pre-terms which is attributed to low levels of complement factors and partly to antibody deficiency. Stoll BJ[28].

In this study out of the 150 culture-positive cases, 66.4% were Bacteria and 33.6 % were Fungal isolates. Similar studies done in the past by workers like R Rani *et al* reported 62.3% Bacterial and 37.7% Fungal agents[29]. Changing trends of higher incidence of candidemia may be due to indiscriminate use of broad-spectrum antibiotics in neonatal septicemic cases.

In our study, Gram-negative isolates predominated (60.6%). *Klebsiella pneumonia* (34.3%) is most commonly isolated. This Gram-negative preponderance was also reported by Sriram R[30]. Amongst Gram-positive isolates, our study reported *Staphylococcus aureus* (26.3%) as the most common one. This is in accordance with the study done by Agnihotri N, *et al*, who reported 35% as *Staphylococcus aureus*[31]. Out of the total 51 (34%) Candida species reported in our study, the highest was *Candida tropicalis* (35.3%). This was similar to the findings of Jain A *et al*, who reported *Candida tropicalis* as the most common isolate[32].

Regarding the Antibiotic susceptibility pattern of the Gram-negative isolates in our study: 100% sensitivity was reported for Amikacin, Colistin followed by Imipenem (96%). These isolates reported 100% resistance to Ampicillin. This is in concordance with

the finding of other workers like Rasool KH, *et al*,[33]. 40% of the Gram-negative isolates were ESBL producers. This was mostly due to the indiscriminate use of third-generation cephalosporins. Our finding corroborated with the findings of Rao YK *et al*, who reported 45.8% ESBL[34].

Gram-positive isolates in our study were 100% sensitive to Vancomycin, Teicoplanin and 97.4% sensitive to Linezolid. These results are very much similar to the study done by Shaw CK[35]. Out of the 26 *Staphylococcus aureus* isolated, 33.3% were found to be Methicillin-resistant Staphylococcus aureus (MRSA). This finding is comparable to the findings of Kayenge N, *et al*, where 28% MRSA was reported[36].

In our study, we also did an estimation of C-reactive protein for all the clinically suspected cases and it was correlated with the Blood Culture reports.

Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) for CRP were 94.66%, 42.85%, 78.02%, and 78.94% respectively. These findings were in concordance with the findings of Mehrotra G[37]. Overall mortality rate in culture-positive cases was 11.3%. This coincides with the mortality rates of studies done by Bhat R, *et al*, and Khinchi YR[28,38].

Conclusion

Neonatal Septicemia being a major killer accounting for one-fourth to nearly half of the neonatal deaths in a developing country like ours, endeavors for rapid diagnosis and appropriate antimicrobial therapy is mandatory. Priority should be laid on the rapid diagnosis of suspected Sepsis cases using Blood Culture, especially when the neonates are of low birth weight, pre-term and male babies. Brain Heart Infusion Biphasic Media can be used for routine culture instead of using only Glucose broth or any other monophasic media, in order to have a rapid and higher rate of Culture positivity. In our study, Gram-negative bacilli were the predominant organism causing Septicemia with Extended-spectrum Beta-lactamase producing *Klebsiella pneumoniae* being the commonest one.

We also reported a significant number of Methicillin-resistant *Staphylococcus aureus*, along with a substantial number of Neonatal Septicemia cases due to various species of Candida.

Antimicrobial sensitivity for Gram-negative isolates was highest for Amikacin, Colistin, and Imipenem. Gram-positive isolates showed maximum sensitivity to Vancomycin, Teicoplanin, and Linezolid.

Empirical antimicrobial therapy should be started as early as possible and then modified after receiving final blood culture and sensitivity reports. However indiscriminate use of antibiotics is always cautioned so as to prevent the emergence of more multi-drug resistant cases. Adherence to infection control policies, including attention to strict hand hygiene practices, and antibiotic stewardship is required to minimize the number of infections in hospitalized neonates.

Limitations of the study : Although we had Fungal isolates also in our study group, we could not perform the antifungal susceptibility testing.

Conflicts of interest : The author declares no conflicts of interest.

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